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Original Article

Development and validation of a novel nomogram model for predicting the survival of patients with T2-4a, N0-x, M0 bladder cancer: a retrospective cohort study

Yu Xia[1*], Xi Liu[1*], Binbin Ma[1], Tao Huang[1], Danfeng Xu[1,2], Chenhui Zhao[1]

[1]Department of Urology, Ruijin Hospital Lu Wan Branch, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [2]Department of Urology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China. [*]Equal contributors.

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Abstract: Objective: Recent developments in bladder cancer treatment strategies have significantly improved the prognosis of clinically curable muscle invasive bladder cancer (MIBC) patients. Here, the prognostic factors of T2-4a, N0-x, M0 MIBC patients were investigated using the Surveillance, Epidemiology, and End Results (SEER) database and a novel nomogram model was established for prognosis prediction. Methods: The data of 7,292 patients with T2-4a, N0-x, M0 MIBC were retrieved from the SEER database (2000-2020) and randomly classified into a training set (n = 5,106) and validation set (n = 2,188). Kaplan-Meier analysis was used to calculate cancer-specific survival (CSS) and overall survival (OS) rates of patients, and differences between survival curves were analyzed using the log-rank test. Cox regression analysis was used to screen and incorporate patient prognosis-affecting independent risk factors into the nomogram model. Consistency index (C-index) values and areas under the time-dependent receiver operating characteristic curve (AUC) were used to evaluate the discriminatory ability, and the calibration curve was used to assess the calibration of the model. Its predictive performance and American Joint Committee on Cancer (AJCC) stage were compared using decision curve analysis (DCA). Results: The 1-, 3-, and 5-year CSS and OS rates of patients with T2-4a, N0-x, M0 MIBC were 76.9%, 56.0%, and 49.9%, respectively, and 71.3%, 47.9%, and 39.5%, respectively. Cox regression analysis showed that age, marital status, race, pathological type, tumor size, AJCC stage, T stage, N stage, surgery of primary tumor, regional lymph node dissection, radiation, and chemotherapy were independent prognostic risk factors of both CSS and OS ($P < 0.05$). The C-index and AUC of the nomogram model constructed based on the training and validation sets were both > 0.7, and calibration curves for predicting the 1-, 3-, and 5-year survival were consistent with the ideal curve. The nomogram model showed a higher net benefit with DCA than AJCC stage analysis. Conclusion: The nomogram model could accurately predict the prognosis of patients with T2-4a, N0-x, M0 MIBC. It may help clinicians perform personalized prognosis evaluations and formulate treatment plans.

Keywords: Muscle invasive bladder cancer, SEER database, nomogram model, survival prognosis

Introduction

The global incidence and mortality associated with bladder cancer (BC), a common malignant tumor, were ranked 10th and 12th, respectively, in 2020. Moreover, an estimated 573,278 new cases and 212,536 deaths were associated with BC worldwide in 2020 [1]. Approximately 25% of patients newly diagnosed with BC have muscle invasive bladder cancer (MIBC) and receive a poor prognosis [2].

At present, the standard clinical treatment for patients with T2-4a, N0-x, M0 MIBC involves a combination of radical cystectomy (RC) and neoadjuvant chemotherapy [3, 4]. However, owing to the difficulty associated with surgical procedures, postoperative complications (such as infection, paralytic intestinal obstruction, and wound healing problems), and serious effects on the postoperative quality of life after RC, new treatment options are being explored continuously [5]. In recent years, many clinical studies have shown that a strict screening process for patients with MIBC can help control tumors to an extent equivalent to that observed with the RC procedure, via bladder-preserving comprehensive treatment, which can help

patients achieve a better quality of life and avoid surgical trauma and potential RC-related complications [6]. At present, bladder-preserving treatment mainly includes the comprehensive treatment of transurethral resection of bladder tumor (TURBT) or partial cystectomy (PC). Among numerous treatment methods, the combination of trimodality bladder-sparing therapy (TMT) of TURBT with chemoradiotherapy has shown significant therapeutic effects [4].

Although the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (8th edition) is commonly used to predict the prognosis of patients with MIBC, this staging system does take potentially important predictive factors such as age, race, pathological type, treatment mode, and other factors into consideration [7]. The present study was based on the updated publicly available Surveillance, Epidemiology, and End Results (SEER) database. The objectives of the study were to explore the prognostic factors of patients with clinically radical T2-4a, N0-x, M0 MIBC, and establish a novel nomogram model that can be used for personalized prognosis prediction of each patient and provide a basis for clinical decision-making.

Methods

Data source and selection criteria

Because the SEER database is a publicly accessible database, there was no need to obtain informed consent from patients. After obtaining approval for the study (serial number: 10133-Nov 2021), we obtained patient records from the SEER database (version: SEER Research Data, 17 Registries, Nov 2022 Sub (2000-2020)) using SEER*Stat software (version: 8.4.1).

The inclusion criteria were as follows: (1) the primary site of the tumor was the bladder (C67.0-C67.6); (2) the pathological tumor types included the urothelial carcinoma (UCA), squamous cell carcinoma (SCA), glandular carcinoma (GCA), and neuroendocrine carcinoma (NCA) (International Classification of Diseases for Oncology-3 codes: 8120/3, 8131/3, 8082/3, 8122/3, 8031/3, 8020/3, 8130/3, 8070/3, 8051/3, 8140/3, 8144/3, 8480/3, 8140/3, 8010/3, 8041/3, 8013/3, and 8240/3); and (3) the tumor TNM stages were T2-4a, N0-x, M0. The exclusion criteria were as follows: (1) patients with multiple primary cancers; (2) nonpathologically diagnosed patients; and (3) patients with missing essential basic data, poor quality data, or incomplete basic data.

The following variables of the selected patients were included: (1) the demographic characteristics of sex (female or male), age (< 60, 60-70, 70-80, or ≥ 80), marital status (married or unmarried), and race (white, black, or other); (2) tumor characteristics of the primary tumor site (lateral wall of bladder (LW), anterior wall of bladder & dome of bladder (AW&D), trigone of bladder & bladder neck & ureteric orifice (T&BN&UO), or posterior wall of bladder (PW)), pathological type (UCA, SCA, GCA, or NCA), tumor size (< 3, 3-6, or ≥ 6 cm), AJCC stage (I-II, III, or IV), T stage (T2, T3, or T4a), and N stage (N0, N1, or N2-3); and (3) treatment information regarding the surgery of primary tumor (none, TURBT, PC, or RC), regional lymph node dissection (none, 1-3, or ≥ 4), radiation (no or yes), and chemotherapy (no or yes). The primary endpoints in this study were cancer-specific mortality and overall mortality.

Statistical analysis

IBM SPSS software (version: 19.0) was used to randomly categorize the selected patients into a training set and validation set in a 7:3 ratio. Categorical variables between the two sets were compared using the Chi-squared test.

Statistical analysis and data visualization were performed using the R software (version: 4.2.1). The Kaplan-Meier method was used to determine the cancer-specific survival (CSS) and overall survival (OS) rates of patients, and the differences in survival curves among various factors were analyzed using the log-rank test (R packages: survival [3.3.1], survival, and ggplot2 [3.3.6]). Univariate and multivariate Cox regression analyses were performed to identify the independent risk factors affecting the prognosis of patients, and significant variables ($P < 0.1$) in the univariate analysis were included in the multivariate analysis (R packages: survival [3.3.1] and rms [6.3-0]).

Nomogram models were constructed using the training set to predict the 1-, 3-, and 5-year CSS and OS rates based on the independent risk

factors of multivariate Cox regression analysis (R packages: survival [3.3.1] and rms [6.3-0]). The validation set was used to assess the performance of the nomogram model (internal validation). The consistency index (C-index), time-dependent receiver operating characteristic curve (tdROC), and areas under the tdROC curve (AUC) were used to evaluate the discriminatory ability of the model (R packages: timeROC [0.4] and ggplot2 [3.3.6]). The calibration curve was used to evaluate the calibration of the model (R packages: survival [3.3.1] and rms [6.3-0]). Finally, the predictive performance of the nomogram model and AJCC stage was compared via decision curve analysis (DCA) (R packages: survival [3.3.1] and stdca.R).

For all data analyses, a two-sided *P*-value < 0.05 was considered statistically significant. All results were reported with 95% confidence interval (CI).

Results

Demographic baseline characteristics

According to the inclusion and exclusion criteria, 7,294 patients with T2-4a, N0-x, M0 MIBC were included in this study. The average age of the patients was 70.6 years (21-90 years), the male to female ratio was 2.1:1, and the married to unmarried ratio was 1.3:1. The ratio of individuals from the white, black, and other races was 14.2:1.1:1, and the ratio of primary tumor sites located in the T&BN&UO, LW, AW&D, and PW was 1.2:2.3:1.1:1. Finally, the ratio of the pathological types, including UCA, SCA, GCA, and NCA, was 28.4:1.4:0.9:1. The patient information is detailed in **Table 1**.

The 7,294 patients were randomly categorized into the training set (5,106 patients) and validation set (2,188 patients) in a 7:3 ratio. There was no statistically significant difference in each variable between the two sets (**Table 1**). The median CSS for the training set was 60 months (95% CI: 53-74), and the 1-, 3-, and 5-year CSS rates were 76.9%, 56.0%, and 49.9%, respectively. The median OS for the training set was 33 months (95% CI: 30-36), with the 1-, 3-, and 5-year OS rates being 71.3%, 47.9%, and 39.5% respectively. The Kaplan-Meier survival curve for the training set is shown in **Figure 1**.

Univariate and multivariate Cox regression analyses

In this study, factors such as sex, age, marital status, race, primary tumor site, pathological type, tumor size, AJCC stage, T stage, N stage, surgery of primary tumor, regional lymph node dissection, radiation, and chemotherapy were included in the univariate and multivariate Cox regression analyses. The results revealed that age, marital status, race, pathological type, tumor size, AJCC stage, T stage, N stage, surgery of primary tumor, regional lymph node dissection, radiation, and chemotherapy were independent prognostic risk factors of CSS and OS (**Tables 2**, **3**). The Kaplan-Meier survival curves of each independent risk factor are shown in **Figures 2**, **3**.

Construction of the nomogram prediction model

The independent risk factors identified from Cox regression analysis were used for the construction of the nomogram model for predicting the 1-, 3-, and 5-year CSS and OS rates of patients with T2-4a, N0-x, M0 MIBC. In the nomogram model, the value level of each variable was scored based on its contribution to the patient outcome, and the total score was obtained by adding the scores together. Finally, the total score was plotted using a vertical line on the bottom scale of the model to obtain the survival probability of the patient at 1, 3, and 5 years (**Figure 4**).

Validation of the nomogram prediction model

The nomogram model was constructed using the training and validation sets. The C-index values of the model for CSS in the training and validation sets were 0.705 and 0.700, respectively, whereas the C-index values of the model for OS were 0.703 and 0.701 for the training and validation sets, respectively. The tdROC curves of the nomogram model for the training set and validation set revealed that the AUC values were 0.761, 0.734, and 0.735, and 0.753, 0.740, and 0.750 during the prediction of 1-, 3-, and 5-year CSS, respectively. Moreover, the model for the training set and validation set demonstrated the AUC values of 0.758, 0.737, and 0.743 and 0.741, 0738, and 0.755 when used to predict 1-, 3-, and 5-year OS, respectively. These results suggested that

Table 1. Baseline and clinical patient characteristics

Characteristics	Whole population	Training set	Validation set	*P* value
n	7,294	5,106	2,188	
Sex, n (%)				0.993
Female	2,343 (32.1%)	1,640 (32.1%)	703 (32.1%)	
Male	4,951 (67.9%)	3,466 (67.9%)	1,485 (67.9%)	
Age (years), n (%)				0.569
< 60	1,405 (19.3%)	967 (18.9%)	438 (20%)	
60-70	1,878 (25.7%)	1,335 (26.1%)	543 (24.8%)	
70-80	2,028 (27.8%)	1,420 (27.8%)	608 (27.8%)	
≥ 80	1,983 (27.2%)	1,384 (27.1%)	599 (27.4%)	
Marital status, n (%)				0.673
Married	4,121 (56.5%)	2,893 (56.7%)	1,228 (56.1%)	
Unmarried	3,173 (43.5%)	2,213 (43.3%)	960 (43.9%)	
Race, n (%)				0.570
White	6,362 (87.2%)	4,455 (87.3%)	1,907 (87.2%)	
Black	483 (6.6%)	330 (6.5%)	153 (7%)	
Other[a]	449 (6.2%)	321 (6.3%)	128 (5.9%)	
Primary tumor site, n (%)				0.200
T&BN&UO	1,519 (20.8%)	1,057 (20.7%)	462 (21.1%)	
LW	2994 (41%)	2,078 (40.7%)	916 (41.9%)	
AW&D	1,476 (20.2%)	1,067 (20.9%)	409 (18.7%)	
PW	1,305 (17.9%)	904 (17.7%)	401 (18.3%)	
Pathological type, n (%)				0.459
UCA	6,539 (89.6%)	4,574 (89.6%)	1,965 (89.8%)	
SCA	312 (4.3%)	224 (4.4%)	88 (4%)	
GCA	213 (2.9%)	155 (3%)	58 (2.7%)	
NCA	230 (3.2%)	153 (3%)	77 (3.5%)	
Tumor size (cm), n (%)				0.291
< 3	1,780 (24.4%)	1,264 (24.8%)	516 (23.6%)	
3-6	4,062 (55.7%)	2,813 (55.1%)	1,249 (57.1%)	
≥ 6	1,452 (19.9%)	1,029 (20.2%)	423 (19.3%)	
T stage, n (%)				0.704
T2	4,937 (67.7%)	3,442 (67.4%)	1,495 (68.3%)	
T3	1,783 (24.4%)	1,262 (24.7%)	521 (23.8%)	
T4a	574 (7.9%)	402 (7.9%)	172 (7.9%)	
N stage, n (%)				0.549
N0	6,179 (84.7%)	4,327 (84.7%)	1,852 (84.6%)	
N1	552 (7.6%)	394 (7.7%)	158 (7.2%)	
N2-3	563 (7.7%)	385 (7.5%)	178 (8.1%)	
AJCC stage, n (%)				0.635
I-II	4,557 (62.5%)	3,174 (62.2%)	1,383 (63.2%)	
III	1,829 (25.1%)	1,296 (25.4%)	533 (24.4%)	
IV	908 (12.4%)	636 (12.5%)	272 (12.4%)	
Surgery of primary tumor, n (%)				0.924
None	103 (1.4%)	73 (1.4%)	30 (1.4%)	
TURBT	3,580 (49.1%)	2,497 (48.9%)	1,083 (49.5%)	
PC	496 (6.8%)	353 (6.9%)	143 (6.5%)	
RC	3,115 (42.7%)	2,183 (42.8%)	932 (42.6%)	

Regional lymph node dissection, n (%)				0.477
1-3	310 (4.3%)	226 (4.4%)	84 (3.8%)	
≥ 4	2,978 (40.8%)	2,089 (40.9%)	889 (40.6%)	
None	4,006 (54.9%)	2,791 (54.7%)	1,215 (55.5%)	
Radiation, n (%)				0.533
None	5,843 (80.1%)	4,100 (80.3%)	1,743 (79.7%)	
Yes	1,451 (19.9%)	1,006 (19.7%)	445 (20.3%)	
Chemotherapy, n (%)				0.196
None	3,768 (51.7%)	2,663 (52.2%)	1,105 (50.5%)	
Yes	3,526 (48.3%)	2,443 (47.8%)	1,083 (49.5%)	

Notes: [a]Other: American Indian/AK native, Asian/Pacific islander, and other races. Abbreviations: LW, lateral wall of bladder; AW&D, anterior wall of bladder & dome of bladder; T&BN&UO, trigone of bladder & bladder neck & ureteric orifice; PW, posterior wall of bladder; SCA, squamous cell carcinoma; UCA, urothelial carcinoma; GCA, glandular carcinoma; NCA, neuroendocrine carcinoma; TURBT, transurethral resection of bladder tumor; RC, radical cystectomy; PC, partial cystectomy.

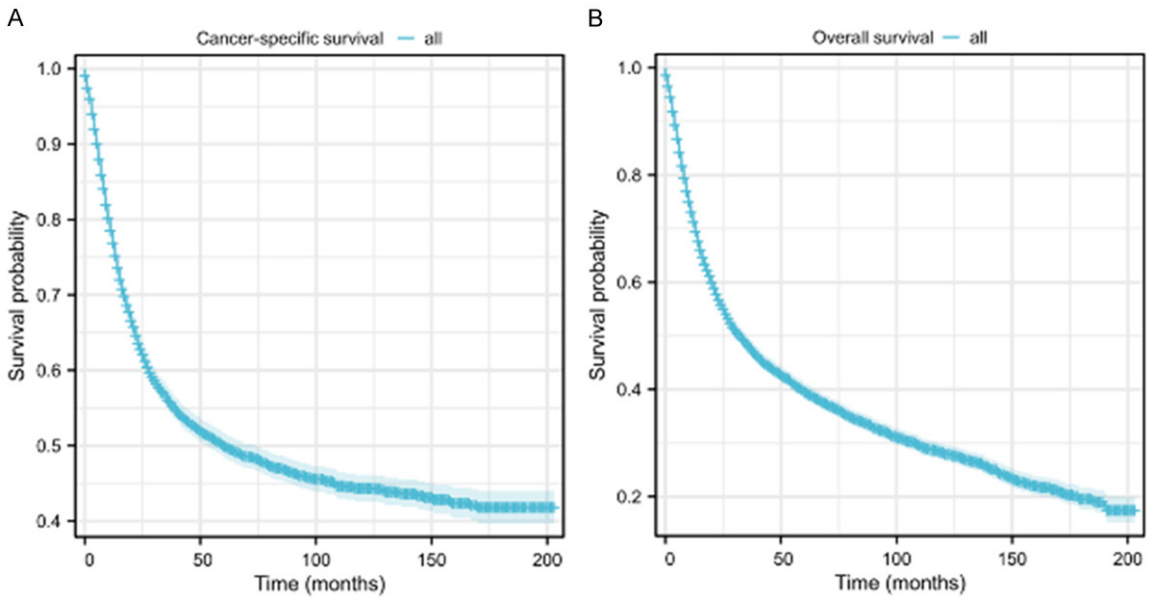

Figure 1. Kaplan-Meier survival curves of patients with T2-4a, N0-x, M0 MIBC in the training set. A. Cancer-specific survival; B. Overall survival.

the nomogram model has a good ability to the predict prognosis of patients with T2-4a, N0-x, M0 MIBC (**Figure 5**).

The calibration curve was assessed by plotting the observed versus predicted outcomes, and a 45° line denotes a perfectly calibrated model. The results showed that the calibration curve and ideal curve of the nomogram model constructed using the training set and validation set exhibited adequate consistency (**Figure 6**).

DCA analysis was used to evaluate the clinical predictive value of the nomogram model for the CSS and OS of patients with T2-4a, N0-x, M0 MIBC in 1-, 3-, and 5-year. The results showed that the nomogram model of the training set had a higher net benefit than the AJCC stage in terms of the clinical predictive value, indicating that the model had good clinical applicability (**Figure 7**).

Discussion

Advances in research on anticancer drugs and clinical research have resulted in improvements in BC treatment. According to the European Society of Urology guidelines of 2023, patients with MIBC who have been strictly screened (cT2 stage, no tumor-related hydro-

Table 2. Univariate and multivariate Cox regression analysis based on all variables for cancer-specific survival

Characteristics	Total (N)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Sex	5,106		< 0.001		
Female	1,640	Reference		Reference	
Male	3,466	0.842 (0.772-0.918)	< 0.001	0.940 (0.857-1.031)	0.186
Age (years)	5,106		< 0.001		
< 60	967	Reference		Reference	
60-70	1,335	0.977 (0.856-1.114)	0.724	1.024 (0.896-1.171)	0.725
70-80	1,420	1.236 (1.088-1.404)	0.001	1.288 (1.129-1.469)	< 0.001
≥ 80	1,384	2.088 (1.847-2.361)	< 0.001	1.823 (1.594-2.084)	< 0.001
Marital status	5,106		< 0.001		
Married	2,893	Reference		Reference	
Unmarried	2,213	1.409 (1.297-1.532)	< 0.001	1.203 (1.101-1.314)	< 0.001
Race	5,106		< 0.001		
White	4,455	Reference		Reference	
Black	330	1.422 (1.222-1.655)	< 0.001	1.213 (1.037-1.420)	0.016
Other[a]	321	0.931 (0.783-1.108)	0.423	0.956 (0.803-1.138)	0.612
Primary tumor site	5,106		0.058		
T&BN&UO	1,057	Reference		Reference	
LW	2,078	0.866 (0.774-0.967)	0.011	0.926 (0.826-1.036)	0.180
AW&D	1,067	0.960 (0.847-1.089)	0.528	0.995 (0.871-1.136)	0.940
PW	904	0.936 (0.820-1.069)	0.330	0.966 (0.844-1.104)	0.608
Pathological type	5,106		< 0.001		
UCA	4,574	Reference		Reference	
SCA	224	1.470 (1.225-1.764)	< 0.001	1.412 (1.168-1.705)	< 0.001
GCA	155	0.902 (0.712-1.143)	0.394	0.901 (0.694-1.170)	0.433
NCA	153	1.115 (0.874-1.422)	0.381	1.069 (0.835-1.368)	0.596
Tumor size (cm)	5,106		< 0.001		
≥ 6	1,029	Reference		Reference	
3-6	2,813	0.697 (0.630-0.772)	< 0.001	0.719 (0.648-0.797)	< 0.001
< 3	1,264	0.507 (0.448-0.574)	< 0.001	0.592 (0.521-0.673)	< 0.001
AJCC stage	5,106		< 0.001		
I-II	3,174	Reference		Reference	
III	1,296	1.268 (1.149-1.400)	< 0.001	1.059 (0.848-1.323)	0.611
IV	636	2.017 (1.807-2.250)	< 0.001	1.711 (1.146-2.553)	0.009
T stage	5,106		< 0.001		
T2	3,442	Reference		Reference	
T3	1,262	1.292 (1.176-1.419)	< 0.001	1.583 (1.284-1.952)	< 0.001
T4a	402	1.936 (1.690-2.219)	< 0.001	1.717 (1.369-2.154)	< 0.001
N stage	5,106		< 0.001		
N0	4,327	Reference		Reference	
N1	394	1.509 (1.311-1.738)	< 0.001	1.216 (0.859-1.721)	0.269
N2-3	385	2.265 (1.989-2.579)	< 0.001	1.906 (1.374-2.644)	< 0.001
Surgery of primary tumor	5,106		< 0.001		
None	73	Reference		Reference	
TURBT	2,497	0.440 (0.327-0.590)	< 0.001	0.633 (0.468-0.855)	0.003
PC	353	0.304 (0.219-0.422)	< 0.001	0.495 (0.346-0.707)	< 0.001
RC	2,183	0.255 (0.189-0.343)	< 0.001	0.513 (0.362-0.728)	< 0.001

Regional lymph node dissection	5,106		< 0.001		
≥ 4	2,089	Reference		Reference	
None	2,791	1.823 (1.668-1.992)	< 0.001	2.097 (1.725-2.550)	< 0.001
1-3	226	1.153 (0.932-1.425)	0.189	1.135 (0.912-1.411)	0.257
Radiation	5,106		0.048		
None	4,100	Reference		Reference	
Yes	1,006	1.112 (1.002-1.234)	0.046	0.801 (0.712-0.901)	< 0.001
Chemotherapy	5,106		< 0.001		
None	2,663	Reference		Reference	
Yes	2,443	0.725 (0.666-0.789)	< 0.001	0.763 (0.694-0.838)	< 0.001

Notes: [a]Other: American Indian/AK native, Asian/Pacific islander, and other races. Abbreviations: LW, lateral wall of bladder; AW&D, anterior wall of bladder & dome of bladder; T&BN&UO, trigone of bladder & bladder neck & ureteric orifice; PW, posterior wall of bladder; SCA, squamous cell carcinoma; UCA, urothelial carcinoma; GCA, glandular carcinoma; NCA, neuroendocrine carcinoma; TURBT, transurethral resection of bladder tumor; RC, radical cystectomy; PC, partial cystectomy.

Table 3. Univariate and multivariate Cox regression analysis based on all variables for OS

Characteristics	Total (N)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Sex	5,106		0.016		
Female	1,640	Reference		Reference	
Male	3,466	0.912 (0.847-0.983)	0.015	1.018 (0.940-1.102)	0.663
Age (years)	5,106		< 0.001		
< 60	967	Reference		Reference	
60-70	1,335	1.147 (1.019-1.291)	0.024	1.173 (1.040-1.323)	0.009
70-80	1,420	1.684 (1.505-1.885)	< 0.001	1.686 (1.502-1.893)	< 0.001
≥ 80	1,384	2.935 (2.630-3.275)	< 0.001	2.414 (2.145-2.716)	< 0.001
Marital status	5,106		< 0.001		
Married	2,893	Reference		Reference	
Unmarried	2,213	1.412 (1.316-1.515)	< 0.001	1.247 (1.157-1.343)	< 0.001
Race	5,106		< 0.001		
White	4,455	Reference		Reference	
Black	330	1.245 (1.088-1.425)	0.001	1.131 (0.984-1.301)	0.084
Other[a]	321	0.837 (0.718-0.974)	0.022	0.848 (0.728-0.988)	0.035
Primary tumor site	5,106		0.280		
T&BN&UO	1,057	Reference			
LW	2,078	0.915 (0.833-1.005)	0.062		
AW&D	1,067	0.961 (0.863-1.070)	0.469		
PW	904	0.928 (0.828-1.039)	0.192		
Pathological type	5,106		0.012		
UCA	4,574	Reference		Reference	
SCA	224	1.233 (1.047-1.452)	0.012	1.294 (1.093-1.533)	0.003
GCA	155	0.810 (0.657-0.999)	0.049	0.976 (0.776-1.227)	0.834
NCA	153	1.088 (0.883-1.341)	0.428	1.064 (0.861-1.315)	0.564
Tumor size (cm)	5,106		< 0.001		
≥ 6	1,029	Reference		Reference	
3-6	2,813	0.763 (0.699-0.833)	< 0.001	0.752 (0.687-0.822)	< 0.001
< 3	1,264	0.583 (0.525-0.647)	< 0.001	0.646 (0.580-0.719)	< 0.001
AJCC stage	5,106		< 0.001		
I-II	3,174	Reference		Reference	
III	1,296	1.080 (0.993-1.175)	0.071	0.986 (0.807-1.204)	0.889
IV	636	1.549 (1.404-1.708)	< 0.001	1.501 (1.036-2.175)	0.032

T stage	5,106		< 0.001		
T2	3,442	Reference		Reference	
T3	1,262	1.080 (0.995-1.171)	0.064	1.493 (1.234-1.805)	< 0.001
T4a	402	1.617 (1.433-1.825)	< 0.001	1.651 (1.345-2.026)	< 0.001
N stage	5,106		< 0.001		
N0	4,327	Reference		Reference	
N1	394	1.265 (1.115-1.435)	< 0.001	1.197 (0.867-1.653)	0.274
N2-3	385	1.794 (1.589-2.025)	< 0.001	1.763 (1.299-2.393)	< 0.001
Surgery of primary tumor	5,106		< 0.001		
None	73	Reference		Reference	
TURBT	2,497	0.446 (0.348-0.573)	< 0.001	0.585 (0.453-0.754)	< 0.001
PC	353	0.267 (0.202-0.353)	< 0.001	0.430 (0.318-0.583)	< 0.001
RC	2,183	0.225 (0.175-0.290)	< 0.001	0.470 (0.349-0.633)	< 0.001
Regional lymph node dissection	5,106		< 0.001		
≥ 4	2,089	Reference		Reference	
None	2,791	2.076 (1.924-2.240)	< 0.001	1.987 (1.680-2.350)	< 0.001
1-3	226	1.216 (1.018-1.453)	0.031	1.148 (0.956-1.379)	0.139
Radiation	5,106		< 0.001		
None	4,100	Reference		Reference	
Yes	1,006	1.253 (1.150-1.366)	< 0.001	0.855 (0.775-0.943)	0.002
Chemotherapy	5,106		< 0.001		
None	2,663	Reference		Reference	
Yes	2,443	0.693 (0.645-0.744)	< 0.001	0.753 (0.695-0.815)	< 0.001

Notes: [a]Other: American Indian/AK native, Asian/Pacific islander, and other races. Abbreviations: LW, lateral wall of bladder; AW&D, anterior wall of bladder & dome of bladder; T&BN&UO, trigone of bladder & bladder neck & ureteric orifice; PW, posterior wall of bladder; SCA, squamous cell carcinoma; UCA, urothelial carcinoma; GCA, glandular carcinoma; NCA, neuroendocrine carcinoma; TURBT, transurethral resection of bladder tumor; RC, radical cystectomy; PC, partial cystectomy.

nephrosis, and no cancer in situ) can choose TMT as an alternative treatment to RC [4]. Although many retrospective studies have confirmed that TMT can control tumors to an extent equivalent to that observed with RC, no randomized clinical trials have been conducted and compelling evidence has not been provided [8-13]. Owing to developments in the treatment of MIBC in recent years, there are limitations associated with the use of the AJCC and TNM staging systems for evaluating the prognosis of MIBC patients. This has necessitated the identification of new independent prognostic risk factors and prognostic models for such patients via public databases or multicenter data.

In the past 5 years, several studies have collected the data of patients with BC from the SEER database for prognostic analysis. These studies have revealed that the independent risk factors of prognosis are age, sex, ethnicity, race, marital status, histologic type, pathological grade, tumor primary site, tumor metastasis, number of primary tumors, pathological stage, AJCC stage, TNM stage, surgical treatment, chemotherapy, and radiation. In these studies, the C-index of the nomogram model based on these risk factors was 0.700-0.782 and the AUC of the model was 0.700-0.824, suggesting a relatively reliable and accurate prediction ability [14-18]. These risk factors were similar to the independent risk factors identified in this study.

Several studies have been conducted on patients with different clinical stages of BC. In 2019, Tang et al. analyzed 6,980 patients with T1 high-grade BC from the SEER database and concluded that age, ethnicity, tumor size, marital status, surgical status, and radiation were the independent risk factors associated with OS and CSS. The C-index values of the nomogram model constructed in that study for OS and CSS were 0.707 and 0.700, respectively [19]. In 2022, Zhan et al. analyzed data for 2,050 patients with BC and positive regional lymph nodes from the SEER database, and

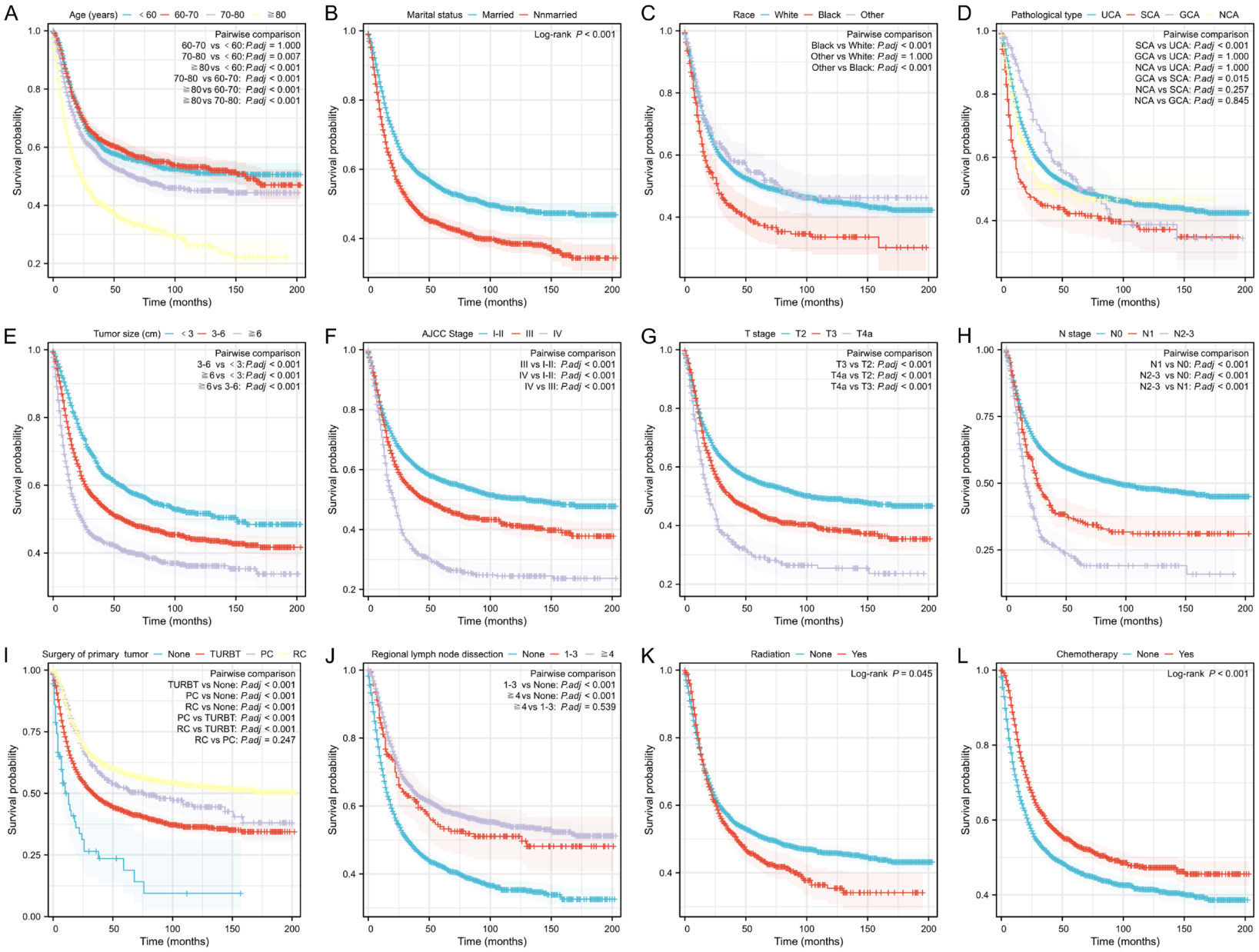

Figure 2. Kaplan-Meier survival curves of independent risk factors for cancer-specific survival. A. Age; B. Marital status; C. Race; D. Pathological type; E. Tumor size; F. AJCC stage; G. T stage; H. N stage; I. Surgery of primary tumor; J. Regional lymph node dissection; K. Radiation; L. Chemotherapy.

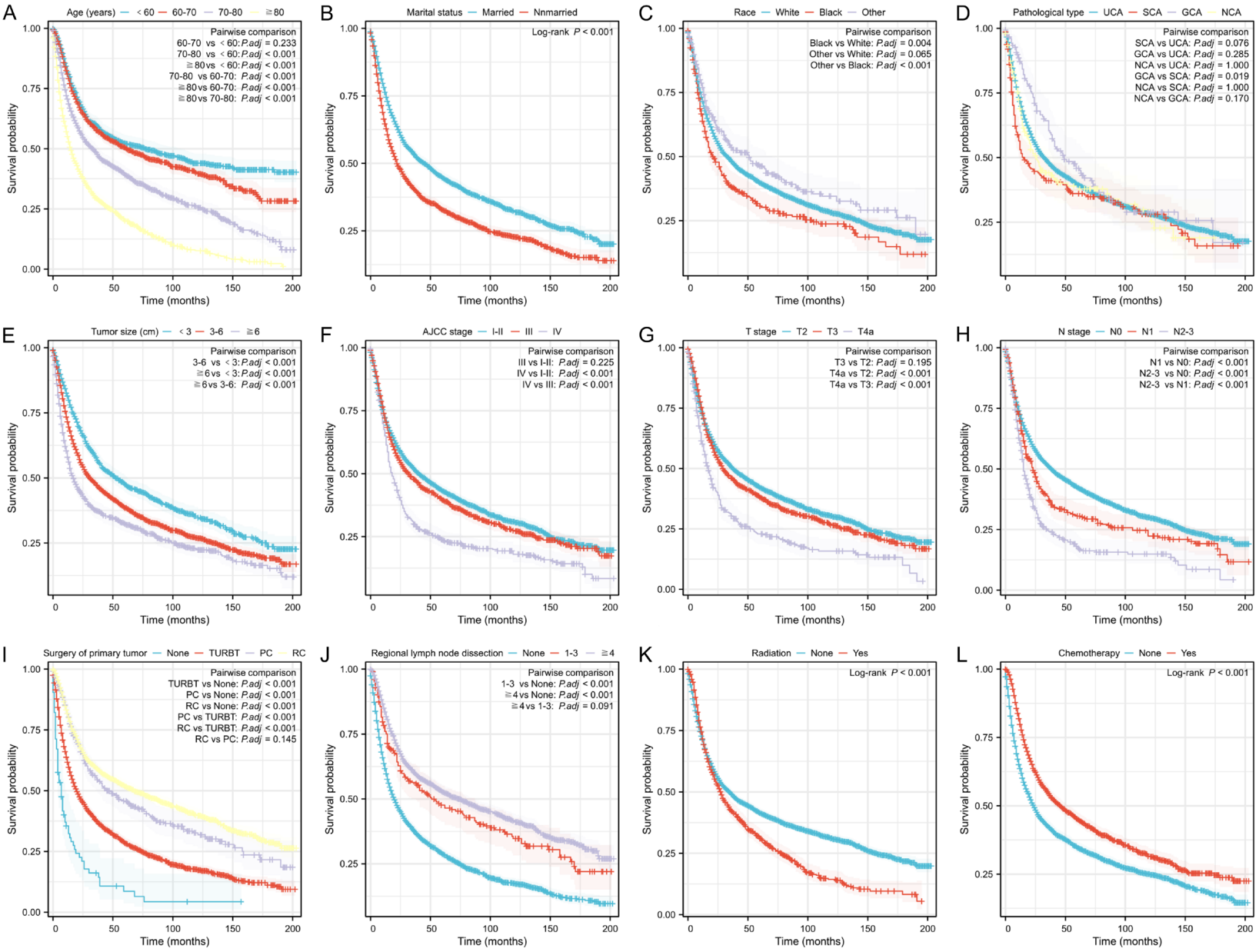

Figure 3. Kaplan-Meier survival curves of independent risk factors for overall survival. A. Age; B. Marital status; C. Race; D. Pathological type; E. Tumor size; F. AJCC stage; G. T stage; H. N stage; I. Surgery of primary tumor; J. Regional lymph node dissection; K. Radiation; L. Chemotherapy.

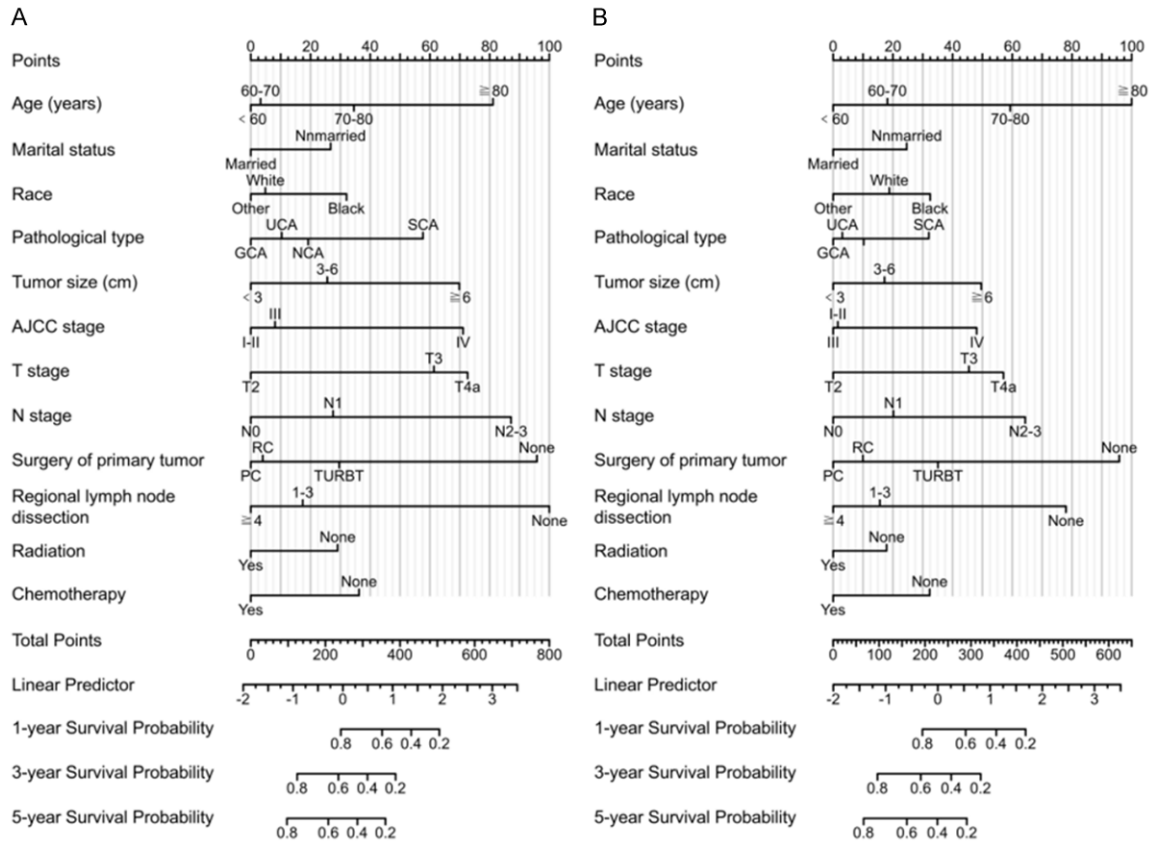

Figure 4. Nomogram model predicting 1-, 3-, and 5-year survival rates of patients with T2-4a, N0-x, M0 MIBC. A. Cancer-specific survival; B. Overall survival.

examined the stage, tumor size, chemotherapy, and regional nodes, and found that positive lymph nodes represented an independent risk factor of CSS. The C-index of the nomogram model in this study was 0.716 and the AUC values of the model for 3- and 5-year CSS were 0.803 and 0.854, respectively [20]. Furthermore, in 2020, Tao et al. analyzed 2,715 patients with distant metastatic BC from the SEER database and identified the marital status, age, grade, history type, surgery of primary site, chemotherapy, and metastasis pattern as the independent factors of OS. The C-index of the nomogram model developed in this study was 0.722 [21].

Some researchers conducted prognostic analysis on the rare pathological types of BC. In 2021, Lu et al. analyzed 1,039 patients with primary GCA from the SEER database and found that age, marital status, primary site, history type, grade, AJCC stage, T stage, SEER stage, surgery, radiation, and chemotherapy were independent risk factors of OS. The C-index of the nomogram model in this study was 0.773, which was higher than that for the TNM stage [22]. In 2022, Li et al. analyzed 906 patients with NCA from the SEER database and concluded that age, marital status, TNM stage, chemotherapy, and surgery were independent risk factors of OS, and the C-index of their nomogram model was 0.702 [23]. Moreover, in 2023, Liu et al. analyzed 219 patients with signet ring cell carcinoma of the bladder from the SEER database and found that race, TNM stage, surgery, and lymph node metastasis were independent risk factors of OS. The C-index of their nomogram model was 0.771, and the AUC values of the model for 1-, 3-, and 5-year OS were 0.713, 0.742, and 0.776, respectively [24]. In 2013, Diamantopoulos et al. analyzed 741 patients with sarcomatoid UCA from the SEER database and found that sex, SEER stage, radical cystectomy, and chemotherapy were the independent prognostic factors of OS, and that age, sex, SEER

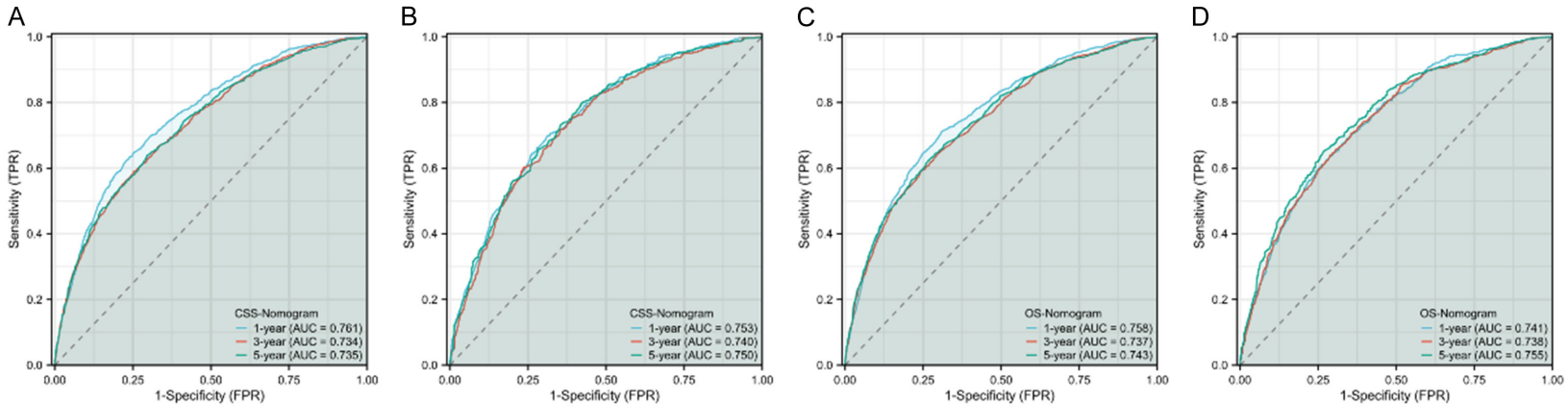

Figure 5. ROC curves of nomogram model for 1-, 3-, and 5-year survival prediction. A. For CSS in the training set. B. For CSS in the validation set. C. For OS in the training set. D. For OS in the validation set.

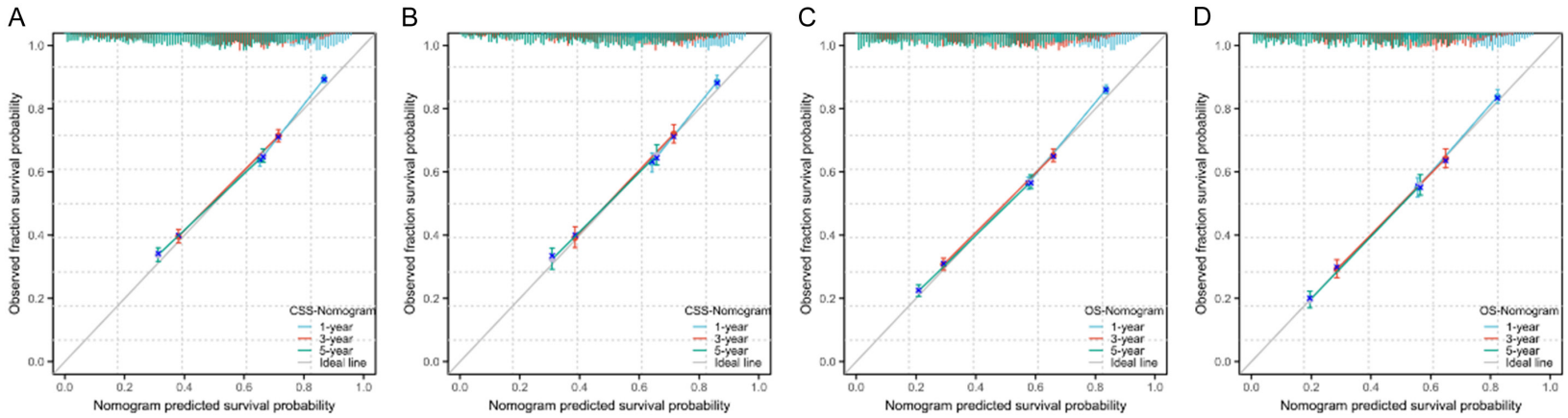

Figure 6. Calibration curves of nomogram model for 1-, 3-, and 5-year survival prediction. A. For CSS in the training set. B. For CSS in the validation set. C. For OS in the training set. D. For OS in the validation set.

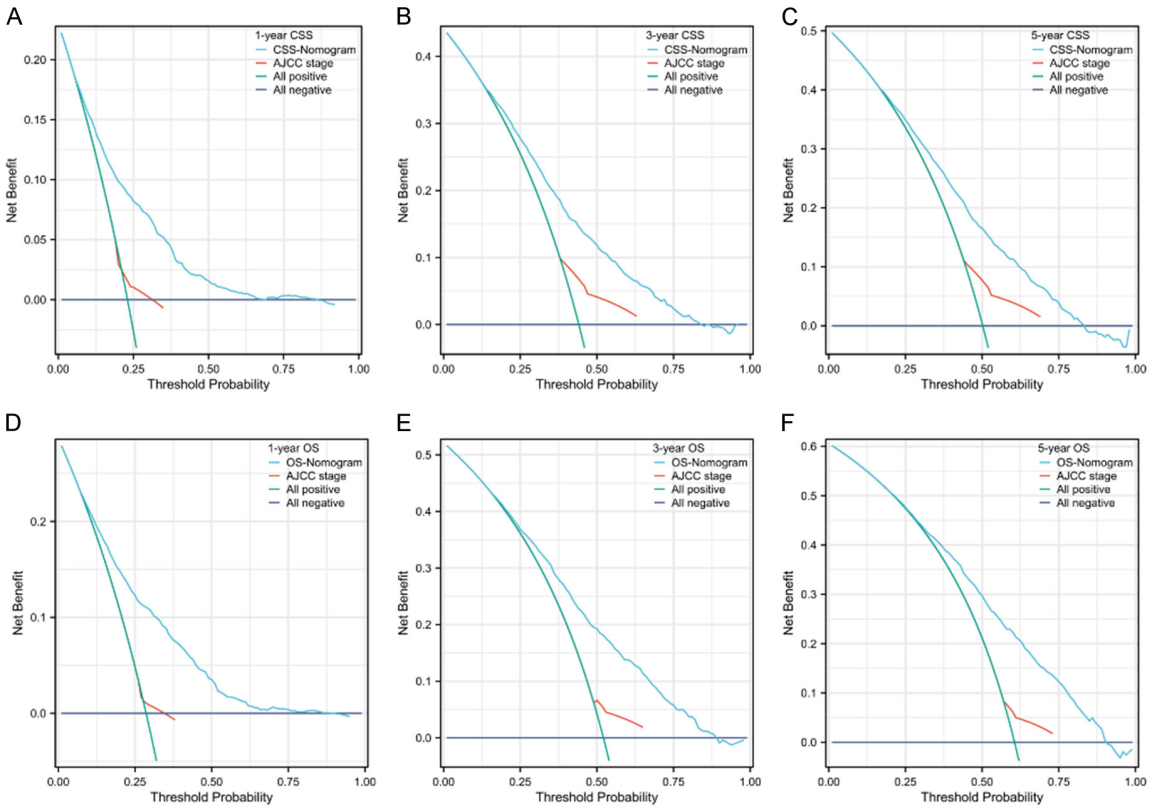

Figure 7. The DCA of 1-, 3-, and 5-year survival prediction for the nomogram model and AJCC stage in the training set. A-C. 1-, 3-, and 5-year CSS. D-F. For 1-, 3-, and 5-year OS.

stage, radical cystectomy, and chemotherapy were independent prognostic factors of CSS. The C-index values of their nomograms for OS and CSS were 0.68 and 0.67, respectively, and the predictive ability of the nomograms was better than that for the AJCC stage [25]. Omar et al. studied 5,018 patients with SCA from the SEER database in 2016 and concluded that RC, a lower SEER stage, and age < 70 years were predictive factors of OS [26]. In the present study, the prognosis of patients with SCA was the worst (CSS for SCA, HR = 1.412, P < 0.001; OS for SCA, HR = 1.294, P = 0.003), and there was no significant difference among the other pathological types (CSS and OS, log rank P > 0.05).

Using the latest SEER database published in 2023, the present study explored the independent risk factors associated with the prognosis of patients with clinically curable T2-4a, N0-x, M0 MIBC, and built a nomogram model to predict the prognosis of each individual. In this study, surgical treatments included RC, PC, and TURBT, which encompassed the current surgical treatment options for MIBC. The study results showed that in comparison with non-surgical treatment, TURBT, PC, and RC could significantly improve the prognosis of patients with T2-4a, N0-x, M0 MIBC (CSS for TURBT, HR = 0.633, P = 0.003; CSS for PC, HR = 0.495, P < 0.001; and CSS for RC, HR = 0.513, P < 0.001. OS for TURBT, HR = 0.585, P < 0.001; OS for PC, HR = 0.430, P < 0.001; and OS for RC, HR = 0.470, P < 0.001). The prognosis of patients treated with RC and PC was better than that of those treated with TURBT (CSS and OS: log-rank P < 0.001), but the differences were not significant (CSS: log-rank P = 0.247; OS: log-rank P = 0.145). These results suggest that TURBT should be recommended to patients with MIBC only after a strict screening process. In addition, the study showed that lymph node dissection could significantly improve the prognosis of patients (CSS: none, HR = 2.097, P < 0.001; OS: none, HR = 1.987, P < 0.001), but the number of lymph nodes dissected did not affect the prognosis (CSS: log-rank P = 0.539; OS: log-rank P = 0.091).

In addition to surgical treatment, chemoradiotherapy is an important treatment for MIBC. At present, the recommended chemotherapy regimens for patients with MIBC include the GC regimen (gemcitabine + cisplatin) and dd-MVAC regimen (methotrexate + vinblastine + doxorubicin + cisplatin) [27, 28]. Previous studies have confirmed that neoadjuvant chemotherapy can reduce the risk of death in patients with MIBC by 16%, improve the 10-year survival rate from 30% to 36% [29], and significantly reduce the pathological stage of patients with high-risk BC [30]. Postoperative adjuvant chemotherapy can also prolong the disease-free survival and OS of patients with high-risk BC [31]. Studies have confirmed that intravenous chemotherapy, including cisplatin, gemcitabine, 5-FU, and mitomycin, can increase the radiosensitivity of patients with BC, and that it plays an important role in TMT [32]. Radiotherapy is mainly used as an adjuvant treatment for patients with MIBC after RC. It is suitable for patients with pT3b-4 and N+ tumors with positive resection margins, who would only undergo palliative surgery or whose postoperative pathology exhibited SCA, adenosquamous carcinoma, carcinosarcoma, sarcomatoid carcinoma, or small cell carcinoma [33]. Radiotherapy is also suitable for patients who did not receive preoperative neoadjuvant chemotherapy [33]. In the present study, chemotherapy and radiotherapy, as the predictive factors of patient prognosis, significantly improved the prognosis of patients with T2-4a, N0-x, M0 MIBC (CSS for chemotherapy, HR = 0.763, P < 0.001; CSS for radiotherapy, HR = 0.801, P < 0.001; OS for chemotherapy, HR = 0.753, P < 0.001; and OS for radiotherapy, HR = 0.855, P = 0.043).

Previous studies have shown that age, sex, and race are important factors affecting the prognosis of patients with BC [34, 35]. In the current study, the average age of patients with MIBC was 70.6 years. In addition, compared with patients whose age was < 60 years, the prognosis of patients who were 60-70, 70-80, and ≥ 80 years old was significantly worsened (CSS for 60-70 years, HR = 1.024, P = 0.725; CSS for 70-80 years, HR = 1.288, P < 0.001; CSS for ≥ 80 years, HR = 1.823, P < 0.001; OS for 60-70 years, HR = 1.173, P = 0.009; OS for 70-80 years, HR = 1.686, P < 0.001; and OS for ≥ 80 years, HR = 2.414, P < 0.001). These results may be attributed to the reduction in the immunity level and physical function in elderly patients [36]. In the present study, the number of male patients was more than twice that of female patients; however, sex had no significant effect on the prognosis of patients (CSS for male, HR = 0.940, P = 0.186; OS for male, HR = 1.018, P = 0.663). The black race was a risk factor of poor CSS in the patients with MIBC patients (CSS for black, HR = 1.213, P = 0.016). However, the other races were the protective factors of OS (OS for other races, HR = 0.848, P = 0.035), which may be related to the genetic characteristics and lifestyles of different races [37]. However, the racial differences of patients with BC still need further study. Although the AJCC stage, T stage, and N stage were also identified as the independent risk factors of prognosis in patients with MIBC in this study, DCA analysis showed that their clinical predictive value was lower than that of the nomogram model.

Certain limitations are associated with the nomogram model. As this study was a retrospective study based on the SEER database, and some patients with incomplete data were excluded during the screening process, the risk of bias during the selection of patients could not be eliminated. Owing to the lack of some clinical data in the SEER database, the model did not include some information on targeted therapy and immunotherapy. The SEER database was the data source for the training and validation sets. These data could not be validated using data from other databases or medical centers. Additional clinical studies are needed to confirm the applicability and accuracy of the nomogram developed in the current study.

Conclusion

The present study conducted a systematic retrospective analysis of patients with T2-4a, N0-x, M0 MIBC based on the updated SEER database and identified independent prognostic risk factors for this cancer type. Based on these factors, a novel nomogram model was established. Subsequent analyses showed that the nomogram model could not only accurately predict the prognosis but also exhibit improved prediction of parameters other than the AJCC stage. Thus, this nomogram model

could help clinicians make individualized prognostic evaluation and treatment plans for patients.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Chenhui Zhao, Department of Urology, Ruijin Hospital Lu Wan Branch, Shanghai Jiao Tong University School of Medicine, Shanghai, China. E-mail: xiayuyang-2015@126.com

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