Original Article

Predictive nomograms for risk and prognostic factors in metastatic bladder cancer: a population-based study

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Background: Given the poor prognosis of patients with metastatic bladder cancer (MBC), the development of an effective diagnostic and prognostic model is significant in cancer management and for guidance in clinical practice.

Methods: We acquired data of 23,180 bladder cancer patients from Surveillance Epidemiology and End Results (SEER) database registered from 2010 to 2019. The optimal cut-off value for patient age and tumor size was determined by x-tile software. Independent risk factors for MBC were identified by univariate and multivariate logistic regression analyses and prognosis factors were identified by univariate and multivariate cox regression analyses, and risk and prognostic nomograms were constructed. The accuracy of the nomograms was verified by receiver operating characteristic (ROC) curves, calibration curves, and its clinical utility was determined by decision curve analysis (DCA) curves and clinical impact curves (CIC). Kaplan-Meier (K-M) survival curves further confirmed the clinical validity of the prognostic model.

Results: Through logistic regression analyses, we derived that age, histological type, tumor size, T stage, and N stage were independent risk factors for metastasis in bladder cancer patients. By cox regression analyses, age, chemotherapy, histological type, bone, lung and liver metastases were identified as risk factors influencing prognosis of MBC patients. Area under the curve (AUC) of the risk nomogram was 0.80, the AUC values of 1/2/3 years were 0.74/0.71/0.71 in the training group and 0.81/0.77/0.77 in the validation group. Based on calibration curves, DCA curves, CIC and K-M curves, the nomograms were validated with excellent predictive performance and clinical utility for MBC.

Conclusions: The nomograms we constructed have perfect predictive accuracy and clinical practicality for MBC patients, enabling clinicians to provide treatment advice and clinical guidance to patients.

Keywords: Metastatic bladder cancer (MBC); risk; prognosis; nomograms; Surveillance Epidemiology and End Results database (SEER database)

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Introduction

Bladder cancer is a malignant disease with high morbidity and mortality rate, which ranks among the top ten cancers in the world, and the sixth in male population. Despite recent advances in surgical techniques and drug therapies, according to a global survey in 2020, there were 573,278 new cases of bladder cancer and 212,536 new deaths reported worldwide (1), causing a global economic burden on healthcare industry. It has been widely recognized that the high incidence of bladder cancer is associated with smoking and secondhand smoke exposure, and the degree of smoking in patients is also linked linearly to tumor malignancy (2). Studies have shown that nearly 4% of all patients diagnosed with bladder cancer are diagnosed as metastatic bladder cancer (MBC) at initial diagnosis (3). MBC means a worse prognosis, with a median overall survival (OS) of only 13–15 months, even when treated with rigorous chemotherapy regimens (4).

Tumor metastasis is a process that involves multiple mechanisms in the final stages of the tumor process and also ultimately leads to the death of patients (5). The main metastatic sites of bladder cancer are bone, lung, liver and brain, etc. (6). Bone metastases are the most common site of MBC, the majority of patients with bladder cancer can be evaluated by routine chest , abdomen and pelvic enhancement Computed Tomography (CT), but sometimes there exists inadequate staging, so positron emission tomography-computed tomography (PET-CT) is increasingly used in the detection of bladder cancer, especially in patients with muscle-invasive bladder cancer and recurrence after radical cystectomy (7). In the evaluation of the prognosis of patients with MBC, there have been nomograms constructed for bone metastasis and brain metastasis to predict the prognosis of patients (6,8), however, predictions for a single metastatic site have limitations, such as the difficulty of applying them broadly to patients with bladder cancer, and they lack application of common clinical indicators. Therefore, the use of common clinical indicators to evaluate the risk and prognosis of MBC is currently needed for providing guidelines to clinicians.

We obtained clinical data of bladder cancer from the Surveillance, Epidemiology, and End Results (SEER) database. After screening, a total of 22,788 patients were included in our study. Two practical nomograms were constructed by clinical information, the risk nomogram for predicting the risk of bladder cancer metastasis and the prognosis nomogram for predicting 1-, 2- and 3-year survival in patients with MBC. Two prediction models have been validated to have favorable clinical utility through the receiver operating characteristic (ROC), decision curve analysis (DCA) curves, clinical impact curves (CIC) and Kaplan-Meier (K-M) survival curves. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1229/rc).

Highlight box

Key findings

- We successfully constructed nomograms to evaluate the risk and prognostic factors of metastatic bladder cancer (MBC) with superior discrimination, ex-cellent calibration abilities, and great clinical benefit.

What is known and what is new?

- MBC has a poor prognosis and is associated with many clinical factors.
- New nomograms were created to predict metastatic and prognostic risk based on extensive patient data.

What is the implication, and what should change now?

- Nomograms constructed on the basis of clinical information can easily predict the risk and prognosis of metastasis bladder cancer patients, which has positive implications for patient management.

Methods

Ethical statement

The ethical approval of this study was exempted by the Ethics Committee of the First Affiliated Hospital of Nanchang University as the data were from the publicly accessible database, SEER. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Patients

We downloaded clinical information from SEER state software (version 8.4.1) of patients with bladder cancer registered from 2010 to 2019. The inclusion criteria were: (I) bladder cancer was the only primary carcinoma; (II) histology type was known; and (III) definitive site of metastasis. Exclusion principles were: (I) unknown cause of death and survival time; (II) unknown race; (III) unknown tumor size; (IV) undetermined T and N stage and grade; (V) lack of surgical, radiotherapy and chemotherapy

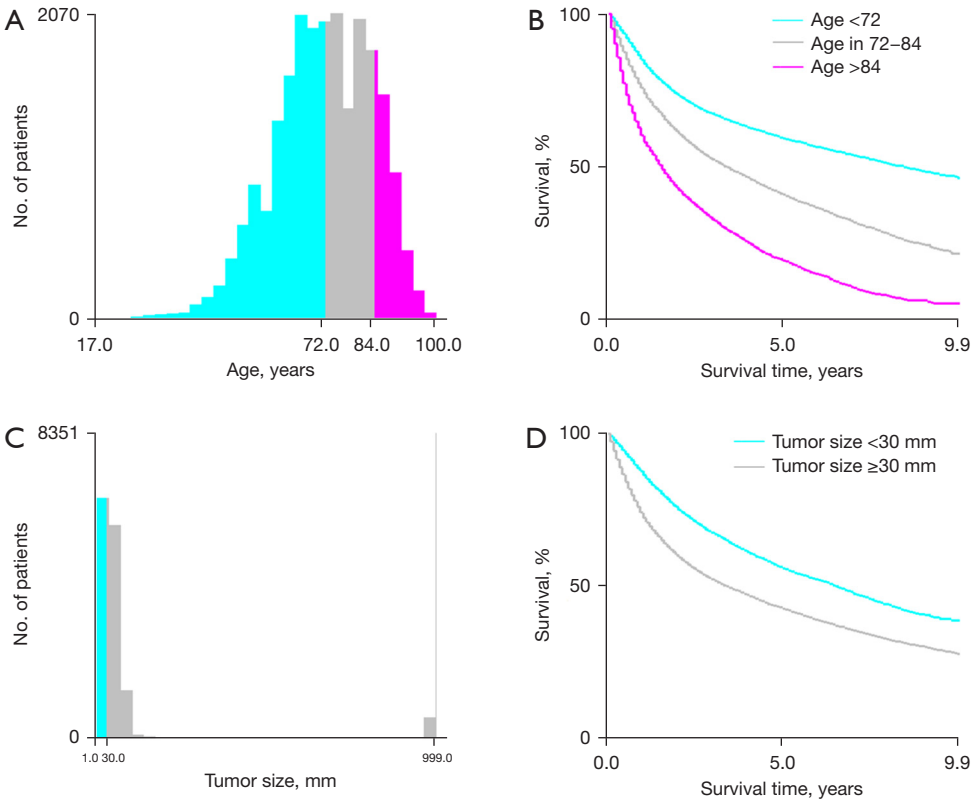

Figure 1 The appropriate cut-off values of age and tumor size was assessed by x-tile software. (A,B) The appropriate cut-off values of age were 72 and 84 years old; (C,D) the appropriate cut-off value of tumor size was 30 mm.

information. Finally, there were 22,788 patients included in the cohort to study the risk factors of metastasis in bladder cancer patients and to establish a risk nomogram. For the exploration of prognostic factors for MBC, a total of 1,150 patients were enrolled in the whole cohort.

In the analysis of metastatic risk, we included the following clinical information: age at diagnosis, sex, race, histological type, tumor size, grade, T-stage (AJCC 7th edition), N-stage (AJCC 7th edition), primary site. Within the analysis of prognostic influences, besides the above factors, we included treatment and metastatic information, such as bone, lung, liver and brain metastases, surgery, radiotherapy and chemotherapy information.

Statistical analysis and nomogram construction

All statistical analyses were performed by SPSS (version 25.0), x-tile software (version 3.6.1), and software packages (rms, pROC, ggDCA, ggplot and rmda) in R software (version 4.2.3). We used x-tile software to calculate the optimal cut-off values for tumor size and age that affect the prognosis of bladder cancer patients, the results are shown in *Figure 1*. Chi-squared test or Fisher exact test were deployed to compare categorical data. Through univariate logistic regression analysis, variables with a $P<0.05$ were included in multivariate logistic regression analysis, the odds ratios (OR) and 95% confidence intervals (CI) were calculated, then the significant risk factors were screened out. Next, risk factors for prognosis in MBC patients were analyzed. All MBC patients were randomly divided into training (n=806) and validation (n=344) cohorts according to the ratio of 7:3 (9). In the training cohort, variables with $P<0.05$ in univariate cox regression analysis were included in the multivariate cox regression analysis to identify significant prognostic factors, the hazard ratios (HR) and 95% CI were calculated. Finally, we established two nomograms based on risk factors and prognostic factors to predict the risk and OS of MBC. In the risk nomogram, its accuracy and discrimination were evaluated by ROC curves (10), bootstrapping (1,000 resamples) calibration curves (11), and

the area under curve (AUC) of ROC. Its clinical utility was assessed by clinical DCA and CIC (12). In the prognostic nomogram, accuracy and discrimination were assessed by ROC curves and calibration curves for 1-, 2-, and 3-year, respectively, and AUC. Its clinical utility was assessed by DCA curves and KM curves. Two tailed P values ≤0.05 was considered statistically significant.

Results

Patient characteristics

After the screening process, date of a total of 22,788 bladder cancer patients were obtained from the SEER database. Among them, 1,150 patients were diagnosed as MBC, 806 cases were grouped into training cohort and 344 cases as validation cohort. Among bladder cancer patients with and without metastasis, there was a difference in the percentage of all risk and prognostic factors except surgery. Whites (88.9%) accounted for the largest proportion of all bladder cancer patients, with little difference in the proportion of transitional cell carcinoma and papillary transitional cell carcinoma (44.8% *vs.* 48.9%). In terms of treatment style, the vast majority of patients underwent local tumor excision (LTE). Bone metastasis accounted for the highest percentage (36.3%), brain metastasis accounted for the least (2.1%) of patients with MBC. The specific clinical information of patients are shown in *Table 1*.

Analysis of independent risk and prognostic factors

In the univariate logistic regression analysis, a total of nine clinical factors were associated with metastasis, while in the multivariate logistic regression analysis, age, histological type, T stage, N stage and tumor size were found to be associated with metastasis, the analysis results are shown in *Table 2*. In order to construct the prognosis nomogram of MBC, we divided the patients into training cohort and validation cohort, the Chi-squared test and Fisher's exact test showed that none of the 16 factors were different between the two groups (*Table 3*). After inclusion of 16 prognostic factors in the training cohort, the prognostic factor of P<0.05 such as age, histological type, tumor size, T stage, N stage, chemotherapy, bone metastasis, liver metastasis and lung metastasis were included in the multivariate cox regression analysis by univariate cox regression analysis. Finally, age, histological type, chemotherapy, bone metastasis, liver metastasis, and lung metastasis were considered to be significantly associated with MBC patient prognosis. The analysis results are shown in *Table 4*.

Risk nomogram construction and validation

With the results of multivariate logistic regression analysis, we constructed the final risk nomogram of bladder cancer, as shown in *Figure 2*. The probability of prediction can be obtained by summing up the scores obtained through the projection of each predictive factor. The AUC of the ROC analysis reached 0.80, demonstrating the excellent discriminatory ability of the risk nomogram (*Figure 3A*). The high overlap between the observed and predicted results in the calibration curve also showed the good reliability of the nomogram (*Figure 3B*). In the evaluation of clinical effect, both DCA and CIC curves showed that patients could get excellent clinical net benefit by this nomogram (*Figure 3C*,*3D*).

Prognostic nomogram construction and validation

Based on the results obtained from the multivariate cox regression analysis of the training cohort, we constructed the prognostic nomogram of MBC (*Figure 4*). The survival rate of prediction can be obtained by summing up the scores obtained through the projection of each predictive factor. The AUC of the ROC curve analysis of the nomogram revealed 1-, 2- and 3-year OS respectively reached 0.74, 0.71 and 0.71 in the training cohort (*Figure 5A*), 1-, 2- and 3-year OS respectively reached 0.81, 0.77 and 0.77 in the validation cohort (*Figure 5B*). The calibration curve of nomogram revealed an excellent consistency between actual observation and prediction both training cohort and validation cohort (*Figure 5C-5H*). As shown in *Figure 6A-6C*, the nomogram demonstrated a significant net benefit of 1-, 2- and 3-year OS, indicating its great clinical practical value in predicting OS of MBC in training cohort, the same results were also shown in validation cohort (*Figure 6D-6F*). Similarly, the prognostic risk factors by nomogram showed differences in the prognosis of all patients with MBC, training cohort and validation cohort in the KM survival analysis, further validated the clinical utility of the prognostic nomogram (*Figure 7A-7C*).

Discussion

As a highly heterogeneous disease, bladder cancer is

Table 1 Characteristic of patients with and without MBC

Characteristics	Without MBC, n (%)	With MBC, n (%)	χ^2	P
All	21,638	1,150		
Age (years)			16.767	<0.001
<72	9,669 (44.7)	564 (49.0)		
72–84	8,373 (38.7)	444 (38.6)		
>84	3,596 (16.6)	142 (12.3)		
Sex			11.786	0.001
Female	5,102 (23.5)	322 (28.0)		
Male	16,536 (76.5)	828 (72.0)		
Race			14.117	0.001
White	19,247 (89.1)	1,001 (87.0)		
Black	1,324 (6.1)	101 (8.8)		
Others	1,067 (4.9)	48 (4.2)		
Histologic type			275.751	<0.001
Transitional cell carcinoma	9,546 (44.1)	674 (58.6)		
Papillary transitional cell carcinoma	10,821 (50.0)	313 (27.2)		
Others	1,271 (5.9)	163 (14.2)		
Tumor size (mm)			121.829	<0.001
<30	4,090 (18.9)	69 (6.0)		
≥30	17,548 (81.1)	1,081 (94.0)		
Grade			68.595	<0.001
Well differentiated; I	630 (2.9)	12 (1.0)		
Moderately differentiated; II	2,189 (10.1)	48 (4.2)		
Poorly differentiated; III	4,836 (22.3)	321 (27.9)		
Undifferentiated; anaplastic; IV	13,983 (64.6)	769 (66.9)		
AJCC T stage			848.243	<0.001
T1	11,337 (52.4)	176 (15.3)		
T2	7,002 (32.4)	605 (52.6)		
T3	2,131 (5.8)	131 (11.4)		
T4	1,168 (9.4)	238 (20.7)		
AJCC N stage			1,671.043	<0.001
N0	20,057 (92.7)	692 (60.2)		
N1	665 (3.1)	114 (9.9)		
N2	762 (3.5)	245 (21.3)		
N3	154 (0.7)	99 (8.6)		

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Without MBC, n (%)	With MBC, n (%)	χ^2	P
Primary site			99.943	<0.001
Anterior wall of bladder	1,088 (5.0)	54 (4.7)		
Bladder neck	1,238 (5.7)	88 (7.7)		
Dome of bladder	1,752 (8.1)	78 (6.8)		
Lateral wall of bladder	6,581(30.4)	257 (22.3)		
Overlapping lesion of bladder	4,873 (22.5)	384 (33.4)		
Posterior wall of bladder	3,162 (14.6)	134 (11.7)		
Trigone of bladder	2,127 (9.8)	118 (10.3)		
Ureteric orifice	817 (3.8)	37 (3.2)		
Surgery			0.59	0.899
No	2,337 (10.8)	117 (10.2)		
LTE	17,209 (79.5)	919 (79.9)		
PC	272 (1.3)	16 (1.4)		
RC	1,820 (8.4)	98 (8.5)		
Radiation			203.391	<0.001
No	19,537 (90.3)	887 (77.1)		
Yes	2,101 (9.7)	263 (22.9)		
Chemotherapy			239.493	<0.001
No	14,003 (64.7)	486 (42.3)		
Yes	7,635 (35.3)	664 (57.7)		
Bone metastasis			–	–
No	–	732 (63.7)		
Yes	–	418 (36.3)		
Brain metastasis			–	–
No	–	1,126 (97.9)		
Yes	–	24 (2.1)		
Liver metastasis			–	–
No	–	936 (81.4)		
Yes	–	214 (18.6)		
Lung metastasis			–	–
No	–	781 (67.9)		
Yes	–	369 (32.1)		

MBC, metastatic bladder cancer; LTE, local tumor excision; PC, partial cystectomy; RC, radical cystectomy.

Table 2 Univariable and multivariable logistic regression of risk factors of MBC patients

Characteristics	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95%CI)	P
Age (years)				
<72	Reference		Reference	
72–84	0.895 (0.895–0.797)	0.088	1.017 (0.887–1.167)	0.807
>84	0.672 (0.557–0.811)	<0.001	0.799 (0.655–0.976)	0.028
Sex				
Female	Reference		Reference	
Male	0.793 (0.905–0.906)	0.001	0.930 (0.806–1.074)	0.322
Race				
White	Reference		Reference	
Black	1.467 (1.186–1.813)	<0.001	1.250 (0.994–1.572)	0.056
Others	0.865 (0.643–1.163)	0.337	0.888 (0.649–1.216)	0.46
Histologic type				
Transitional cell carcinoma	Reference		Reference	
Papillary transitional cell carcinoma	0.410 (0.357–0.470)	<0.001	0.745 (0.641–0.865)	<0.001
Others	1.816 (1.516–2.176)	<0.001	1.635 (1.330–2.010)	<0.001
Tumor size (mm)				
<30	Reference		Reference	
≥30	3.652 (2.856–4.669)	<0.001	2.915 (2.263–3.755)	<0.001
Grade				
Well differentiated; I	Reference		Reference	
Moderately differentiated; II	1.151 (0.608–2.181)	0.666	0.910 (0.467–1.774)	0.782
Poorly differentiated; III	3.485 (1.947–6.238)	<0.001	1.721 (0.933–3.174)	0.082
Undifferentiated; anaplastic; IV	2.887 (1.623–5.135)	<0.001	1.573 (0.857–2.888)	0.144
AJCC T stage				
T1	Reference		Reference	
T2	5.566 (4.693–6.600)	<0.001	3.574 (2.977–4.290)	<0.001
T3	3.960 (3.144–4.988)	<0.001	1.281 (0.984–1.669)	0.066
T4	13.126 (10.704–16.095)	<0.001	3.766 (2.960–4.791)	<0.001
AJCC N stage				
N0	Reference		Reference	
N1	4.969 (4.017–6.146)	<0.001	3.293 (2.616–4.145)	<0.001
N2	9.319 (7.920–10.965)	<0.001	6.016 (4.987–7.257)	<0.001
N3	18.633 (14.315–24.253)	<0.001	13.487 (10.130–17.958)	<0.001

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95%CI)	P
Primary site				
Anterior wall of bladder	Reference			
Bladder neck	1.432 (0.011–2.029)	0.043	1.332 (0.921–1.927)	0.127
Dome of bladder	0.897 (0.625–1.279)	0.549	0.972 (0.670–1.411)	0.882
Lateral wall of bladder	0.787 (0.583–1.602)	0.118	0.879 (0.641–1.205)	0.422
Overlapping lesion of bladder	1.588 (1.185–2.127)	0.002	1.208 (0.887–1.646)	0.23
Posterior wall of bladder	0.854 (0.618–1.180)	0.338	1.011 (0.719–1.421)	0.95
Trigone of bladder	1.118 (0.803–1.555)	0.509	1.074 (0.758–1.421)	0.687
Ureteric orifice	0.912 (0.595–1.400)	0.675	1.301 (0.830–2.038)	0.251

MBC, metastatic bladder cancer; OR, odds ratios; CI, confidence interval.

Table 3 Characteristics of MBC patients in training and validation cohorts.

Characteristics	Training cohort, N or N (%)	Validation cohort, N or N (%)	χ^2	P
All	806	344		
Age (years)			0.363	0.834
<72	402 (49.9)	166 (48.3)		
72–84	307 (38.1)	133 (38.7)		
>84	97 (12.0)	45 (13.1)		
Sex			0.451	0.502
Female	221 (27.4)	101 (29.4)		
Male	585 (72.6)	243 (70.6)		
Race			3.389	0.384
White	708 (87.8)	293 (85.2)		
Black	70 (8.7)	31 (9.0)		
Others	28 (3.5)	20 (5.8)		
Histologic type			0.179	0.914
Transitional cell carcinoma	473 (58.7)	201 (58.6)		
Papillary transitional cell carcinoma	217 (26.9)	96 (27.2)		
Others	116 (14.4)	47 (14.2)		
Tumor size (mm)			0.03	0.893
<30	49 (6.1)	20 (5.8)		
≥30	757 (93.9)	324 (94.2)		

Table 3 (*continued*)

Table 3 (*continued*)

Characteristics	Training cohort, N or N (%)	Validation cohort, N or N (%)	χ^2	P
Grade			4.554	0.21
Well differentiated; I	11 (1.4)	1 (0.3)		
Moderately differentiated; II	35 (4.3)	13 (3.8)		
Poorly differentiated; III	215 (26.7)	106 (30.8)		
Undifferentiated; anaplastic; IV	545 (67.6)	224 (65.1)		
AJCC T stage			1.954	0.582
T1	122 (15.1)	54 (15.7)		
T2	416 (51.6)	189 (54.9)		
T3	93 (11.5)	38 (11.0)		
T4	175 (21.7)	63 (18.3)		
AJCC N stage			2.618	0.454
N0	482 (59.8)	210 (61.0)		
N1	83 (10.3)	31 (9.0)		
N2	166 (20.6)	79 (23.0)		
N3	75 (9.3)	24 (7.0)		
Primary site			3.939	0.787
Anterior wall of bladder	38 (4.7)	16 (4.7)		
Bladder neck	62 (7.7)	26 (7.6)		
Dome of bladder	57 (7.1)	21 (6.1)		
Lateral wall of bladder	178 (22.1)	79 (23.0)		
Overlapping lesion of bladder	271 (33.6)	113 (32.8)		
Posterior wall of bladder	99 (12.3)	35 (10.2)		
Trigone of bladder	79 (9.8)	39 (11.3)		
Ureteric orifice	22 (2.7)	15 (4.4)		
Surgery			2.533	0.469
No	79 (9.8)	38 (11.0)		
LTE	651 (80.8)	268 (77.9)		
PC	13 (1.6)	3 (0.9)		
RC	63 (7.8)	35 (10.2)		
Radiation			2.199	0.138
No	612 (75.9)	275 (79.9)		
Yes	194 (24.1)	69 (20.1)		
Chemotherapy			1.193	0.275
No	349 (43.3)	137 (39.8)		
Yes	457 (56.7)	207 (60.2)		

Table 3 (*continued*)

Table 3 (*continued*)

Characteristics	Training cohort, N or N (%)	Validation cohort, N or N (%)	χ^2	P
Bone metastasis			0.165	0.684
No	510 (63.3)	222 (64.5)		
Yes	296 (36.7)	122 (35.5)		
Brain metastasis			1.615	0.204
No	792 (98.3)	334 (97.1)		
Yes	14 (1.7)	10 (2.9)		
Liver metastasis			1.759	0.185
No	648 (80.4)	288 (83.7)		
Yes	158 (19.6)	56 (16.3)		
Lung metastasis			1.415	0.234
No	556 (69.0)	225 (65.4)		
Yes	250 (31.0)	119 (34.6)		

MBC, metastatic bladder cancer; LTE, local tumor excision; PC, partial cystectomy; RC, radical cystectomy.

Table 4 Univariable and multivariable cox regression of prognosis factors of MBC patients

Characteristic	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age (years)				
<72	Reference		Reference	
72–84	1.381 (1.215–1.571)	<0.001	1.440 (1.114–1.863)	0.005
>84	1.730 (1.435–2.084)	<0.001	1.500 (1.040–2.163)	0.03
Sex				
Female	Reference			
Male	0.919 (0.806–1.049)	0.211		
Race				
White	Reference			
Black	1.076 (0.874–1.325)	0.488		
Others	0.795 (0.585–1.079)	0.141		
Histologic type				
Transitional cell carcinoma	Reference		Reference	
Papillary transitional cell carcinoma	0.745 (0.580–0.957)	0.021	0.699 (0.537–0.909)	0.008
Others	0.847 (0.612–1.174)	0.32	0.729 (0.514–1.035)	0.077
Tumor size (mm)				
<30	Reference		Reference	
≥30	0.683 (0.528–0.883)	0.004	1.539 (0.921–2.571)	0.1

Table 4 (*continued*)

Table 4 (*continued*)

Characteristic	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Grade				
Well differentiated; I	Reference			
Moderately differentiated; II	0.750 (0.396–1.417)	0.375		
Poorly differentiated; III	0.868 (0.488–1.547)	0.632		
Undifferentiated; anaplastic; IV	0.789 (0.446–1.396)	0.415		
AJCC T stage				
T1	Reference		Reference	
T2	0.984 (0.829–1.167)	0.853	0.939 (0.683–1.292)	0.7
T3	0.712 (0.563–0.901)	0.005	0.878 (0.558–1.383)	0.575
T4	0.970 (0.795–1.184)	0.762	1.074 (0.720–1.602)	0.727
AJCC N stage				
N0	Reference		Reference	
N1	0.805 (0.656–0.989)	0.039	0.729 (0.483–1.100)	0.132
N2	1.042 (0.898–1.208)	0.59	1.176 (0.891–1.551)	0.253
N3	0.770 (0.619–0.958)	0.019	1.057 (0.663–1.685)	0.817
Primary site				
Anterior wall of bladder	Reference			
Bladder neck	1.139 (0.802–1.618)	0.467		
Dome of bladder	0.902 (0.629–1.292)	0.574		
Lateral wall of bladder	1.090 (0.804–1.477)	0.581		
Overlapping lesion of bladder	1.110 (0.826–1.492)	0.49		
Posterior wall of bladder	1.124 (0.810–1.559)	0.484		
Trigone of bladder	1.192 (0.854–1.663)	0.301		
Ureteric orifice	1.334 (0.869–2.084)	0.188		
Surgery				
No	Reference			
LTE	1.250 (0.980–1.593)	0.072		
PC	1.325 (0.719–2.440)	0.367		
RC	1.272 (0.905–1.788)	0.166		
Radiation				
No	Reference			
Yes	1.013 (0.880–1.167)	0.857		
Chemotherapy				
No	Reference		Reference	
Yes	0.451 (0.399–0.509)	<0.001	0.330 (0.256–0.425)	<0.001

Table 4 (*continued*)

Table 4 (*continued*)

Characteristic	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Bone metastasis				
No	Reference		Reference	
Yes	1.388 (1.227–1.570)	<0.001	1.470 (1.147–1.883)	0.002
Brain metastasis				
No	Reference			
Yes	1.456 (0.970–2.183)	0.07		
Liver metastasis				
No	Reference		Reference	
Yes	1.577 (1.354–1.836)	<0.001	1.778 (1.300–2.432)	<0.001
Lung metastasis				
No	Reference		Reference	
Yes	1.226 (1.080–1.392)	0.002	1.558 (1.224–1.983)	<0.001

MBC, metastatic bladder cancer; LTE, local tumor excision; PC, partial cystectomy; RC, radical cystectomy; HR, hazard ratios; CI, confidence intervals.

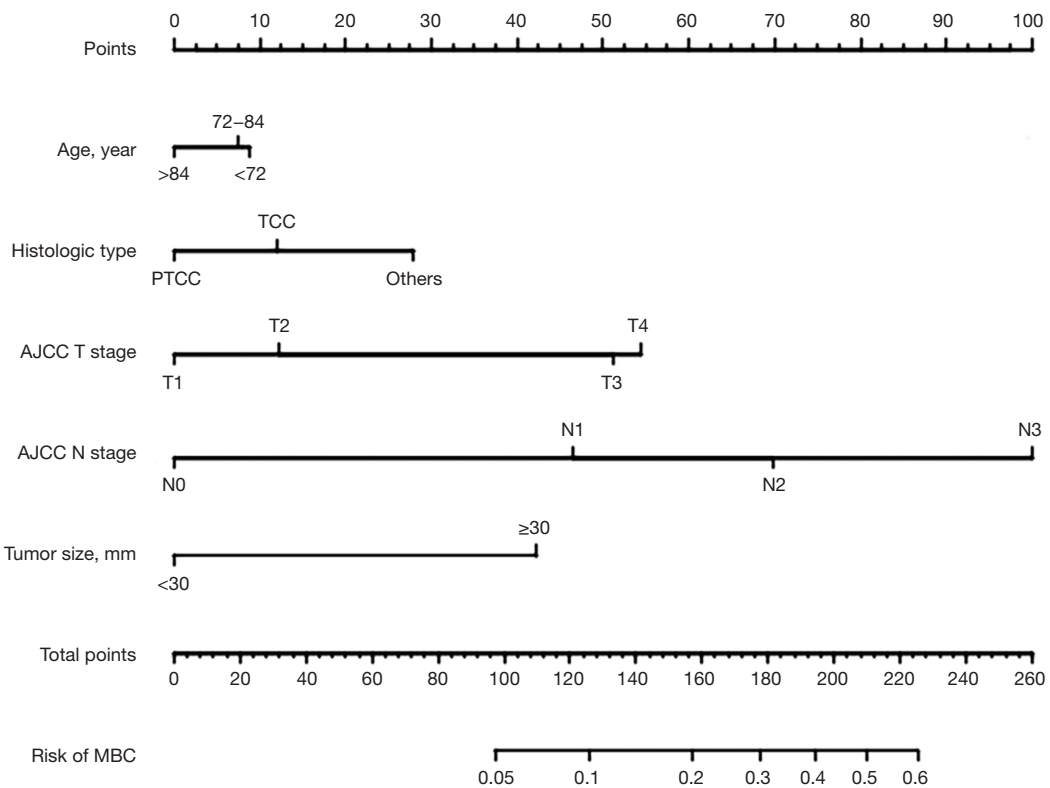

Figure 2 Nomogram to estimate the risk of MBC. TCC, transitional cell carcinoma; PTCC, papillary transitional cell carcinoma; MBC, metastatic bladder cancer; AJCC, American Joint Committee on Cancer.

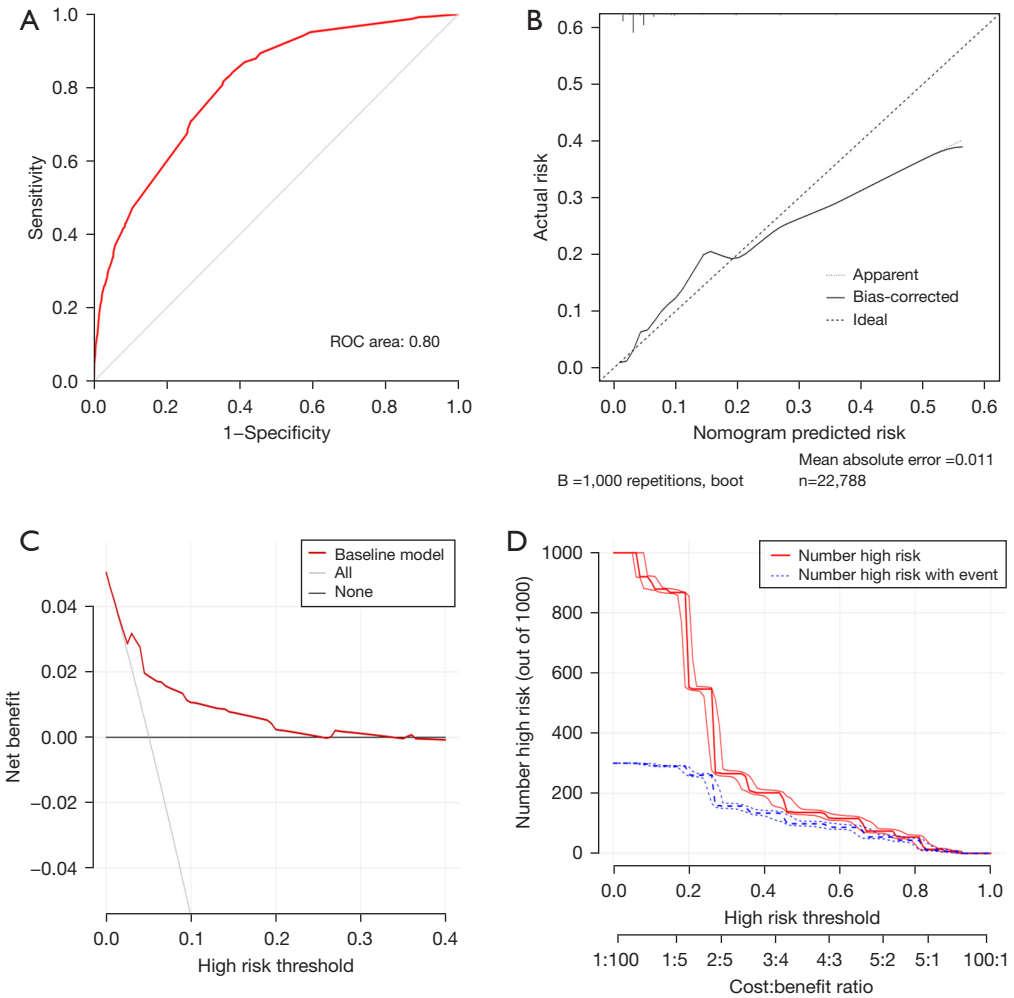

Figure 3 ROC, calibration, DCA curves and CIC of the nomogram for the risk of MBC. (A) The ROC curve of the risk model; (B) the calibration curve of the risk model; (C) the DCA curve of the risk model; (D) the CIC curve of the risk model. ROC, receiver operating characteristic; DCA, decision curve analysis; CIC, clinical impact curves; MBC, metastatic bladder cancer.

mainly classified into non-muscle invasive bladder cancer (NMIBC), muscle invasive bladder cancer (MIBC) and MBC, with different subtypes also imply different clinical outcomes (13). The main treatment for patients with MIBC is neoadjuvant therapy followed by radical cystectomy, and urinary diversion, or a bladder-sparing protocol, such as chemoradiation or partial cystectomy (14). Treatment of MIBC primarily aims at preventing local recurrence (15). Even so, approximately half of the postoperative patients still experience distant metastasis (16,17), necessitating more management and monitoring measures for the treatment of MBC patients and those who experience metastasis. There are currently prognostic nomograms constructed based on bone metastasis (8) and brain metastasis, but comprehensive nomograms constructed based on clinical information may lead to better management of MBC patients. We screened 22,788 patients with bladder cancer from the SEER database, including 1,150 patients with MBC, independent clinical risk factors related to risk and prognosis were identified by logistic and cox regression analyses, finally, age, histological type, tumor size, T stage, and N stage were considered as independent risk factors for MBC, while age, histological type, chemotherapy, bone, liver and lung metastases were independent risk factors for the prognosis of MBC; ROC, CIC and DCA curves, etc. showed the powerful predictive ability and clinical application ability of the prediction model, which enable doctors to provide better clinical consultation and follow-up strategies for

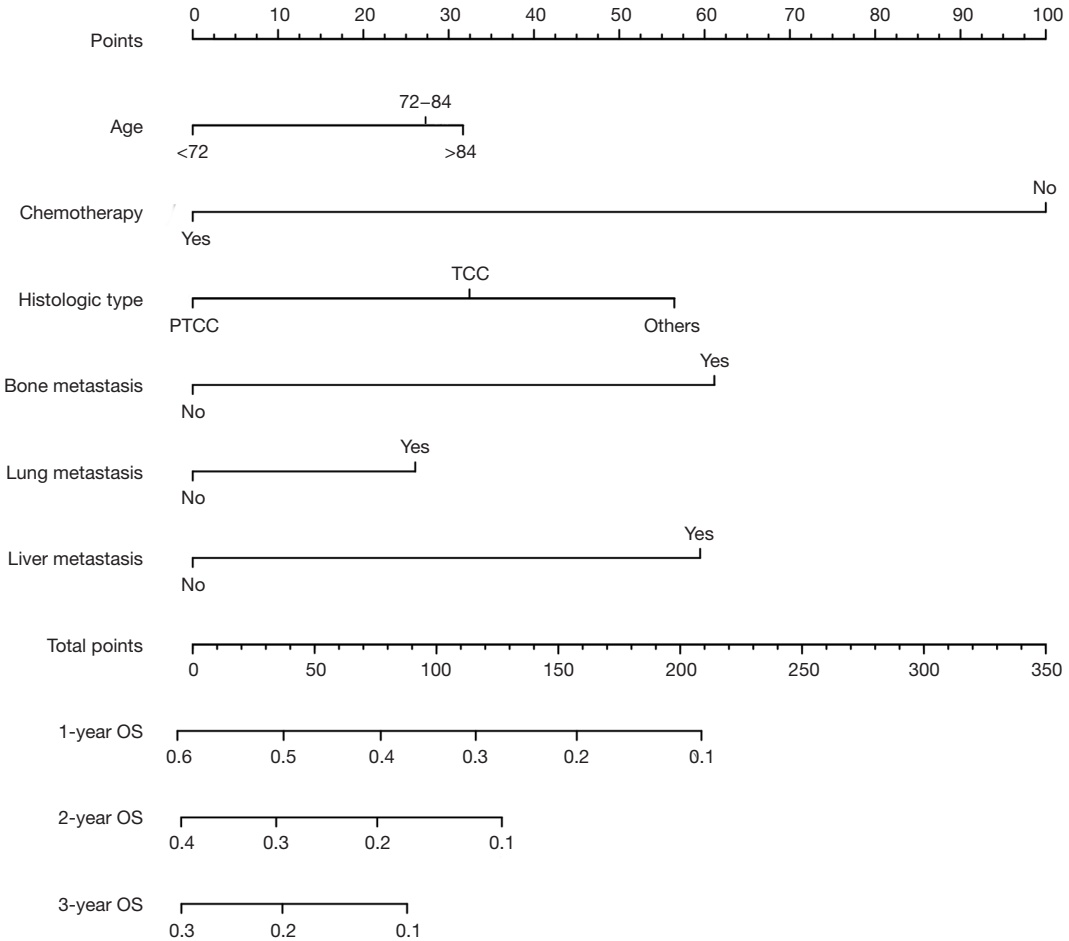

Figure 4 Nomogram for predicting the OS of patients with MBC. MBC, metastatic bladder cancer; TCC, transitional cell carcinoma; PTCC, papillary transitional cell carcinoma; OS, overall survival.

patients in clinical practice.

In all patients with bladder cancer, especially MIBC, the possibility of lymph node metastasis is very high (18), and it means a worse prognosis. Although the exact surgical procedure for lymphadenectomy is controversial (19), there is no doubt that Lymphadenectomy can be beneficial to patients. It is very important to evaluate the patient's lymph node metastasis status by imaging methods before surgery (20), however, a quarter of patients are still found with lymph node metastasis after undergoing surgery (21). Therefore, lymph node metastasis is critical for treatment assessment, and in our study, lymph node staging had the highest score for assessing patients' risk of metastasis. In addition, histological type, T stage, and tumor size also play a role in predicting the risk of metastasis.

Unfortunately, bladder cancer is diagnosed at an older age than other types of cancer (22). Most elderly patients pose a substantial challenge to treatment because of the high incidence of complications and frail status. With the aging of society, the number of patients with bladder cancer will also increase and it is noteworthy that cardiovascular disease is a common illness among elderly patients, however a study found that cardiovascular disease was an independent protective factor for bladder cancer, but this effect was not observed in high-risk tumors (23), therefore, for such high risk tumor, to construct an effective assessment tool can help physicians make better decisions (24). In our analysis, the best cut-off value of age was obtained by x-tile software

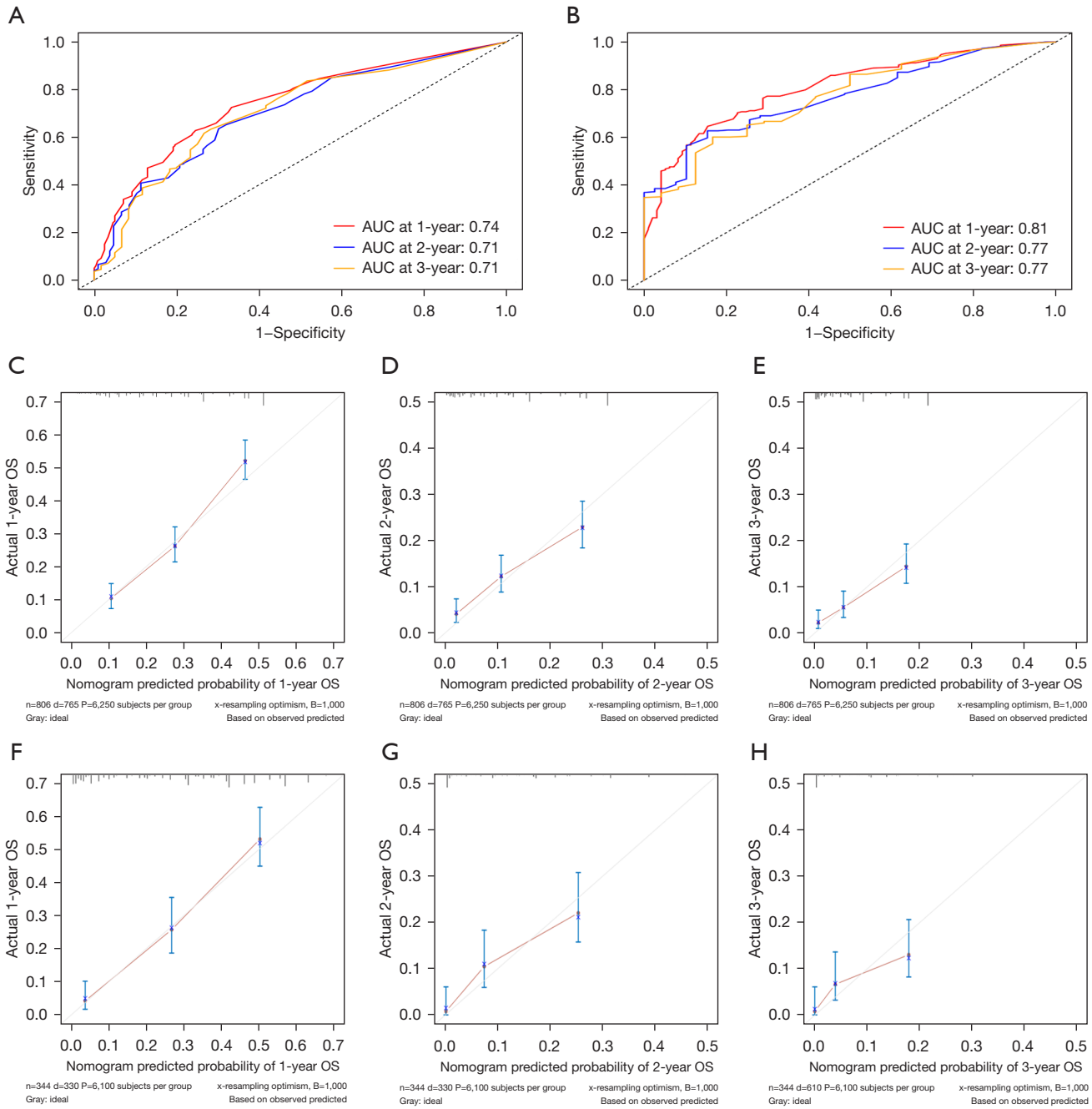

Figure 5 ROC and calibration curves of the nomogram for predicting the overall survival of MBC. (A) The ROC curves of the prognosis nomogram in training cohort; (B) the ROC curves of the prognosis nomogram in validation cohort; (C-E) the calibration curves of the prognosis nomogram of 1-, 2- and 3-year OS in training cohort; (F-H) the calibration curves of the prognosis nomogram of 1-, 2- and 3-year OS in validation cohort. AUC, area under the curve; OS, overall survival; ROC, receiver operating characteristic; MBC, metastatic bladder cancer.

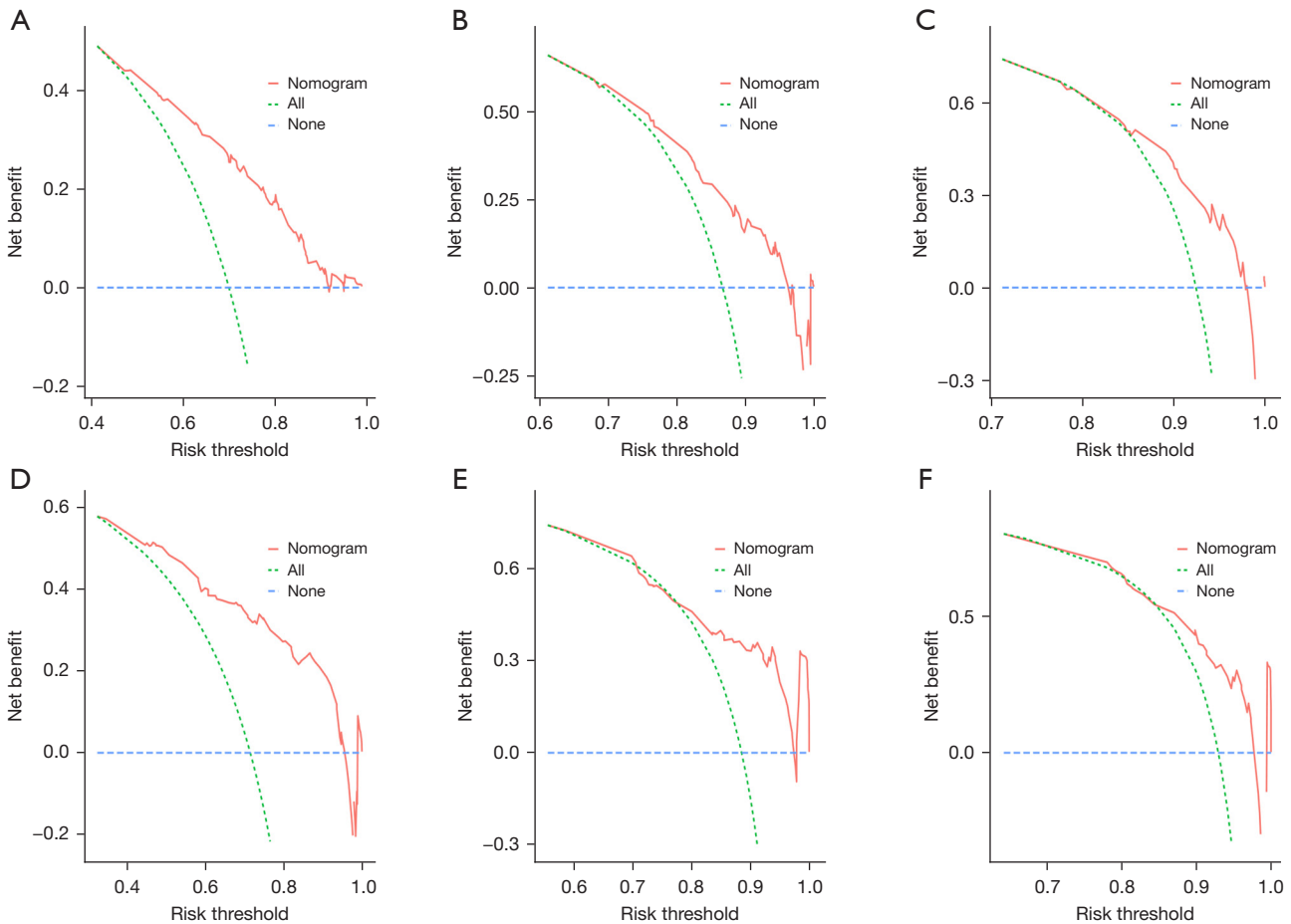

Figure 6 DCA curves of the nomogram for predicting the overall survival of MBC. (A-C) The DCA curves of the prognosis nomogram of 1-, 2- and 3-year OS in training cohort; (D-F) the DCA curves of the prognosis nomogram of 1-, 2- and 3-year OS in validation cohort. DCA, decision curve analysis; MBC, metastatic bladder cancer; OS, overall survival.

and age acted as the predictive factor of prognosis in patients with MBC. It showed the association of older age with worse prognosis. Therefore, geriatric assessment of elderly patients is recommended as a practice, but it has not been validated on a large-scale study and we were unable to obtain relevant information from the SEER database. Similarly, in the study of metastatic patterns of MBC (25), the largest proportion of patients with bone metastases and the poorest prognosis of patients with liver metastases were observed, and few patients with brain metastases were not included in our model to assess the prognosis of MBC.

The prognosis for patients with untreated bladder cancer is very poor, with low survival rates even at 1 year (26), in a multicenter study of bladder carcinoma in situ, 70 years old was used as cut-off value, it was found that patients over 70 years old had an increased risk of recurrence and progression with a poor recurrence free survival (27), but in our study, multivariate logistic regression analysis showed that patients over 84 years old had a reduced risk of metastasis, but multivariate cox regression analysis showed that with increasing age, OS became worsened. According to treatment guidelines, the first-line therapy for MBC is cisplatin-based cytotoxic chemotherapy (28). Vinflunine is the only approved second-line therapy drug in Europe (29), in addition, second-line immunotherapy with programmed cell death protein 1/programmed cell death-ligand 1 (PD-1/PD-L1) checkpoint inhibitors has also been established (30). In general, chemotherapy has brought

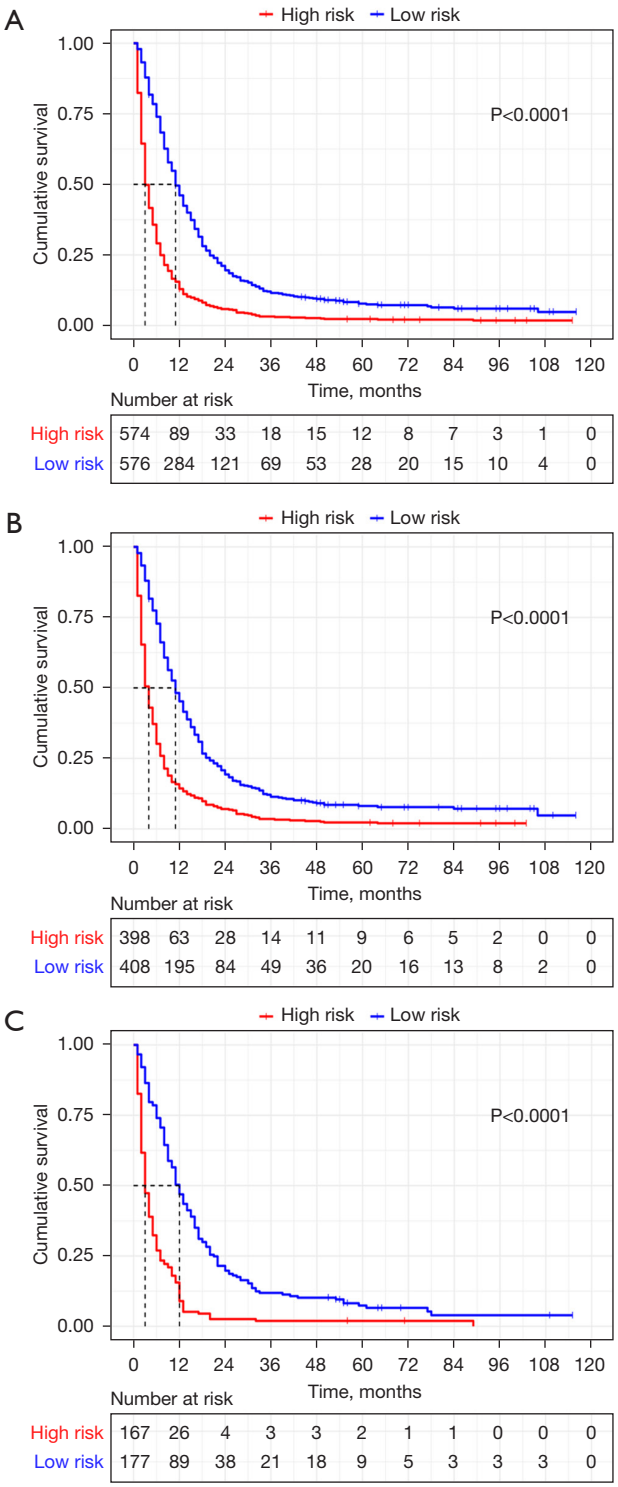

Figure 7 K-M curves of OS for patients in low-risk and high-risk groups. (A) The K-M curve of the whole MBC patients; (B) the K-M curve of training cohort; (C) the K-M curve of validation cohort. K-M, Kaplan-Meier; OS, overall survival; MBC, metastatic bladder cancer.

some benefits to the survival of patients with bladder cancer (31), however, the proportion of patients without chemotherapy in our study population with MBC reached 76.6%, which also had the most significant impact on prognosis, such a low chemotherapy rate also means a worse prognosis for these patients, which is consistent with the above results.

In conclusion, our nomograms are constructed based on clinical information, which have the convenience for clinical application, and their differentiation and validity have been verified by ROC, DCA and other curves, which can provide better reference for patients by judging the risk of metastasis and prognosis. Inevitably, our study has certain limitations. Firstly, this was a retrospective study, excluded many cases with some missing data, which may cause bias. Secondly, there are also clinical factors such as laboratory test results affecting the prognosis of MBC patients, in addition, some diagnostic tools based on artificial intelligence (AI) technology that have shown perfect results in cystoscopy, urine testing, and imaging analysis can be used for MBC patients (32), unfortunately, these data are not available in the SEER database. Thirdly, the efficacy of nomogram has only been internally validated, and we need more data of external clinical application to test its performance in the future.

Conclusions

In summary, we constructed risk and prognosis nomograms for MBC patients based on clinical risk factors and demonstrated their perfect utility through multiple validations. It could be used to provide counseling recommendations for patients and follow-up guidance for clinicians.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1229/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1229/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1229/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The SEER Program has a strict policy to protect patient privacy, and all data were de-identified prior to analysis. The ethical approval of this study was exempted by the Ethics Committee of the First Affiliated Hospital of Nanchang University as the data were from the publicly accessible database, SEER. No informed consent was required for this retrospective study.

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