Trends of incidence and prognosis of primary adenocarcinoma of the bladder

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Abstract

Background: Primary adenocarcinoma of the bladder (ACB) is a rare malignant tumor of the bladder with limited understanding of its incidence and prognosis.

Methods: Patients diagnosed with ACB between 2004 and 2015 were obtained from the SEER database. The incidence changes of ACB patients between 1975 and 2016 were detected by Joinpoint software. Nomograms were constructed based on the results of multivariate Cox regression analysis to predict overall survival (OS) and cancer-specific survival (CSS) in patients with ACB, and the constructed nomograms were validated.

Results: The incidence of ACB was trending down from 1991 to 2016. A total of 1039 patients were included in the study and randomly assigned to the training cohort (727) and validation cohort (312). In the training cohort, multivariate Cox regression showed that age, marital status, primary site, histology type, grade, AJCC stage, T stage, SEER stage, surgery, radiotherapy, and chemotherapy were independent prognostic factors for OS, whereas these were age, marital status, primary site, histology type, grade, AJCC stage, T/N stage, SEER stage, surgery, and radiotherapy for CSS. Based on the above Cox regression results, we constructed prognostic nomograms for OS and CSS in ACB patients. The C-index of the nomogram OS was 0.773 and the C-index of CSS was 0.785, which was significantly better than the C-index of the TNM staging prediction model. The area under the curve (AUC) and net benefit of the prediction model were higher than those of the TNM staging system. In addition, the calibration curves were very close to the ideal curve, suggesting appreciable reliability of the nomograms.

Conclusion: The incidence of ACB patients showed a decreasing trend in the past 25 years. We constructed a clinically useful prognostic nomogram for calculating OS and CSS of ACB patients, which can provide a personalized risk assessment for ACB patient survival.

Keywords: adenocarcinoma bladder, bladder cancer, prognostic nomogram, SEER

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Introduction

Bladder cancer comprises 81,190 cancer cases and 17,240 deaths in the United States each year.[1] As a subtype of non-urothelial carcinoma, primary adenocarcinoma of bladder (ACB) is a rare malignancy with a poor prognosis, and is estimated to account for 0.5–2% of all bladder malignancies.[2] Some studies suggested that non-urothelial subtypes have lower survival rates than urothelial carcinoma, and that the former will be diagnosed in more advanced stages and be more aggressive.[3–5] Surgical resection has been the standard treatment for ACB, but the 5-year survival rate of 11–61% is unsatisfactory.[3,6–8]

Due to the rarity of ACB, the identification and clinical management of the disease relies on retrospective reviews and case reports, and there is no consensus on its survival prognosis, but there have been several studies revolving around possible factors and measures.[9–11] One study involving 185 cases of ACB showed that tumor stage, grade,

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and lymph node involvement were the only significant prognostic factors.[12] Furthermore, Zaghloul *et al.*[13] reported adeno-subclassification was associated with the prognostic outcomes of ACB. Currently, the Tumor-Node-Metastasis (TNM) staging system devised by the American Joint Committee on Cancer (AJCC) is a globally recognized method for predicting patient prognosis. However, the TNM system ignores other possible factors, such as demographic information and treatment, which may be strongly associated with the survival outcomes, although some of these factors have not been thoroughly studied. In addition, the current AJCC system only serves to classify patients into groups, rather than predicting individualized survival probability. In conclusion, clinicians are in need of a convenient, comprehensive, and accurate prognostic model.

As a graphical tool for statistical analysis, nomogram can improve the accuracy of predicting prognosis.[14,15] Because the nomogram takes into account a variety of important clinical and pathological factors, generating individualized survival probability results at specific time points, it has been shown to be more accurate than risk group allocation models and staging systems as a reliable tool for prognosis, guidance, and treatment.[16–18]

Currently, there are no validated prognostic models for patients with ACB, although this is one of the most lethal histological types of bladder cancer. The aim of this study was to establish nomograms to predict the prognostic outcome of patients with ACB based on important clinicopathologic parameters, demographic information, and treatments.

Patients and methods

Study population

In this study, all data of patients were obtained from the Surveillance, Epidemiology, and End Results (SEER) database between 1975 and 2016, which collects and publishes data including cancer incidence and mortality from 18 cancer registries that cover approximately 28% of the population of the United States.[19] The study cohort consists of patients who met the following criteria: (1) age greater than 18 years; (2) positive histology; (3) histological type limited to primary adenocarcinomas of bladder (ICD-O-3 codes: 8140/3, 8260/3, 8310/3, 8323/3, 8480/3, 8490/3); (4) active follow-up with complete date; (5) clear TNM staging. We excluded patients with unknown survival time, multiple tumors, Ta, Tis, and T0 stages. After selection, 1039 constructive patients were enrolled in the cohort (Figure 1).

Study variables and outcome

The variables analyzed in this study were age at diagnosis, sex, marital status, race, primary site, histology, grade, pathological stage (AJCC stage, T stage, N stage, M stage, and SEER stage), surgery of the primary tumor, chemotherapy, and radiotherapy. We regrouped some variables: age at diagnosis was grouped as "<68," "68–79," and ">79" using X-tile software (Figure S1); patients whose marital status was "Single," "Divorced," "Separated," "Widowed," or "Unmarried or Domestic Partner" were regrouped as "Unmarried"; and patients whose race was recorded as American Indian/Alaska Native or Asian/Pacific Islander were grouped as "Other" racial categories. The gross pathologic types of ACB include six types: "Adenocarcinoma, NOS," "Mucinous adenocarcinoma," "Signet cell carcinoma," "Clear cell adenocarcinoma," "Papillary adenocarcinoma," and "Mixed subtype adenocarcinoma." The surgical treatment variable was grouped into "Surgery, NOS," "Partial cystectomy," "Radical cystectomy," and "No/Unknown." The chemotherapy and radiotherapy variable were grouped into "Yes or No/Unknown." Additionally, T stage was regrouped into T1, T2, T3, T4, and Unknown, N stage was regrouped into N0, N1, N2, N3, and Unknown, M stage was regrouped into M0, M1, and Unknown. The primary endpoints of the study were overall survival (OS) and cancer-specific survival (CSS). Survival time was calculated from the date of diagnosis to death or last follow-up. Frequency and proportion were reported for each variable analyzed in this study.

Statistical analysis

The incidence of ACB patients between 1975 and 2016 was analyzed using Joinpoint software (Version 4.8.0.1), and the incidence rate is expressed as the annual percentage change (APC) and the 95% confidence interval (CI). Using RStudio software (Version 1.2.5033), all patients were randomized into a training set and validation set in a 7:3 ratio. In the training set, univariate Cox regression analysis was used to verify whether the association between each variable and OS and

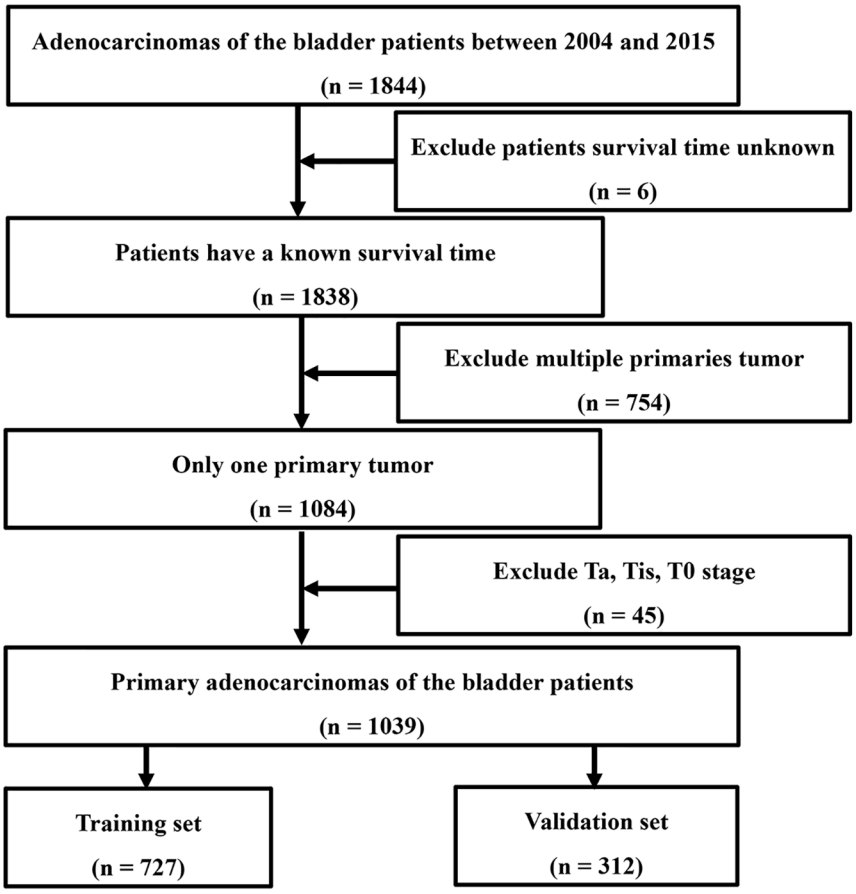

Figure 1. Flow chart of this study.

CSS was significant. After excluding the non-significant variables, multivariate Cox regression analysis was then used to calculate the association between each variable and OS and CSS to find independent risk factors. The measure of association was presented in the form of hazard ratio (HR) and 95% CI. Nomograms in this study were created using information obtained from multivariate Cox regression analysis. Receiver operating characteristic (ROC) curves, concordance index (C-index), decision curve analysis (DCA) curves, and internal validation were used to assess the predictive performance of nomograms. The area under the ROC curve is represented by AUC and the C-index assessment was performed using RStudio software. Calibration curves of the nomograms were applied to evaluate the consistency between predicted survival and observed survival bootstraps with 1000 resamples were used for the validation.[20]

In the RStudio software, analysis and validation were performed using survival, rms, Hmisc, lattice, Formula, ggplot2, rmda, pROC, and timeROC packages. All statistical tests were considered statistically significant at $p < 0.05$.

Results

Incidence trends of ACB patients

Figure 2 shows the change in the incidence of ACB between 1975 and 2016. We found that in all populations, the incidence of ACB increased from 1975 to 1991 (1975–1986 APC = 0.47; 1986–1991 APC = 3.34) and decreased from 1991 to 2016 (1991–2009 APC = −0.58; 2009–2016 APC = −2.82). In addition, the incidence in males was generally consistent with the overall trend (Figure 2b), while the incidence of females declined annually over the past 40 years (Figure 2c).

Patients' baseline characteristics

According to the inclusion criteria, we selected a total of 1039 patients in this study, including 727

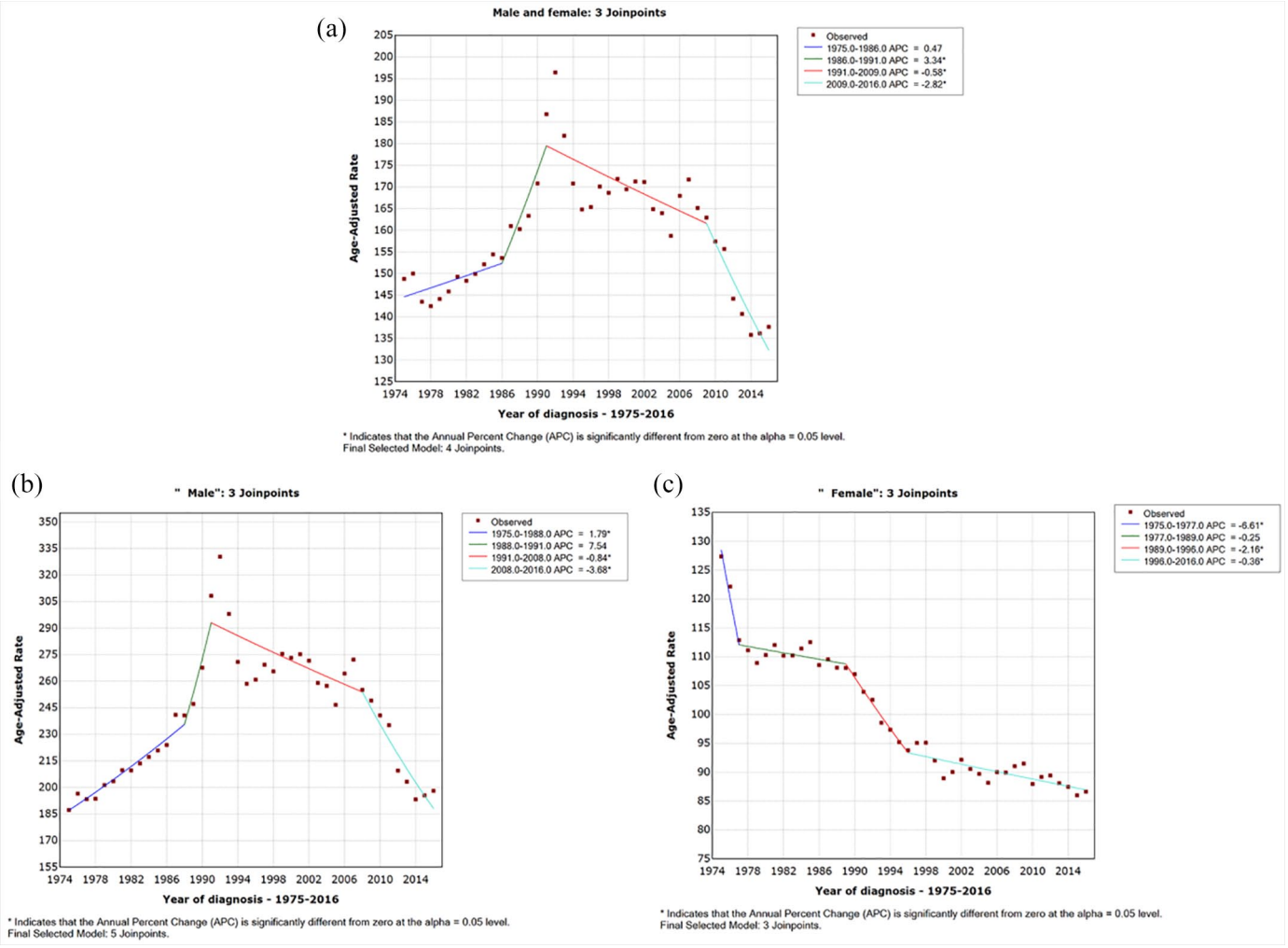

Figure 2. Incidence of adenocarcinoma of the bladder (ACB) patients from 1975 to 2016. In all populations. (a) The incidence of ACB increased from 1975 to 1991 and decreased from 1991 to 2016. Incidence in male patients (b) was generally consistent with the overall trend; the incidence of female patients (c) declined annually over the past 40 years.

in the training set and 312 in the validation set. The demographic, tumor, and treatment characteristics of the cohort are listed in Table 1. In general, the majority of patients were white (806, 77.6%) married (512, 49.3%), and younger than 68 years old (603, 58%), male (635, 61.1%), with grade III (348, 33.5%). With regard to therapy, most patients have partial cystectomy (665, 64.0%), without chemotherapy (725, 69.8%), or radiation (891, 85.8%).

Univariable and multivariable Cox regression in the cohort

We used univariate and multivariate Cox regression to analyze the relationship between these selected characteristics and OS or CSS. As shown in Table 2, in the training set, multivariate Cox regression showed that age, marital status, primary site, histology type, grade, AJCC stage, T stage, SEER stage, surgery, radiotherapy, and chemotherapy were independent prognostic factors for OS. Age, marital status, primary site, histology type, grade, AJCC stage, T stage, N stage, SEER stage, surgery and chemotherapy were independent prognostic factors for CSS (Table 3).

According to Tables 2 and 3, prognostic outcomes and mortality risk of patients can be intuitively evaluated. For example, older patients may have higher possibilities to experience worse OS and CSS outcomes. Similarly, single patients with histology of papillary adenocarcinoma are more likely to have poor prognoses. As for therapy, a

Table 1. Baseline demographic and clinical characteristics.

Variables	All patients *n* (%)	Training set	Validation set
		n (%)	*n* (%)
Total	1039	727	312
Sex			
Male	635 (61.1)	454 (62.4)	181 (58.0)
Female	404 (38.9)	273 (37.6)	131 (42.0)
Age, years			
<68	603 (58.0)	428 (58.9)	175 (56.1)
68–79	230 (22.1)	150 (20.6)	80 (25.6)
>79	206 (19.8)	149 (20.5)	57 (18.3)
Marital status			
Married	512 (49.3)	357 (49.1)	155 (49.7)
Unmarried	477 (45.9)	330 (45.4)	147 (47.1)
Unknown	50 (4.8)	40 (5.5)	10 (3.2)
Race			
White	806 (77.6)	564 (77.6)	242 (77.6)
Black	149 (14.3)	103 (14.2)	46 (14.7)
Others	84 (8.1)	60 (8.3)	24 (7.7)
Primary site			
Trigone, bladder neck, ureteric orifice	116 (11.2)	81 (11.1)	35 (11.2)
Anterior, posterior, lateral wall	159 (15.3)	101 (13.9)	58 (18.6)
Urachus/dome	328 (31.6)	233 (32.0)	95 (30.4)
NOS/overlap	436 (42.0)	312 (42.9)	124 (39.7)
Histology			
Papillary adenocarcinoma	31 (3.0)	22 (3.0)	9 (2.9)
Signet cell carcinoma	176 (16.9)	122 (16.8)	54 (17.3)
Adenocarcinoma, NOS	541 (52.1)	378 (52.0)	163 (52.2)
Clear cell adenocarcinoma	51 (4.9)	31 (4.3)	20 (6.4)
Mixed subtype adenocarcinoma	12 (1.2)	8 (1.1)	4 (1.3)
Mucinous adenocarcinoma	228 (21.9)	166 (22.8)	62 (19.9)
Grade			
Grade I	61 (5.9)	45 (6.2)	16 (5.1)
Grade II	258 (24.8)	181 (24.9)	77 (24.7)

(Continued)

Table 1. (continued)

Variables	All patients *n* (%)	Training set	Validation set
		n (%)	*n* (%)
Grade III	348 (33.5)	240 (33.0)	108 (34.6)
Grade IV	118 (11.4)	76 (10.5)	42 (13.5)
Unknown	254 (24.4)	185 (25.4)	69 (22.1)
AJCC stage			
I	182 (17.5)	130 (17.9)	52 (16.7)
II	213 (20.5)	138 (19.0)	75 (24.0)
III	204 (19.6)	148 (20.4)	56 (17.9)
IV	351 (33.8)	250 (34.4)	101 (32.4)
Unknown	89 (8.6)	61 (8.4)	28 (9.0)
T stage			
T1	213 (20.5)	152 (20.9)	61 (19.6)
T2	291 (28.0)	183 (25.2)	108 (34.6)
T3	231 (22.2)	167 (23.0)	64 (20.5)
T4	189 (18.2)	138 (19.0)	51 (16.3)
Unknown	115 (11.1)	87 (12.0)	28 (9.0)
N stage			
N0	759 (73.1)	523 (71.9)	236 (75.6)
N1	81 (7.8)	58 (8.0)	23 (7.4)
N2	86 (8.3)	63 (8.7)	23 (7.4)
N3	3 (0.3)	3 (0.4)	0 (0.0)
Unknown	110 (10.6)	80 (11.0)	30 (9.6)
M stage			
M0	777 (74.8)	540 (74.3)	237 (76.0)
M1	213 (20.5)	154 (21.2)	59 (18.9)
Unknown	49 (4.7)	33 (4.5)	16 (5.1)
SEER stage			
Localized	191 (18.4)	135 (18.6)	56 (17.9)
Regional	537 (51.7)	369 (50.8)	168 (53.8)
Distant	257 (24.7)	184 (25.3)	73 (23.4)
Unstaged	54 (5.2)	39 (5.4)	15 (4.8)

(Continued)

Table 1. (continued)

Variables	All patients *n* (%)	Training set	Validation set
		n (%)	*n* (%)
Surgery			
No/Unknown	161 (15.5)	120 (16.5)	41 (13.1)
Surgery, NOS	9 (0.9)	6 (0.8)	3 (1.0)
Partial cystectomy	665 (64.0)	461 (63.4)	204 (65.4)
Radical cystectomy	204 (19.6)	140 (19.3)	64 (20.5)
Chemotherapy			
Yes	314 (30.2)	210 (28.9)	104 (33.3)
No/Unknown	725 (69.8)	517 (71.1)	208 (66.7)
Radiotherapy			
Yes	148 (14.2)	100 (13.8)	48 (15.4)
No/Unknown	891 (85.8)	627 (86.2)	264 (84.6)

AJCC, American Joint Committee on Cancer; NOS, not otherwise specified; SEER, Surveillance, Epidemiology, and End Results.

Table 2. Univariate and multivariate analysis of overall survival (OS) rates in training set.

Variables	Univariate analysis		Multivariate analysis[a]	
	p Value		HR (95% CI)	*p* Value
Sex				
Male	Reference			
Female	1.143 (0.953–1.379)	0.149		
Age, years				
<68	Reference		Reference	
68–79	1.494 (1.193–1.872)	<0.001	1.310 (1.030–1.666)	0.028
>79	2.612 (2.110–3.235)	<0.001	2.164 (1.693–2.765)	<0.001
Marital status				
Married	Reference		Reference	
Unmarried	1.327 (1.105–1.592)	0.002	1.306 (1.077–1.584)	0.007
Unknown	1.064 (0.704–1.608)	0.769	0.936 (0.599–1.462)	0.771
Race				
White	Reference		Reference	
Black	0.971 (0.749–1.259)	0.823	–	0.893

(Continued)

Table 2. (continued)

Variables	Univariate analysis		Multivariate analysis[a]	
	***p* Value**		**HR (95% CI)**	***p* Value**
Others	0.747 (0.509–1.097)	0.137	–	0.289
Primary site				
Trigone, bladder neck, ureteric orifice	Reference		Reference	
Anterior, posterior, lateral wall	0.862 (0.597–1.244)	0.427	0.826 (0.571–1.196)	0.312
Urachus/dome	0.489 (0.343–0.699)	<0.001	0.580 (0.404–0.832)	0.003
NOS/overlap	0.879 (0.653–1.183)	0.394	0.901 (0.671–1.211)	0.490
Histology				
Papillary adenocarcinoma	Reference		Reference	
Signet cell carcinoma	3.823 (1.797–8.133)	<0.001	3.408 (1.610–7.216)	0.001
Adenocarcinoma, NOS	3.340 (1.615–6.909)	0.001	2.947 (1.424–6.101)	0.004
Clear cell adenocarcinoma	2.377 (1.018–5.549)	0.045	2.196 (0.947–5.091)	0.067
Mixed subtype adenocarcinoma	5.897 (1.843–18.873)	0.003	5.677 (1.784–18.067)	0.003
Mucinous adenocarcinoma	2.165 (1.009–4.643)	0.047	1.940 (0.905–4.159)	0.089
Grade				
Grade I	Reference		Reference	
Grade II	1.486 (0.836–2.641)	0.177	1.320 (0.747–2.332)	0.340
Grade III	2.651 (1.506–4.667)	0.001	2.411 (1.380–4.211)	0.002
Grade IV	2.162 (1.161–4.028)	0.015	2.149 (1.160–3.980)	0.015
Unknown	2.041 (1.150–3.620)	0.015	1.645 (0.934–2.898)	0.085
AJCC stage				
I	Reference		Reference	
II	1.325 (0.943–1.862)	0.105	0.507 (0.194–1.322)	0.165
III	1.346 (0.969–1.870)	0.077	0.994 (0.387–2.553)	0.990
IV	4.030 (3.023–5.373)	<0.001	1.523 (0.588–3.946)	0.386
Unknown	2.183 (1.476–3.228)	<0.001	2.117 (0.911–4.920)	0.081
T stage				
T1	Reference		Reference	
T2	1.468 (1.103–1.953)	0.008	1.551 (1.005–2.395)	0.047
T3	1.084 (0.806–1.457)	0.594	1.683 (1.009–2.810)	0.046
T4	2.939 (2.210–3.910)	<0.001	2.492 (1.293–4.802)	0.006

(Continued)

Table 2. (continued)

Variables	Univariate analysis		Multivariate analysis[a]	
	***p* Value**		**HR (95% CI)**	***p* Value**
Unknown	2.731 (1.978–3.773)	<0.001	1.155 (0.603–2.214)	0.664
N stage				
N0	Reference		Reference	
N1	1.999 (1.481–2.700)	<0.001	–	0.982
N2	2.802 (2.098–3.742)	<0.001	–	0.014
N3	1.985 (0.636–6.193)	0.238	–	0.336
Unknown	2.123 (1.626–2.770)	<0.001	–	0.279
M stage				
M0	Reference		Reference	
M1	1.554 (0.939–2.570)	0.086	–	0.157
Unknown	0.692 (0.379–1.265)	0.232	–	0.171
SEER stage				
Localized	Reference		Reference	
Regional	4.394 (1.705–11.322)	0.002	4.828 (1.929–12.084)	0.001
Distant	5.259 (1.748–15.823)	0.003	6.636 (2.502–17.600)	<0.001
Unstaged	1.800 (0.614–5.271)	0.284	1.844 (0.664–5.123)	0.241
Surgery				
No/Unknown	Reference		Reference	
Surgery, NOS	0.248 (0.094–0.651)	0.005	0.386 (0.149–1.005)	0.051
Partial cystectomy	0.510 (0.363–0.717)	<0.001	0.465 (0.333–0.649)	<0.001
Radical cystectomy	0.288 (0.192–0.431)	<0.001	0.327 (0.222–0.481)	<0.001
Chemotherapy				
Yes	Reference		Reference	
No/Unknown	1.902 (1.508–2.399)	<0.001	1.577 (1.249–1.992)	<0.001
Radiotherapy				
Yes	Reference		Reference	
No/Unknown	0.709 (0.545–0.921)	0.010	0.729 (0.560–0.947)	0.018

[a]Model was adjusted by gender, age, race, grade, AJCC stage, TNM stage, histology, SEER stage, chemotherapy and radiotherapy.
AJCC, American Joint Committee on Cancer; CI, confidence intervals; HR, hazard ratio; OS, overall survival; NOS, not otherwise specified; SEER, Surveillance, Epidemiology, and End Results.

Table 3. Univariate and multivariate analysis of cancer-specific survival (CSS) rates in training set.

Variables	Univariate analysis		Multivariate analysis[a]	
	p Value		HR (95% CI)	*p* Value
Sex				
Male	Reference		Reference	
Female	1.281 (1.026–1.598)	0.028	–	0.253
Age, years				
<68	Reference		Reference	
68–79	1.333 (1.011–1.758)	0.042	1.212 (0.905–1.624)	0.198
>79	1.993 (1.515–2.622)	<0.001	1.963 (1.440–2.676)	<0.001
Marital status				
Married	Reference		Reference	
Unmarried	1.395 (1.115–1.744)	0.004	1.392 (1.100–1.760)	0.006
Unknown	0.709 (0.384–1.309)	0.272	0.827 (0.436–1.567)	0.560
Race				
White	Reference		Reference	
Black	0.993 (0.718–1.374)	0.968	–	0.967
Others	0.931 (0.603–1.437)	0.746	–	0.905
Primary site				
Trigone, bladder neck, ureteric orifice	Reference		Reference	
Anterior, posterior, lateral wall	0.767 (0.487–1.209)	0.254	0.791 (0.502–1.248)	0.314
Urachus/dome	0.506 (0.328–0.781)	0.002	0.563 (0.364–0.871)	0.010
NOS/overlap	0.853 (0.592–1.230)	0.395	0.829 (0.579–1.189)	0.309
Histology				
Papillary adenocarcinoma	Reference		Reference	
Signet cell carcinoma	2.955 (1.137–7.677)	0.026	2.751 (1.070–7.072)	0.036
Adenocarcinoma, NOS	2.428 (0.964–6.116)	0.060	2.208 (0.876–5.563)	0.093
Clear cell adenocarcinoma	1.794 (0.619–5.198)	0.281	1.746 (0.608–5.016)	0.301
Mixed subtype adenocarcinoma	8.811 (2.333–33.274)	0.001	9.391 (2.503–35.234)	0.001
Mucinous adenocarcinoma	1.675 (0.637–4.406)	0.296	1.566 (0.598–4.101)	0.361
Grade				
Grade I	Reference		Reference	
Grade II	2.202 (0.926–5.235)	0.074	2.034 (0.862–4.800)	0.105

(Continued)

Table 3. (continued)

Variables	Univariate analysis		Multivariate analysis[a]	
	***p* Value**		**HR (95% CI)**	***p* Value**
Grade III	4.161 (1.774–9.760)	0.001	3.802 (1.634–8.851)	0.002
Grade IV	2.944 (1.183–7.330)	0.020	2.814 (1.137–6.969)	0.025
Unknown	3.074 (1.299–7.275)	0.011	2.500 (1.063–5.877)	0.036
AJCC stage				
I	Reference		Reference	
II	1.482 (0.932–2.359)	0.097	0.361 (0.106–1.225)	0.102
III	1.758 (1.134–2.724)	0.012	0.822 (0.247–2.731)	0.749
IV	5.915 (4.016–8.711)	<0.001	1.377 (0.415–4.570)	0.601
Unknown	1.798 (1.005–3.217)	0.048	1.259 (0.416–3.811)	0.683
T stage				
T1	Reference		Reference	
T2	1.775 (1.221–2.580)	0.003	1.767 (0.998–3.127)	0.051
T3	1.451 (0.993–2.119)	0.055	1.924 (0.997–3.711)	0.051
T4	3.818 (2.643–5.515)	<0.001	3.079 (1.333–7.112)	0.008
Unknown	2.780 (1.798–4.297)	<0.001	1.011 (0.600–1.706)	0.966
N stage				
N0	Reference		Reference	
N1	2.351 (1.658–3.334)	<0.001	1.190 (0.750–1.887)	0.460
N2	3.600 (2.604–4.977)	<0.001	1.676 (1.157–2.428)	0.006
N3	2.019 (0.501–8.137)	0.323	2.156 (1.519–3.060)	<0.001
Unknown	1.847 (1.293–2.636)	0.001	1.667 (1.094–2.539)	0.017
M stage				
M0	Reference		Reference	
M1	1.757 (0.984–3.138)	0.057	–	0151
Unknown	0.708 (0.294–1.703)	0.440	–	0.439
SEER stage				
Localized	Reference		Reference	
Regional	6.287 (1.908–20.713)	0.003	6.661 (2.142–20.714)	0.001
Distant	8.329 (2.146–32.332)	0.002	9.559 (2.883–31.691)	<0.001
Unstaged	2.479 (0.585–10.511)	0.218	2.742 (0.697–10.785)	0.149

(Continued)

Table 3. (continued)

Variables	Univariate analysis		Multivariate analysis[a]	
	p Value		HR (95% CI)	*p* Value
Surgery				
No/Unknown	Reference		Reference	
Surgery, NOS	0.144 (0.033–0.634)	0.010	0.277 (0.065–1.188)	0.084
Partial cystectomy	0.668 (0.429–1.041)	0.075	0.657 (0.428–1.008)	0.055
Radical cystectomy	0.374 (0.224–0.623)	<0.001	0.430 (0.266–0.695)	0.001
Chemotherapy				
Yes	Reference		Reference	
No/Unknown	1.916 (1.445–2.541)	<0.001	1.616 (1.223–2.134)	0.001
Radiotherapy				
Yes	Reference		Reference	
No/Unknown	0.727 (0.531–0.994)	0.045	–	0.377

[a]Model was adjusted by gender, age, race, grade, AJCC stage, TNM stage, histology, SEER stage, chemotherapy and radiotherapy.
AJCC, American Joint Committee on Cancer; CI, confidence intervals; CSS, cancer-specific survival; HR, hazard ratio; NOS, not otherwise specified; SEER, Surveillance, Epidemiology, and End Results.

"surgery, NOS" cystectomy with chemotherapy may help patients to get an advantageous consequence for both OS and CSS, as other studies reported.

Prognostic nomograms for OS and CSS and validations

All independent risk factors in the multivariate Cox regression analyses were taken into consideration in nomograms for 3- and 5-year OS and CSS, as shown in Figure 3. We found that SEER stage contributes the most to OS and CSS. According to the HR, each variable was assigned a point. The total points for each variable are then summed and positioned on the total points table to obtain the probability of 3 and 5 years of OS and CSS. For example, with the nomogram for OS, one can conclude that if a 70-year-old married man with primary site of bladder neck, grade III, T2, III for AJCC stage, Regional of SEER stage, papillary adenocarcinoma has taken partial cystectomy, chemotherapy without radiotherapy, he would score about 290 points, which means that this patient has approximately 40% possibility of survival in the third year and approximately 30% possibility of survival in the fifth year.

Subsequently, we tested the predictive ability of the nomograms using the C-index, ROC curves and DCA curves. We found that the predictive ability of the nomogram was better than the TNM stage in both the training and validation sets (Table 4 and Figure 4). In addition, the nomograms were also able to predict 3-year and 5-year OS and CSS better, and the AUCs of the nomograms were greater than 0.8, suggesting that the nomograms had good predictive ability (Figure 5). Moreover, we used calibration curves to detect comparisons between the predicted and actual survival times of the nomograms. The calibration curve in Figure 6 is very close to the ideal curve, showing good agreement between the predictions of the nomograms and the actual observations in the training and validation sets, suggesting appreciable reliability of the nomograms.

Discussion

In this study, we found that the incidence of ACB patients showed a decreasing trend in the past 25 years. Using the large cohort of ACB patients from the SEER dataset, two novel comprehensive nomograms were established to predict individual OS and CSS outcomes in patients with rare

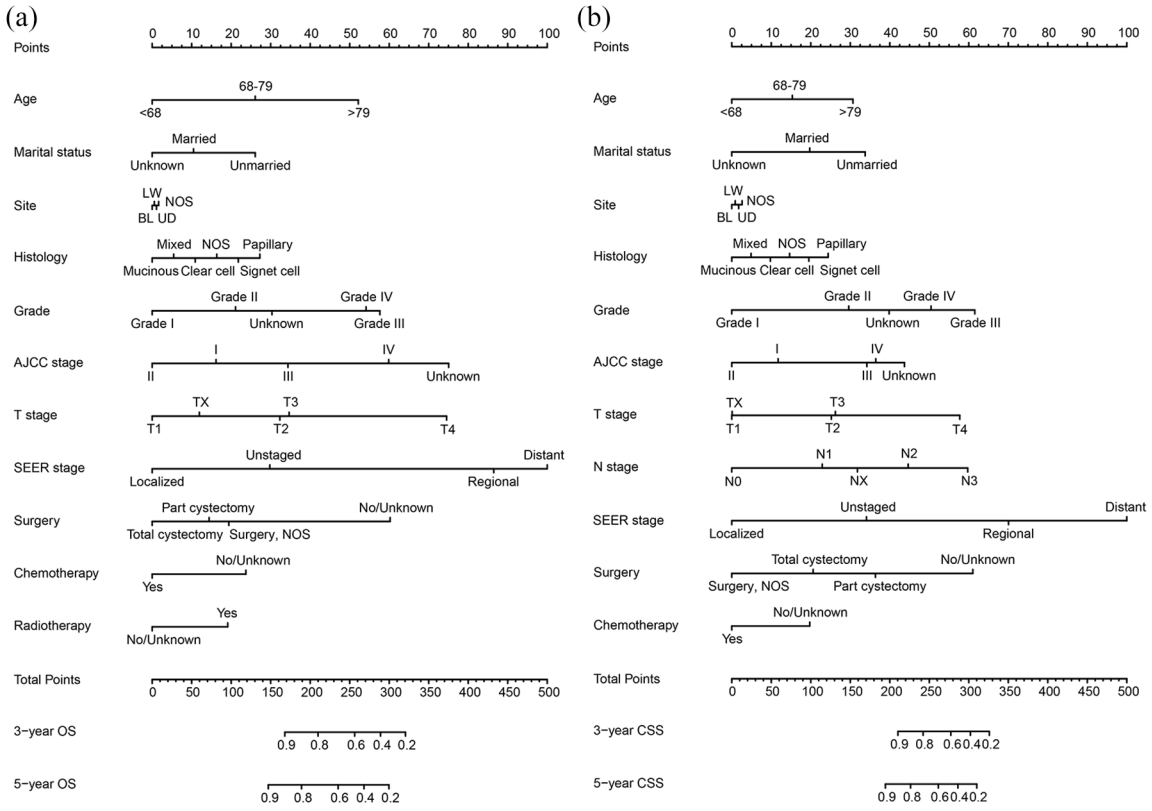

Figure 3. Prognostic nomogram of (a) overall survival (OS) and (b) cancer-specific survival (CSS) in patients with adenocarcinoma of the bladder.

Table 4. Comparison of C-indexes and AUC between the nomogram and SEER stage in patients with adenocarcinoma of the bladder.

Characteristics		Training set		Validation set	
		HR	95% CI	HR	95% CI
C-indexes					
OS	Nomogram	0.773	0.752–0.794	0.782	0.753–0.811
	TNM stage	0.687	0.664–0.710	0.689	0.651–0.727
CSS	Nomogram	0.785	0.761–0.810	0.788	0.749–0.827
	TNM stage	0.713	0.684–0.742	0.714	0.665–0.763
AUC					
OS	Nomogram	0.827	0.798–0.854	0.833	0.787–0.873
	TNM stage	0.737	0.703–0.768	0.744	0.692–0.792
CSS	Nomogram	0.741	0.708–0.773	0.771	0.720–0.816
	TNM stage	0.711	0.676–0.743	0.713	0.660–0.763

AUC, area under the curve; CI, confidence interval; HR, hazard ratio; SEER, Surveillance, Epidemiology, and End Results.

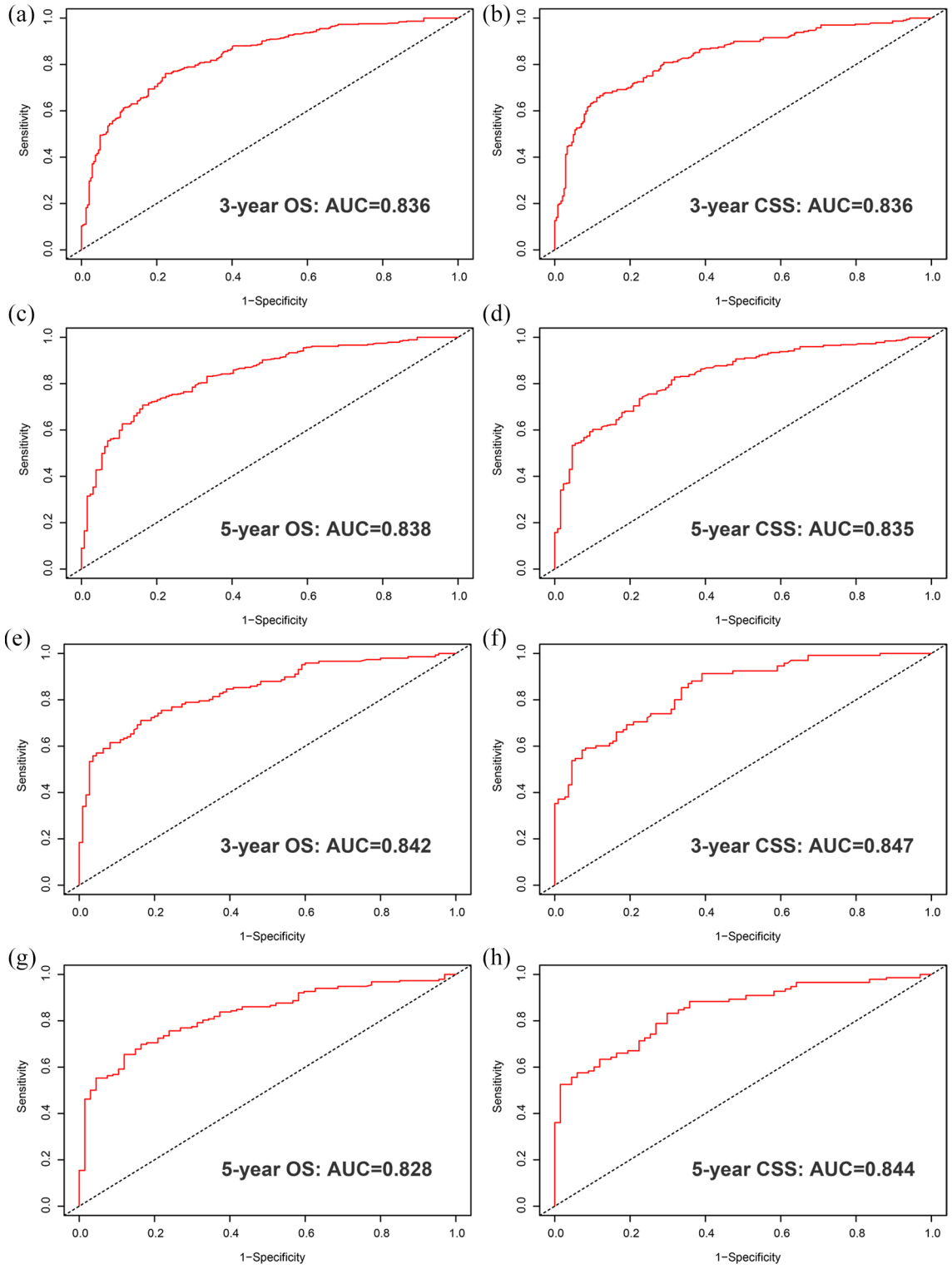

Figure 4. The receiver operating characteristic (ROC) curves evaluates the predictive ability of the nomogram: (a) 3-year overall survival (OS) rates in the training set; (b) 3-year cancer-specific survival (CSS) rates the training set; (c) 5-year OS rates the training set; (d) 5-year CSS rates the training set; (e) 3-year OS rates in the validation set; (f) 3-year CSS rates the validation set; (g) 5-year OS rates the validation set; (h) 5-year CSS rates the validation set.

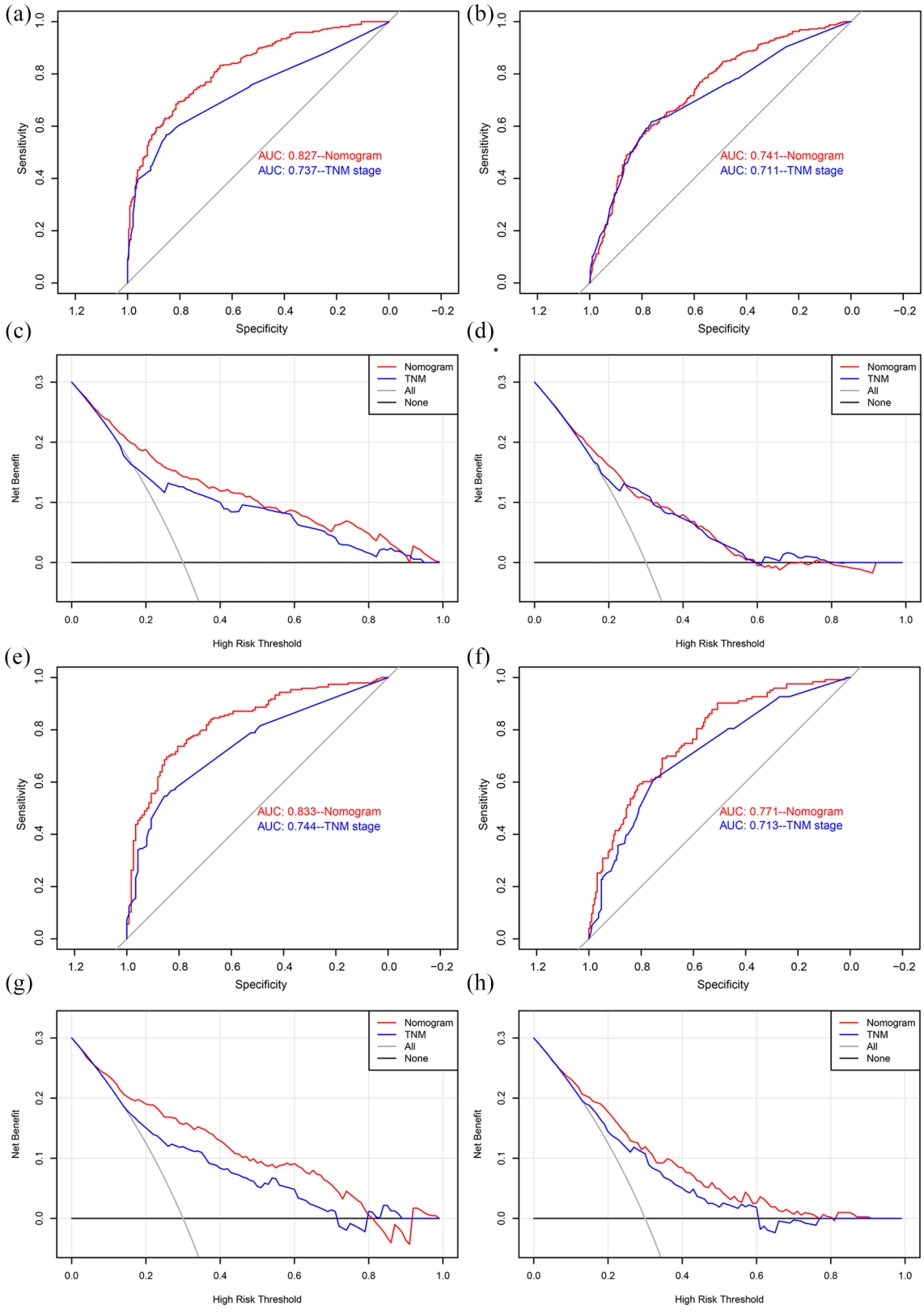

Figure 5. The receiver operating characteristic (ROC) curves and decision curve analysis (DCA) evaluates the predictive ability of the nomogram: (a) overall survival (OS) rates in the training set; (b) cancer-specific survival (CSS) rates in the training set; (c) DCA curves in the training set; (d) DCA curves in the training set; (e) OS in the validation set; (f) CSS in the validation set; (g) DCA curves in the validation set; (h) DCA curves in the validation set.

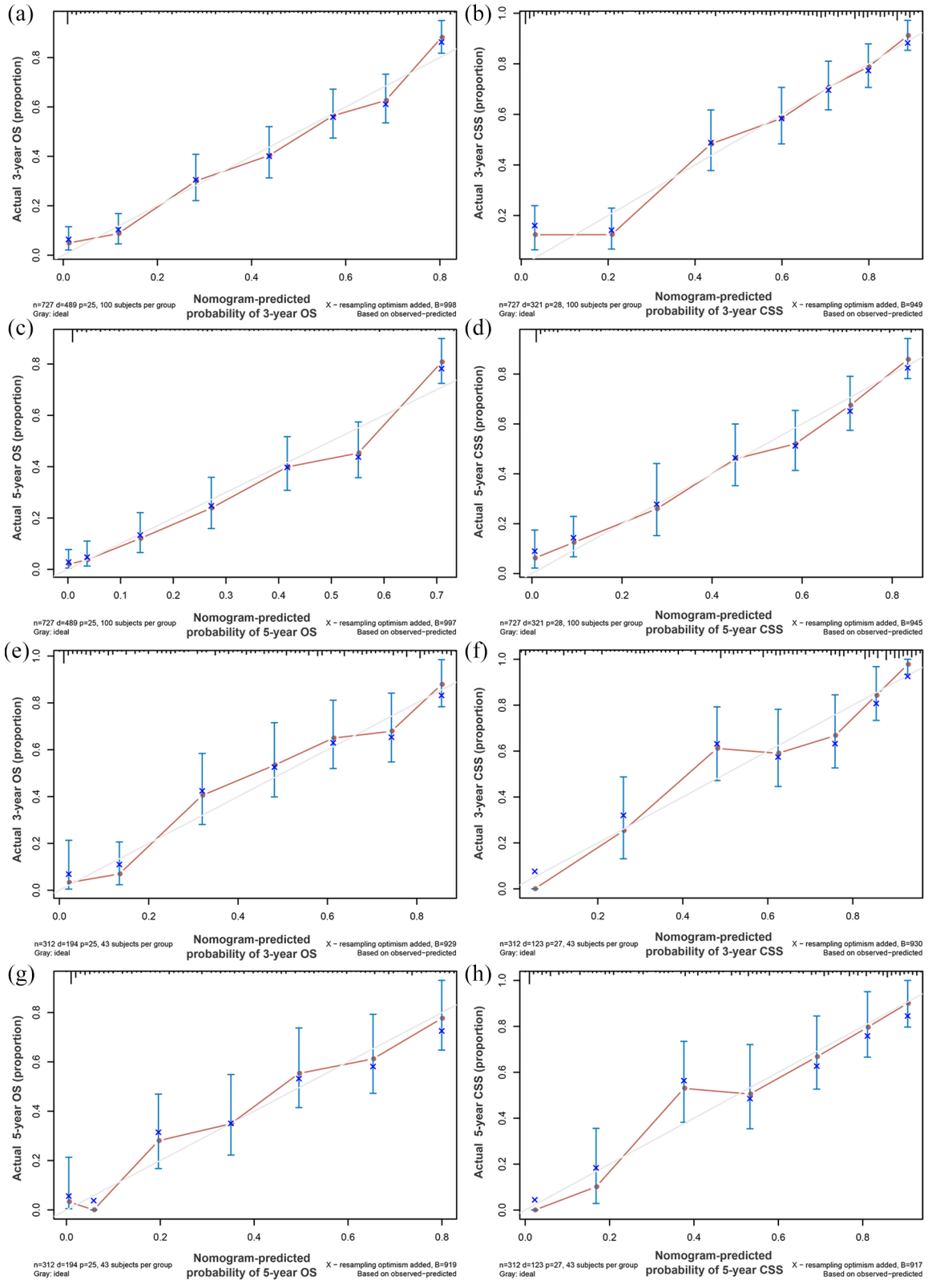

Figure 6. Calibration plot of the nomogram for predicting 3- and 5-year overall survival (OS) and cancer-specific survival (CSS): (a) 3-year OS rates in the training set; (b) 3-year CSS rates the training set; (c) 5-year OS rates in the training set; (d) 5-year CSS rates in the training set; (e) 3-year OS rates in the validation set; (f) 3-year CSS rates in the validation set; (g) 5-year OS rates in the validation set; (h) 5-year CSS rates in the validation set.

primary ACB. When properly used in training and validation sets, the nomogram showed satisfactory accuracy and robustness, indicating good clinical applicability for this rare genitourinary tumor.

Unlike urothelial bladder cancer, primary ACB has several particularities that should be noted. First, the low prevalence leads to a vague understanding of ACB[2] and limited experience with chemotherapy or radiotherapy.[11] El-Mekresh *et al.*[12] reviewed 185 patients with primary ACB and showed an overall 5-year disease-free survival rate of 55%. As for treatment, the management of primary ACB involves a multimodal approach. There are no standard guidelines for ACB, nor are there multicenter randomized controlled trials available to guide treatment decisions. Therefore, patient survival may be significantly affected by their treatment options.

Due to the rarity of primary ACB, there are no staging systems or predictive models specifically designed or widely accepted for it to date. Currently, the AJCC staging system for urothelial cancers based on T, N, and M information has also been applied to ACB. However, Natale *et al.*[21] reviewed 2305 patients with primary ACB from 1973 to 2015 and showed that gender, stage, grade, primary tumor location, and histological subtype have independent prognostic value. In addition, the AJCC staging system, which relies solely on pathological features, has a limited impact on the prognosis of ACB because it does not consider the impact of various treatments on the survival of patients.

The prognostic nomogram is a visualization of a complex statistical model used to predict individual survival outcomes. Prognostic nomograms have been widely used in clinical practice due to their high accuracy and comprehensibility.[17,22,23] For bladder malignancies, a series of nomograms has been developed for patients with urothelial bladder cancer.[24–26] Our study was based on extensive ACB data to develop a reliable prognostic prediction model for patients with primary ACB. This might be considered an update and expansion of the previously published studies that also used population-based data, but instead establishes a reliable prognostic prediction model for patients with primary ACB.[21]

Numerous studies proved that female patients were associated with higher cancer-specific mortality in urothelial bladder cancer.[27–29] The role of gender in predicting prognosis of ACB patients seemed to be completely different from that of patients with primary small-cell carcinoma (SCC) of the bladder. Such disparity might be a reflection of differences between ACB and SCC in genetic, hormonal, societal, and environmental factors, which all had significant impact on gender-related cancer prognosis.[30,31] Moreover, this is the first time that marital status was introduced to primary ACB's prognostic nomogram. This study indicates that marriage can bring prognostic differences, so this is worthy of more attention as marriage may include complicated mechanisms that improve OS.

The recommended nomogram included three treatment factors: radical cystectomy, chemotherapy, and radiotherapy, which perform well in predicting the survival outcomes of ACB patients. Among all therapies, radical cystectomy remains the standard of treatment for ACB, and chemotherapy as adjuvant or neoadjuvant therapy appears to remain the primary treatment for patients with ACB. The 2019 National Comprehensive Cancer Center Network guidelines for patients with advanced or metastatic ACB recommend chemotherapy. However, some study protocols showed poor response rates in ACB.[32,33] It has been found that this and postoperative radiotherapy may have a role in improving disease-free survival, especially in the early stages.[12] From our study, we found that radiotherapy appears to be a completely independent prognostic factor for OS, rather than CSS, and that patients who received radiotherapy had a higher overall mortality rate compared with those who did not, a result similar to that of Natale *et al.*[21] We suspect that for some patients, it is too late for cystectomy, or the body is unable to tolerate anesthesia, and these patients simply choose to preserve their bladder and receive radiotherapy, thereby increasing overall mortality.

Generally speaking, the new nomograms in our research are innovative in several ways. First, we created OS and CSS prognostic nomograms for patients with ACB, making personalized prognostic prediction possible. Second, we found that the current AJCC stage or TNM stage of bladder cancer is actually less appropriate for primary ACB. Therefore, we established a new aggregation-based nomograms system and further demonstrated that the newly established nomograms can easily stratify patients into different risk strata.

Finally, and most importantly, we used DCA curve, a relatively new method of analyzing net benefit; we applied it to our nomograms and found that the new nomograms have broader clinical applicability than the current TNM staging.

However, there are still several limitations. First of all, our analysis is based on the SEER database, which lacks some accurate information. For example, assigning two categories to chemotherapy ("No/Unknown" or "Yes") may lead to limitations in the completeness of the variables and might cause other relevant bias. Second, the SEER database does not include the socioeconomic status of individuals,[34] such as education level and household income level, which may also be related to the prognosis of bladder cancer patients.[35] As for the establishment of nomograms, improving the accuracy of the model sometimes comes at the cost of increased complexity. It is not easy to strike a balance between comprehensibility and comprehensiveness. This is a common problem when developing new nomograms. Furthermore, although the C-index of the two nomograms is greater than 0.7, it shows that the accuracy of OS and CSS is indeed very high, but not perfect. The quality and quantity of data and the reliability of the algorithm can still be improved, and the nomograms would need to be tested in other cohorts. In addition, the study was conducted retrospectively, and there may be selection bias.

Conclusions

Over the past 25 years, the incidence of patients with primary ACB has shown a decreasing trend. Based on the results of multivariate Cox regression analysis, we constructed a clinically useful prognostic nomogram for assessing OS and CSS in patients with ACB, superior to the traditional TNM staging system, which provides personalized risk assessment for ACB patient survival.

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Author contributions

Conception and design: HL, WM, MC, LZ, and BX; Administrative support: WZ, WM, and BX; Provision of study materials or patients: HL and YW; Collection and assembly of data: HL, WM, and YW; Data analysis and interpretation: HL, WZ, WM, and FZ; Manuscript writing: HL, WC, WM, and WL. Final approval of manuscript: All authors.

Availability of data

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Ethical approval

The SEER database consists of de-identified information that is freely available within the public domain, so ethical approval was not required.

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Supplemental material

Supplemental material for this article is available online.

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