Application of nomograms in the prediction of overall survival and cancer-specific survival in patients with T1 high-grade bladder cancer

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Abstract. To predict survival outcomes for individual patients with clinical T1 high-grade (T1HG) bladder cancer (BC), data from the Surveillance Epidemiology and End Results (SEER) database were analyzed in the present study. The data of 6,980 cases of T1HG BC between 2004 and 2014 were obtained from the SEER database. Uni- and multivariate Cox analyses were performed to identify significant prognostic factors. Subsequently, prognostic nomograms for predicting 3- and 5-year overall survival (OS) and cancer-specific survival (CSS) rates were constructed based on the SEER database. Clinical information from the SEER database was divided into internal and external groups and used to validate the nomograms. In addition, calibration plot diagrams and concordance indices (C-indices) were used to verify the predictive performance of the nomogram. A total of 6,980 patients were randomly allocated to the training cohort (n=4,886) or the validation cohort (n=2094). Univariate and multivariate Cox analyses indicated that age, ethnicity, tumor size, marital status, radiation and surgical status were independent prognostic factors. These characteristics were used to establish nomograms. The C-indices for OS and CSS rate predictions for the training cohort were 0.707 (95% CI, 0.693-0.721) and 0.700 (95% CI, 0.679-0.721), respectively. Internal and external calibration plot diagrams exhibited an excellent consistency between actual survival rates and nomogram predictions, particularly for 3- and 5-year OS and CSS. The significant prognostic factors in patients with T1HG BC were age, ethnicity, marital status, tumor size, status of surgery and use of radiation. In the present study, a nomogram was developed that may serve as an effective and convenient evaluation tool to help surgeons perform individualized survival evaluations and mortality risk determination for patients with T1HG BC.

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Abbreviations: T1HG, T1 high-grade; BC, bladder cancer; SEER, Surveillance Epidemiology and End Results; OS, overall survival; CSS, cancer-specific survival; UC, urothelial carcinoma; NMIBC, non-muscle invasive bladder cancer

Key words: clinical T1 high-grade bladder cancer, Surveillance Epidemiology and End Results database, nomogram, overall survival, cancer-specific survival

Introduction

Bladder cancer (BC) is a common urological malignancy; it is the 4th most common malignancy in males worldwide (1) and one of the most expensive cancers to manage (2). In the US, >79,030 new cases of urothelial carcinoma (UC) were diagnosed in 2017 (3). Approximately 75% of UC cases are initially identified as non-muscle invasive BC (NMIBC) (4-6). However, NMIBC is a major challenge in urological practice due to its high recurrence rate (60-70% of patients) and rapid progression (20-30% of patients) (5,7). In particular, T1 high-grade (T1HG) BC accounts for 25% of NMIBC cases and is characterized by rapid progression and a high mortality rate (5,8,9). T1HG BC is a highly malignant tumor type with variable and unpredictable biological potential (10). Babjuk *et al* (11) suggested that patients with T1HG cancers may undergo a range of treatments from conservative therapy to early radical cystectomy, as these are currently the optimal treatment strategies. However, the potential risk of morbidity and negative impact on quality of life should be considered when selecting the treatment strategy. It is important to identify prognostic factors for patients with T1HG BC. Identification of clinicopathological factors associated with cancer recurrence

and progression is crucial to the prognosis and management of patients with T1HG BC.

Previous studies have demonstrated that tumor multiplicity, tumor size, the T stage, the tumor grade and female sex are risk factors for poor prognoses of patients with BC (5,12). Previous studies also indicated that independent prognostic factors for patients with T1HG BC include female sex, the presence of carcinoma *in situ* in the prostatic urethra and recurrence within 3 months (5). However, single prognostic factors exert limited influence in certain patients with T1HG BC, while precise individualized predictions may be required. A prognostic nomogram is an efficient statistical tool that has been suggested as a novel standard to predict an individual patient's survival. Nomograms, which are graphic calculating scales, have been indicated to be a useful tool in the management of several cancer types (13-15). There are several advantages to prognostic nomograms, including strong robustness and improved predictive accuracy, which enhance their potential in maximizing the predictive accuracy of an individual prognosis (15). However, the use of prognostic nomograms for patients with T1HG BC, which may be applied to predict the overall survival (OS) and cancer-specific survival (CSS), has not been previously reported, to the best of our knowledge.

In the present study, the clinical information of cases with T1HG BC from 2004 to 2014 in the SEER dataset was collected and analyzed. Surveillance Epidemiology and End Results (SEER) is a US population-based cancer database containing ~28% of the overall population of the US (15) and collects clinical information of patients with tumors in 18 registries. The present study aimed to develop validated prognostic nomograms that are able to predict the OS and CSS of patients with T1HG BC.

Materials and methods

Patient eligibility and variables. Patient information was collected from the SEER database. The SEER database is a public database comprising 18 cancer registries and covers ~28% of the US population. For the present study, the data of patients with T1HG BC (2004-2014) were downloaded from the SEER database using SEER*Stat software (version 8.3.5; National Cancer Institute).

The inclusion criteria for patients with T1HG BC were as follows: i) Patients diagnosed with clinical T1HG BC without evidence of lymph node involvement or metastasis (T1N0M0) as the primary malignancy between 2004 and 2014 according to the reclassification of stages in the 8th Edition of the Cancer Staging Manual from the American Joint Committee on Cancer (16); ii) patients with tumor grades III (poorly differentiated) and IV (undifferentiated); iii) patients with known survival time following diagnosis and cause of death; iv) patients with documentation of tumor size and age at diagnosis; and v) patients with only primary tumors so that analyses of CSS were more feasible. Survival time was defined as the time from the date of disease diagnosis to the date of OS and CSS. Patients with histological confirmation of urothelial carcinoma (International Classification of Diseases for Oncology, 3rd: 8120 and 8130) and missing data were excluded from the present analysis.

The clinicopathological features of patients with T1HG BC included in the present analysis were sex, age, ethnicity, tumor size, marital status, surgical status, use of radiation, use of chemotherapy and survival time. Cutoff values for the age at diagnosis and tumor size were calculated using X-tile software (Version 3.6.1; Copyright Yale University). It was applied to stratify the patients by age and tumor size according to survival time and status. X-tile software is a novel tool, which was initially developed to determine the best cutoff values of variables in cohorts with breast malignancies (17). The optimal cutoff value for the tumor size of the T1HG BC lesions in the present study was identified as 3.4 cm (Fig. 1). The optimal cutoff values for age in the cohort of T1HG BC patients were 63, 72 and 80 years. Regarding ethnicity, the cohort was divided into black, white and other. Marital status was divided into married and single/other. In terms of surgical resection, patients were divided into those who underwent local tumor destruction/excision, partial cystectomy, complete/radical cystectomy and those who did not undergo any surgical resection. Regarding radiation, the cohort was divided into those who were treated with radiation and those who did not receive any radiation treatment. Nuances including radiation type and fractionation were not available from the SEER database. In terms of chemotherapy, the patients were divided into those who received chemotherapy and those who did not receive chemotherapy.

Statistical analysis. All of the patients with T1HG BC identified according to the above-mentioned inclusion and exclusion criteria (n=6,980) were randomly divided into the training cohort (n=4,886) to construct and validate the prognostic nomograms, and the validation cohort (n=2,094) to validate the nomograms. Chi-square tests were applied to compare clinical characteristics between the training and validation cohort.

Categorical variables were presented as the number of patients with T1HG BC and the respective percentages. Cutoff values for tumor size and age at diagnosis were calculated using X-tile software based on OS (Fig. 1). The prognostic factors (sex, age, race, tumor size, marital status, surgical status, use of radiation and use of chemotherapy) were all incorporated in the univariate and multivariate Cox proportional hazards model analysis for OS and CSS, respectively. Hazard ratios and corresponding 95% confidence intervals (95% CIs) of variables were listed. Variables determined to be significant in the univariate and multivariate Cox proportional hazards regression analyses were used to generate nomograms to predict 3- and 5-year OS and CSS. The training cohort was used to establish the nomograms. Internal and external validation of the prognostic nomograms were based on the training cohort and the validation cohort, respectively. Harrell's concordance-index (C-index) (17) was applied to evaluate the performances of the prognostic nomograms. The C-index value ranges from 0.5 to 1.0, where 0.5 indicates total chance and 1.0 indicates perfect matching. Consistency between the predicted probability and the observed probability were assessed using calibration curves of the nomograms. Chi-square test, and univariate and multivariate Cox proportional hazards regression analysis, were performed in SPSS 22.0 (IBM Corp.). The rms package (version 3.3.3) in R was applied to construct and

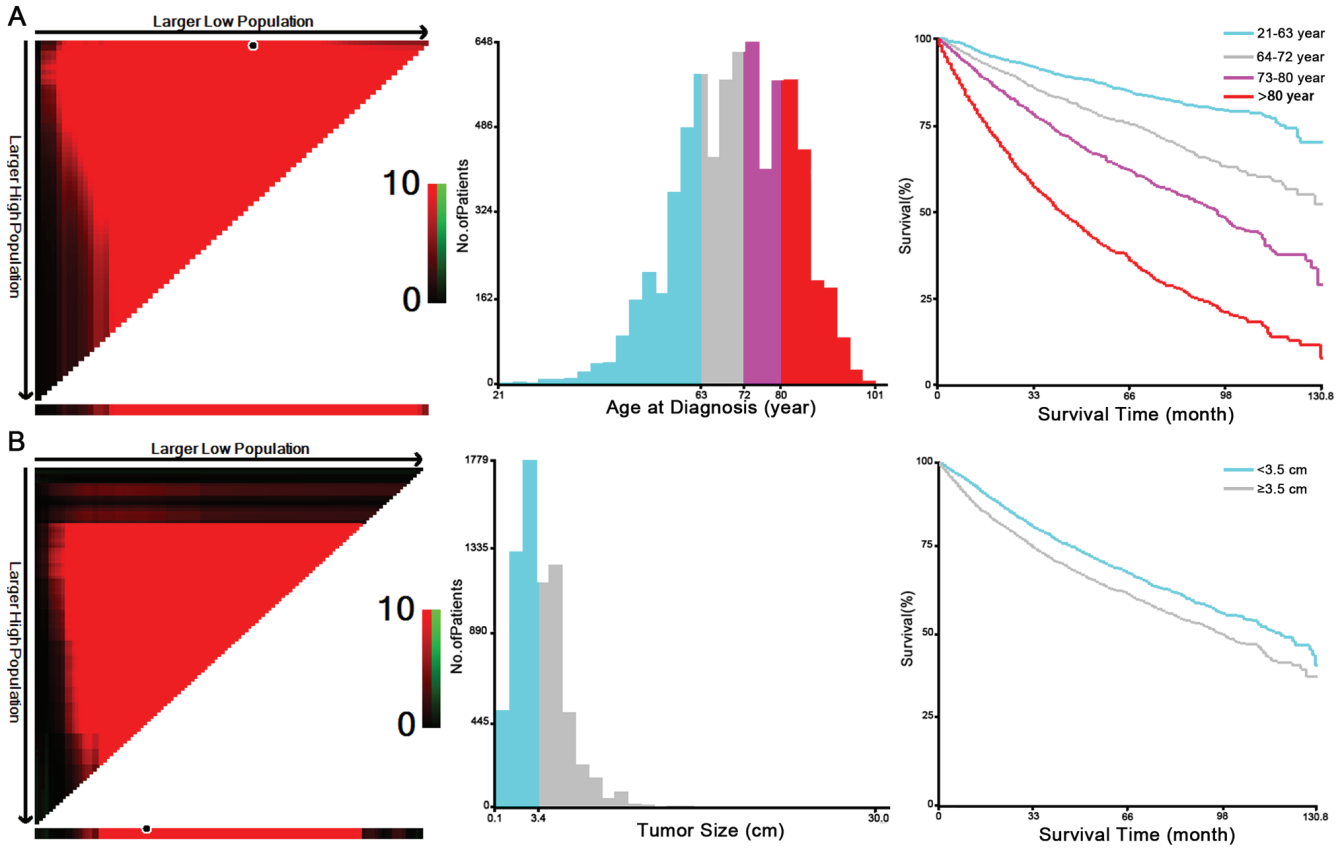

Figure 1. Graphs for determining the optimal cutoff values for (A) age and (B) tumor size via X-tile analysis. The optimal cutoff values for age and tumor size calculated and selected by X-title analysis. Histograms and the Kaplan-Meier plots were generated using these cutoff values. The optimal cutoff values of age were identified as 63, 72 and 80 years according to overall survival information. The optimal cutoff value of tumor size was identified as 3.4 cm according to overall survival information.

validate the nomograms. Statistical significance was defined as a two-sided P<0.05.

Results

Patient characteristics at baseline. A total of 6,980 patients with T1HG BC were divided into the training cohort (n=4,886) and the validation cohort (n=2,094). The characteristics of all the patients with T1HG BC are summarized in Table I. The total cohort comprised 5,452 (78.1%) male patients and 1,528 (21.9%) female patients. A total of 361 (5.2%) patients were black, 6,212 (89.0%) were white and 407 (5.8%) were designated as other. A total of 4,538 (65.0%) patients were married and 2,442 (35%) patients were single or other. Among the patients with T1HG BC, 6,472 (92.7%) patients underwent local tumor destruction/excision, 83 (1.2%) underwent a partial cystectomy, 338 (4.8%) underwent complete/radical cystectomy and 87 (1.2%) patients did not undergo surgical resection. A total of 858 (12.3%) deaths were attributed to T1HG BC and 1,054 (15.1%) patients died from other causes. There were no significant differences in sex, age, ethnicity, tumor size, marital status, surgical status, use of chemotherapy and use of radiation between the training and validation cohorts.

OS of the training cohort. Sex, age, ethnicity, tumor size, marital status, surgical status, use of chemotherapy and use of radiation in the training cohort were selected as variables for the univariate Cox analyses (Table II). The results of the analysis revealed that all of the above-mentioned variables were associated with OS (P<0.05;). Furthermore, all of these variables except for the use of chemotherapy were associated with CSS (P<0.05). Multivariate Cox analyses were then performed to control for the confounding variables (Table III). According to the multivariate analysis, age, ethnicity, tumor size, marital status, surgical status and use of radiation were identified as significant prognostic factors for OS and CSS (P<0.05).

Construction and validation of OS and CSS nomograms. The six aforementioned variables were used to construct prognostic nomograms to predict 3- and 5- year OS and CSS of patients with T1HG BC (Fig. 2; Table IV). Internal and external validation of prognostic nomograms were performed. The predictive accuracy of the final prognostic nomogram models was evaluated by the C-index. The C-indices for the internal validation of the OS and CSS nomograms were 0.707 (95% CI, 0.693-0.721) and 0.700 (95% CI, 0.679-0.721), respectively. In the external validation, the C-indices for the OS and CSS nomograms were 0.700 (95% CI, 0.677-0.723) and 0.698 (95% CI, 0.666-0.730), respectively. Calibration plots revealed a good agreement between actual survival and the nomogram prediction (Fig. 3). These prognostic nomograms are easy to use by surgeons for the prognostication of patients with T1HG BC.

Table I. Demographics and clinicopathological characteristics of patients with T1 high-grade bladder cancer.

Variable	Training cohort (n=4,886)	Validation cohort (n=2,094)	Total (n=6,980)	P-value
Sex				0.426
Male	3,829 (78.4)	1,623 (77.5)	5,452 (78.1)	
Female	1,057 (21.6)	471 (22.5)	1,528 (21.9)	
Age (years)				0.203
21-63	1,281 (26.2)	501 (23.9)	1,782 (25.5)	
64-72	1,275 (26.1)	547 (26.1)	1,822 (26.1)	
73-80	1,151 (23.6)	520 (24.8)	1,671 (23.9)	
>80	1,179 (24.1)	526 (25.1)	1,705 (24.4)	
Ethnicity				0.271
Black	239 (4.9)	122 (5.8)	361 (5.2)	
White	4,361 (89.3)	1,851 (88.4)	6,212 (89.0)	
Other	286 (5.9)	121 (5.8)	407 (5.8)	
Marital status				0.107
Single/other	1,680 (34.4)	762 (36.4)	2,442 (35.0)	
Married	3,206 (65.6)	1,332 (63.6)	4,538 (65.0)	
Surgery				0.927
None	63 (1.3)	24 (1.1)	87 (1.2)	
Local tumor destruction/excision	4,527 (92.7)	1,945 (92.9)	6,472 (92.7)	
Partial cystectomy	60 (1.2)	23 (1.1)	83 (1.2)	
Complete/radical cystectomy	236 (4.8)	102 (4.9)	338 (4.8)	
Tumor size (cm)				0.773
<3.5	2,592 (53.0)	1,103 (52.7)	3,695 (52.9)	
≥3.5	2,294 (47.0)	991 (47.3)	3,285 (47.1)	
Radiation				0.381
Yes	107 (2.2)	39 (1.9)	146 (2.1)	
No	4,779 (97.8)	2,055 (98.1)	6,834 (97.9)	
Chemotherapy				0.155
Yes	1,045 (21.4)	480 (22.9)	1,525 (21.8)	
No	3,841 (78.6)	1,614 (77.1)	5,455 (78.2)	

Values are expressed as n (%).

Discussion

Due to heterogeneity of T1HG cancers, it is difficult to predict the behavior of T1HG BC and the prognosis of affected patients (18,19). Various prognostic factors may influence the survival rate of patients with cancer. Therefore, understanding the role of prognostic factors in the evaluation of patients with T1HG BC is important. However, a single prognostic factor may only have limited utility in individual survival prediction. Nomograms, a tool commonly used for estimating the survival of individual patients, are capable of considering the accumulated effect of all prognostic factors, thus being able to predict 3- and 5-year survival probabilities (20-22). To date, several nomograms have been established for patients with BC (23-25).

However, to the best of our knowledge, prognostic nomograms have not been constructed for patients with T1HG BC, and the present study was the first to establish comprehensive prognostic nomograms to predict 3- and 5-year OS and CSS for patients with T1HG BC using the SEER database. These validated nomograms may be used in the clinical setting based on specific clinicopathological information, which is most likely available to the surgeon to evaluate a patient's prognosis. Several clinical characteristics were determined to be independent prognostic factors for OS or CSS, including patient age, ethnicity, tumor size, marital status, status of surgery and use of radiation.

By using the optimal cutoff values for age in the present study, it was revealed that the survival rates of patients with T1HG BC worsened with increasing age, and it was suggested that age is a strong and independent risk factor for T1HG BC patient survival. The present study indicated that a larger tumor size (>3.5 cm) was an independent prognostic factor in patients with T1HG BC. A previous study indicated that recurrence, progression and poorer survival rates were more common in patients with larger tumors (26). In the present study, the marital status had a significant prognostic value. In a previous study, the mean relative survival was significantly

Table II. Univariate Cox regression analysis of prognostic factors in patients with T1 high-grade bladder cancer.

	Cancer-specific survival			Overall survival		
Variable	HR	95% CI	P-value	HR	95% CI	P-value
Sex (female vs. male)	1.502	1.272-1.774	<0.001	1.302	1.158-1.465	<0.001
Age (years)						
21-63	Reference			Reference		
64-72	1.358	1.053-1.751	0.019	1.770	1.459-2.147	<0.001
73-80	1.933	1.514-2.469	<0.001	3.092	2.508-3.705	<0.001
>80	4.079	3.259-5.105	<0.001	6.426	5.414-7.627	<0.001
Ethnicity						
Black	Reference			Reference		
White	0.521	0.393-0.690	<0.001	0.606	0.493-0.744	<0.001
Other	0.460	0.300-0.705	<0.001	0.415	0.302-0.572	<0.001
Marital status (married vs. single/other)	0.623	0.535-0.725	<0.001	1.033	0.453-2.355	<0.001
Surgery	14.476	3.391-61.792	<0.001	9.955	2.376-41.720	0.002
None	Reference			Reference		
Local tumor destruction/excision	0.429	0.257-0.716	0.001	0.493	0.341-0.712	<0.001
Partial cystectomy	0.673	0.329-1.377	0.278	0.506	0.290-0.880	0.016
Complete/radical cystectomy	0.447	0.245-0.815	0.005	0.346	0.221-0.541	<0.001
Tumor size (≥3.5 vs. <3.5 cm)	1.451	1.247-1.688	<0.001	1.329	1.199-1.473	<0.001
Radiation (yes vs. no)	5.070	3.809-6.749	<0.001	3.413	2.696-14.321	<0.001
Chemotherapy (yes vs. no)	0.315	0.738-1.103	0.315	0.859	0.745-0.990	0.035

HR, hazard ratio.

Table III. Multivariate Cox regression analysis for prognosis factors in patients with T1 high-grade bladder cancer.

	Cancer-specific survival			Overall survival		
Covariates	HR	95% CI	P-value	HR	95% CI	P-value
Sex (female vs. male)	1.114	0.931-1.332	0.237	0.969	0.854-1.100	0.629
Age (years)						
21-63	Reference			Reference		
64-72	1.409	1.091-1.819	<0.001	1.808	1.490-2.195	<0.001
73-80	1.941	1.518-2.483	<0.001	3.106	2.590-3.725	<0.001
>80	3.854	3.063-4.848	<0.001	6.203	5.210-7.384	<0.001
Ethnicity						
Black	Reference			Reference		
White	0.526	0.394-0.701	<0.001	0.552	0.477-0.680	<0.001
Other	0.473	0.306-0.730	0.001	0.402	0.291-0.556	<0.001
Marital status (married vs. single/other)	0.792	0.672-0.933	0.005	0.856	0.764-0.959	0.007
Surgery						
None	Reference			Reference		
Local tumor destruction/excision	0.521	0.311-0.873	0.013	0.561	0.387-0.811	0.002
Partial cystectomy	0.588	0.286-1.210	0.149	0.438	0.251-0.765	0.004
Complete/radical cystectomy	0.703	0.383-1.290	0.255	0.547	0.348-0.859	0.009
Tumor size (≥3.5 vs. <3.5 cm)	1.323	1.135-1.541	<0.001	1.237	1.115-1.372	<0.001
Radiation (yes vs. no)	3.906	2.911-5.241	<0.001	2.766	2.169-3.526	<0.001
Chemotherapy (yes vs. no)				0.884	0.765-1.022	0.095

HR, hazard ratio.

Table IV. Specific scores of prognosis factors in prognostic nomograms in patients with T1 high-grade bladder cancer.

Characteristic	OS nomogram	CSS nomogram
Age (years)		
21-63	0	0
64-72	3.2	2.5
73-80	6.2	4.9
>80	10.0	10.0
Ethnicity		0
Black	5.1	5.5
White	1.8	0.7
Other	0	0
Marital status		
Single/other	0.8	1.9
Married	0	0
Surgery		
None	4.7	4.8
Local tumor destruction/excision	1.5	0
Partial cystectomy	0	1.0
Complete/radical cystectomy	1.3	2.2
Tumor size (cm)		
<3.5	0	0
≥3.5	1.2	6.5
Radiation		
No	0	0
Yes	5.4	10.0

OS, overall survival; CSS, cancer-specific survival.

increased among married patients with BC (27). It may be hypothesized that support from a spouse is key to increasing the OS of patients with T1HG BC and this may include complex mechanisms. Ethnicity was also an independent prognostic factor for survival, as white and black patients with T1HG BC had poorer survival compared with other ethnicities with T1HG BC, particularly black patients. The results were similar to those of previous studies that suggest that ethnicity influence prognosis (28,29). The differential rates may reflect underlying sociodemographic and economic factors. These factors may affect access to care and lifestyle characteristics, including obesity and smoking, as well as education (30-32).

The goal in the treatment of patients with T1HG BC is to minimize the recurrence and progression of the disease, as well as patient mortality, while maximizing the patient's quality of life. This particularly applies to patients newly diagnosed with T1HG BC or those with recurrent T1HG BC. In the present study, surgical status and use of radiation were also identified as independent prognostic factors. The proposed nomograms included four treatment strategies: Local tumor destruction/excision, partial cystectomy, complete/radical cystectomy and radiation, which are significant predictors of survival outcomes for patients with T1HG BC. It is noteworthy that adjuvant radiotherapy was associated with poorer survival rates. Although radiotherapy has improved or preserved organ function in patients with T1HG BC, a recent phase-III trial indicated that radiotherapy alone was not superior to other conservative treatment strategies (33). However, the ultimate value of radiotherapy should be determined in a randomized trial using a multicenter approach to recruit a sufficient amount of patients. Among these treatment strategies, surgical therapy remains the most frequently used therapeutic method for patients with T1HG BC.

T1HG BC is heterogeneous in nature and challenging to treat. Bladder cystectomy is the current standard treatment modality for patients with T1HG BC. A recent study reported that patients with T1HG BC have a considerable risk of progression and strongly advocated for immediate/early cystectomy for patients with T1HG BC who have a long life expectancy (34). However, whether patients with T1HG BC should undergo immediate radical cystectomy or bladder preservation remains a much-debated issue (35). Certain studies have indicated that immediate or early cystectomy for patients with T1HG BC reduced the risk of recurrence, progression and metastasis (36,37). However, cystectomy may severely affect the quality of life of patients with T1HG BC. Transurethral resection with intravesical therapy is the first-line therapy for patients with NMIBC (11). However, recurrence or progression occurs in more than half of all patients, which requires a second resection or cystectomy (38-40). Therefore, the overall situation and the prognosis of the patient must be taken into account when selecting the most appropriate surgical treatment.

Significant prognostic factors identified in the present study were used to construct nomograms to estimate the 3- and 5-year OS and CSS of patients with T1HG BC. Individual survival rates of patients with T1HG BC may be precisely evaluated via these nomograms. A practicable nomogram may help surgeons estimate the precise likelihood of survival at different time-points. Such prognostic nomograms may increase the surgeon's ability to identify patients with T1HG BC with an elevated risk of progression and mortality.

As an example for the application of the nomogram, a 75-year-old single white patient diagnosed with conventional T1HG BC with a primary tumor size of 5.0 cm is discussed. The patient would not have undergone surgery or received radiation therapy. Corresponding points may be acquired from the vertical line of each significant prognostic factor in the nomogram point scale. This patient receives 14.7 and 18.8 points in the OS and CSS prognostic nomograms, respectively. Therefore, the estimated 3- and 5-year OS probability of this patient would be 52.5 and 35%, respectively, from the OS nomogram scale. The 3- and 5-year CSS probability of this patient would be 54 and 41%, respectively, from the CSS nomogram scale.

Several potential limitations of the present study should still be considered. First, the only 3- and 5-year survival were considered as the end-points, but did not local recurrence, as it

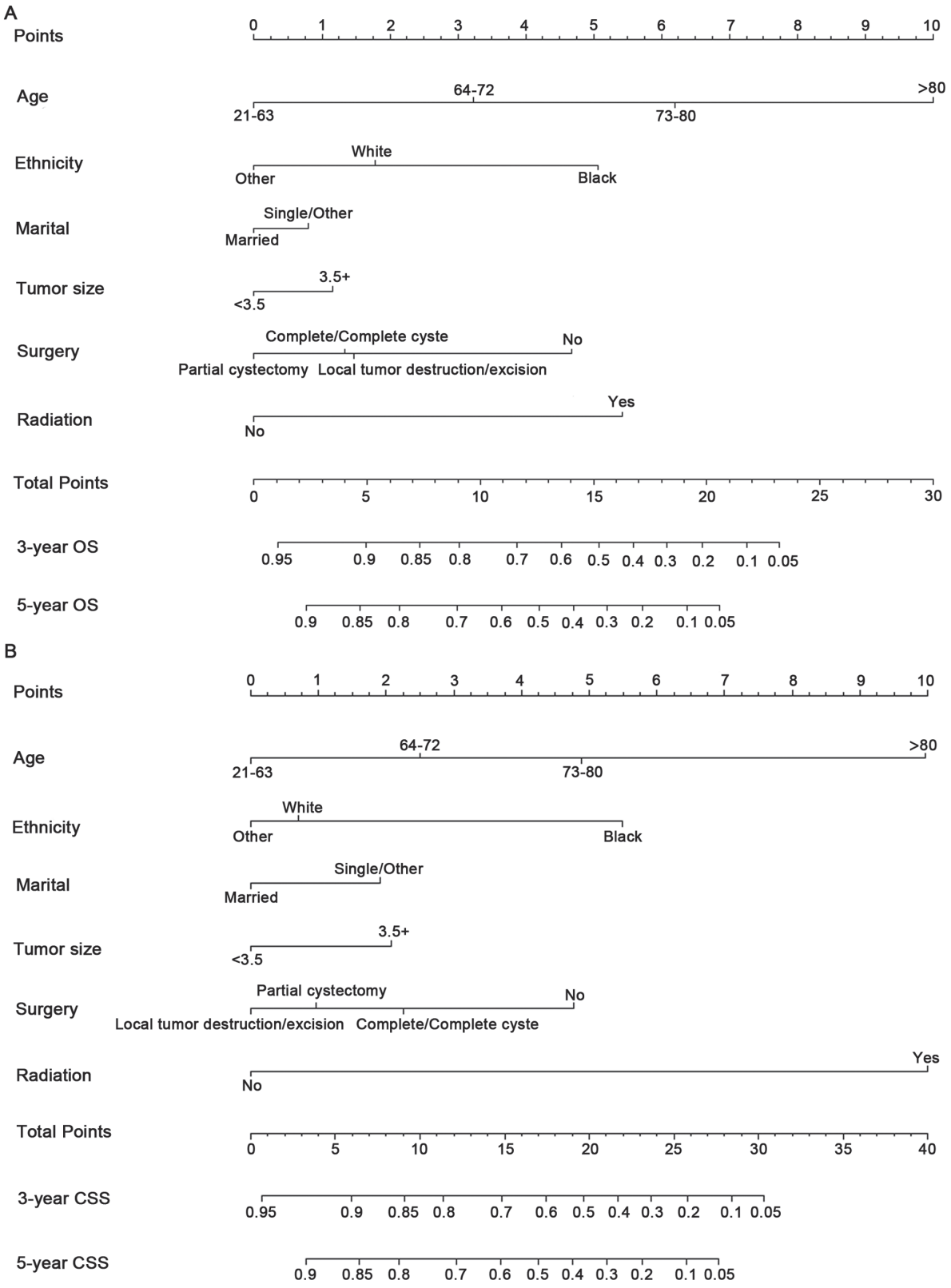

Figure 2. Nomograms for predicting 3- and 5-year (A) OS and (B) CSS of patients with T1 high-grade bladder cancer. The nomograms were used by totaling the points at the top of the scale and finding the corresponding percentage probability at the bottom of the scale. OS, overall survival; CSS, cancer-specific survival.

was not available from the SEER database. Furthermore, the information used to construct and validate the nomograms was from the same SEER database, which may reduce the reliability of the nomogram. The prognostic nomograms provided by the present study may be more credible if they were validated by another dataset.

In summary, nomograms for predicting 3- and 5-year OS and CSS of patients with T1HG BC were constructed and

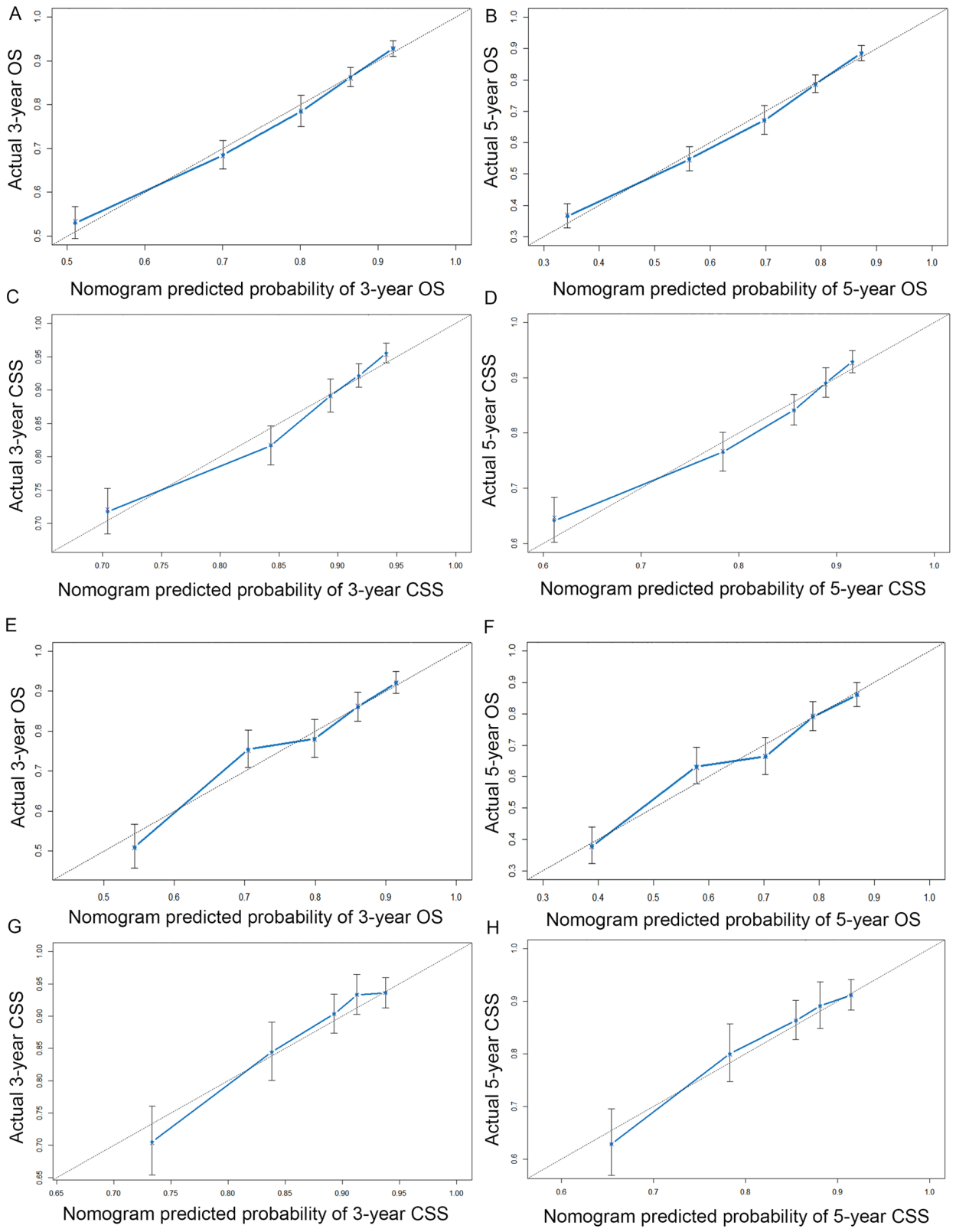

Figure 3. (A and B) Internal calibration plots for prognostic nomograms for (A) 3-year OS and (B) 5-year OS prediction in the training cohort. (C and D) Internal calibration plots for prognostic nomograms for (C) 3-year CSS and (D) 5-year CSS prediction in the training cohort. (E and F) External calibration plots for prognostic nomograms for (E) 3-year OS and (F) 5-year OS prediction in the validation cohort. (G and H) External calibration plots for prognostic nomograms for (G) 3-year CSS and (H) 5-year CSS prediction in the validation cohort. In each graph, the 45-degree line represents an ideal match between the actual survival and nomogram-predicted survival. The perpendicular lines indicate the 95% confidence intervals. OS, overall survival; CSS, cancer-specific survival.

validated in the present study. The nomograms were based on the patients' age, ethnicity, tumor size, marital status, status of surgery and use of radiation. They may serve as effective and convenient evaluation tools to help surgeons perform personalized survival prediction and mortality risk identification in patients with T1HG BC.

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Availability of data and materials

The datasets analyzed during the present study were downloaded from the SEER database (https://seer.cancer.gov/).

Authors' contributions

ZH, FT and ZL conceived the study. FT, ZL, WW and YC performed the experiments. GW and YL analyzed the data. ZH, FT and ZL wrote the paper. All the authors read and approved the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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