Original Article

Development and validation of a nomogram for predicting survival in patients with non-metastatic primary adenocarcinoma of the bladder

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Background: To develop a nomogram for predicting cancer-specific survival (CSS) of patients with non-metastatic primary adenocarcinoma of the bladder (NMACB).

Methods: We used a retrospective cohort study design. Patient data were obtained from the SEER database, univariate and multivariate Cox regression analyses were performed to identify factors associated with CSS. A nomogram visualization model was established using R language software to predict survival rate. Harrell's concordance index (C-index), area under the receiver operating characteristic (ROC) curve (AUC) in addition to calibration plots were used to assess the performance of the model.

Results: A total of 1,635 patients were included in the study. A multivariate Cox regression model indicated that age, histological type, grade, stage, and surgery were independent covariates associated with CSS. Using these prognostic factors, a nomogram was constructed. Harrell's C indices for CSS were 0.729 in the training cohort and 0.716 in the validation cohort. AUC values were 0.769, 0.735 and 0.724 for 1, 3, and 5-year in the training cohort, and 0.738, 0.727 and 0.713 for 1, 3 and 5-year in the validation cohort, respectively. The AUC values and calibration plots indicated that the nomogram provided good predictive performance.

Conclusions: A nomogram for predicting CSS in patients with NMACB was developed to assist clinicians in the accurate prediction of mortality risk to allow them to recommend a personalized treatment modality.

Keywords: Cancer-specific survival (CSS); nomogram; non-metastatic primary adenocarcinoma of the bladder (NMACB); Surveillance, Epidemiology, and End Results (SEER)

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Introduction

Bladder cancer is the most common cancer of the urinary system (1), of which greater than 90% of pathological types are urothelial carcinoma (2). Primary adenocarcinoma of the bladder (ACB) is a rare form that has a high degree of malignancy, late staging, and poor prognosis (3), accounting for approximately 0.5–2.0% of all bladder malignant tumors. ACB is classified as a primary non-urachal or urachal adenocarcinoma (4). Schistosomiasis (5) and bladder exstrophy (6) are thought to be associated with ACB. Bladder urothelial carcinoma has been widely investigated (7-9), while conversely, ACB has been rarely studied due to

its low incidence rate.

Accurate estimates of prognosis based on clinicopathological factors play an important role in the selection of treatment strategies (10). Nomograms have been widely used to estimate a specific end point in cancer patients because they can improve relative predictive accuracy (11,12). Multiple nomograms have been established to inform clinical practice in bladder cancer (13-15). The majority of nomograms focus on urothelial carcinoma of the bladder. There are significant differences in etiology, treatment, and prognosis between primary bladder adenocarcinoma and urothelial cancer. Nomograms developed for use with bladder urothelial carcinoma are not suitable for patients with ACB. However no predictive nomograms have been developed for ACB due to its low incidence rate. Prognosis and therapeutic options for non-metastatic versus metastatic ACB vary widely. The present study focused on non-metastatic primary adenocarcinoma of the bladder (NMACB).

Here, we developed and validated a nomogram to predict survival in patients with NMACB from data in the surveillance, epidemiology and end results (SEER) database. The present study aimed at the identification of independent prognostic factors in patients with NMACB and also predict their cancer-specific survival (CSS). We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-354).

Methods

We used a retrospective cohort study design. Patient data were obtained from the National Cancer Institute's SEER program, which encompasses approximately 28% of the U.S. population. We used the International Statistical Classifications of Diseases for Oncology, 3rd edition (ICD-O-3) site codes C670-C679 and histology codes 8140–8147 and 8255–8490 to identify primary bladder tumors with adenocarcinoma. Additional inclusion criteria included: (I) bladder adenocarcinoma that was the first malignancy; (II) cancer at a non-metastatic tumor stage; (III) patients for whom information about CSS, duration of survival (in months) and therapy provided, were available; (IV) diagnosis by histological confirmation only. Cases diagnosed by clinical presentation, radiography or autopsy alone were excluded. This study was conducted in accordance with standard guidelines and was approved by the local Ethics Committee. We also got permission from the National Cancer Institute USA to access the SEER dataset for research purposes only (reference number: 18015-Nov2017). All the data from the SEER database were de-identified, and the extracted data did not require informed consent.

Statistical analysis

Patients were randomly assigned to either the training or validation cohort. Continuous variables such as age are presented as medians and the median value of the interquartile range (IQR). Categorical variables such as race are presented as counts and percentages. Univariate analysis was used to identify potential risk factors. Multivariate analyses were performed after the risk factors were identified. A statistical significance level of 0.05 was used to select variables for the nomogram. After comparing three different models (full model, stepwise model, multivariable fractional polynomial model), the full model displayed the best fit. A nomogram was developed based on a multivariate model derived from a Cox regression model. Harrell's concordance index (C-index) and area under the receiver operating characteristic (ROC) curve (AUC), in addition to calibration plots, were used to assess the performance of the model. Data were analyzed with the use of the statistical package R (R foundation; http://www.r-project.org; version 3.4.3) and EmpowerStats software (www.empowerstats.com, X&Y solutions, Inc. Boston MA).

Results

Demographic characteristics

A total of 1,635 patients that satisfied the inclusion criteria described above were included in the analysis (*Figure 1*). The demographic and clinicopathological characteristics of the study patients are presented in *Table 1*. Median age was 66 years of age (range, 17 to 101 years). The majority of patients, 1,437 (87.89%) suffered non-urachal primary adenocarcinomas of the bladder, 1,312 (80.24%) were white and 1,050 (64.22%) were male. Median follow-up time was 38 months (range, 1 to 403 months). A total of 1,120 (68.50%) patients had died prior to the final follow-up, of which 715 (43.73%) had died due to primary adenocarcinoma of the bladder (ACB). There were no significant differences of the variables between the training and validation cohorts.

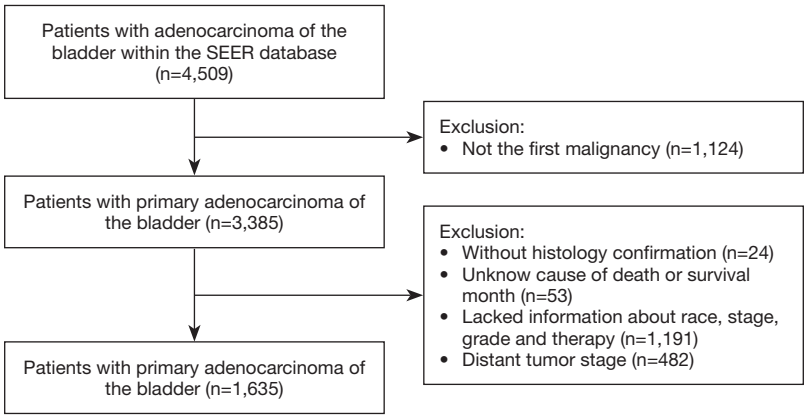

Figure 1 Flow-chart of the participants' selection.

Pathologic and clinical characteristics

When referring to stage and grade, the majority of patients, 1,156 (70.70%) were of regional tumor stage and 698 (42.69%) had poorly differentiated (Grade III) tumors. A total of 1,585 (96.94%) patients underwent cancer-directed surgery. Of these, 616 (37.68%) underwent transurethral surgery, 423 (25.87%) received partial cystectomy and 491 (30.03%) had complete cystectomy. In patients with a urachal primary site, most patients received either partial (151, 76.26%) or complete cystectomy (25, 12.63%). A small proportion of patients received chemotherapy (326, 19.94%) or radiation treatment (182, 11.13%).

Survival and mortality analyses

Univariate Cox analysis of the training cohort (n=1,226) (*Table 2*) indicated that worse prognosis was associated with older age (HR: 1.02, P<0.0001), being moderately differentiated (HR: 1.97, P=0.0016), poorly differentiated (HR: 3.64, P<0.0001), undifferentiated or anaplastic (HR: 2.90, P<0.0001),or with a regional stage (HR: 2.13, P<0.0001).

Using adenocarcinoma not otherwise specified (NOS) as a reference, signet cell carcinoma (HR: 2.12, P<0.0001) was shown to confer the worst survival outcome of the various histological subtypes while mucinous adenocarcinoma (HR: 0.95, P=0.6277) and other adenocarcinoma subtypes (HR: 0.98, P=0.8662) conferred similar survival outcomes.

Multivariate cox regression analysis (*Table 3*) demonstrated that worse prognosis was related to older age (HR: 1.02, P<0.0001), being moderately differentiated (HR: 1.86, P=0.0047), poorly differentiated (HR: 2.53, P<0.0001), undifferentiated or anaplastic (HR: 2.01, P=0.0035), a tumor that is at a regional stage (HR: 2.59, P<0.0001) or is a mucinous adenocarcinoma (HR: 1.36, P=0.0138). However, being female (HR: 1.17, P=0.0905) or having a non-urachal primary site (HR: 1.27, P=0.1839) were statistically insignificant in the multivariate cox regression model. Signet cell carcinoma (HR: 1.80, P=0.0009) was also shown to represent a survival disadvantage compared with adenocarcinoma NOS. Patients who had received surgery (HR: 0.38, P<0.0001 for transurethral surgery; HR: 0.15, P<0.0001 for partial cystectomy; HR: 0.24, P<0.0001 for cystectomy; HR: 0.33, P=0.0006 for other forms of surgery) had a better prognosis than those who had not, while radiotherapy (HR: 1.07, P=0.6124) and chemotherapy (HR: 1.20, P=0.1139) became statistically insignificant which was due mostly to tumor stage (exclusion of tumor stage in the complete model had the greatest influence on the regression coefficient for radiotherapy and chemotherapy, data not shown in the article).

Development and validation of the nomogram

Univariate analysis was used to identify potential risk factors. Independent prognostic factors were selected from the results of multivariate cox analyses. A statistical significance level of 0.05 was used to select the variables in multivariate analyses to develop a nomogram for predicting the 1, 3 and 5-year CSS of ACB patients. A total of 1,635 patients were randomly assigned to the training (n=1,226) and validation cohort (n=409) cohorts. The nomogram for predicting 1, 3 and 5-year CSS in patients with ACB is presented in *Figure 2*.

Table 1 Clinical characteristics of the 1,635 patients with primary adenocarcinoma of the bladder

Variable	Training cohort (n=1,226)	Validation cohort (n=409)	Total (n=1,635)	P value
Age at diagnosis, median (IQR), year	65 (55 to 75)	66 (54 to 77)	66 (54 to 76)	0.305
Sex				0.968
Male	787 (64.19)	263 (64.30)	1,050 (64.22)	
Female	439 (35.81)	146 (35.70)	585 (35.78)	
Race, n (%)				0.111
White	974 (79.45)	338 (82.64)	1,312 (80.24)	
Black	166 (13.54)	54 (13.20)	220 (13.46)	
Other	86 (7.01)	17 (4.16)	103 (6.30)	
Primary site, n (%)				0.308
Urachus	151 (12.32)	47 (11.49)	198 (12.11)	
Non-urachus	1,075 (87.68)	362 (88.51)	1,437 (87.89)	
Grade, n (%)				0.863
Well differentiated, Grade I	117 (9.54)	38 (9.29)	155 (9.48)	
Moderately differentiated, Grade II	397 (32.38)	140 (34.23)	537 (32.84)	
Poorly differentiated, Grade III	524 (42.74)	174 (42.54)	698 (42.69)	
Undifferentiated, anaplastic, Grade IV	188 (15.33)	57 (13.94)	245 (14.98)	
Histologic type, n (%)				0.786
Adenocarcinoma NOS	664 (54.16)	214 (52.32)	878 (53.70)	
Mucinous adenocarcinoma	243 (19.82)	84 (20.54)	327 (20.00)	
Signet ring cell adenocarcinoma	149 (12.15)	47 (11.49)	196 (11.99)	
Other adenocarcinoma subtypes	170 (13.87)	64 (15.65)	234 (14.31)	
SEER historic stage A, n (%)				0.057
Localized	344 (28.06)	135 (33.01)	479 (29.30)	
Regional	882 (71.94)	274 (66.99)	1,156 (70.70)	
Radiation, n (%)				0.122
Yes	145 (11.83)	37 (9.05)	182 (11.13)	
None/unknown	1,081 (88.17)	372 (90.95)	1,453 (88.87)	
Chemotherapy, n (%)				
Yes	250 (20.39)	76 (18.58)	326 (19.94)	0.428
None/unknown	976 (79.61)	333 (81.42)	1,309 (80.06)	
Surgery, n (%)				0.77
No cancer-direct surgery	39 (3.18)	11 (2.69)	50 (3.06)	
Transurethral resection	452 (36.87)	164 (40.10)	616 (37.68)	
Partial cystectomy	317 (25.86)	106 (25.92)	423 (25.87)	
Cystectomy	376 (30.67)	115 (28.12)	491 (30.03)	
Other surgery type	42 (3.43)	13 (3.18)	55 (3.36)	

Localized, confined entirely to the organ of origin. Regional, has extended (I) beyond the limits of the organ of origin directly into surrounding organs or tissues; (II) into regional lymph nodes by way of the lymphatic system; or (III) by a combination of extension and regional lymph nodes. Distant, has spread to parts of the body remote from the primary tumor either by direct extension or by discontinuous metastasis. IQR, interquartile range.

Table 2 Univariate Cox regression analysis of prognostic factors for cancer specific survival in ACB

Variable	Level	HR	95% CI	P value
Age at diagnosis (years)	65 (55 to 75)	1.02	1.01–1.03	<0.0001***
Sex				
Male	787 (64.19)	Reference		
Female	439 (35.81)	1.27	1.07–1.51	0.0068**
Race				
white	974 (79.45)	Reference		
black	166 (13.54)	1.21	0.96–1.53	0.101
other	86 (7.01)	0.91	0.65–1.29	0.6102
Primary site				
Urachus	151 (12.32)	Reference		
Non-urachus	1,075 (87.68)	2.17	1.58–2.99	<0.0001***
Grade				
Well differentiated, Grade I	117 (9.54)	Reference		
Moderately differentiated, Grade II	397 (32.38)	1.97	1.29–2.99	0.0016**
Poorly differentiated, Grade III	524 (42.74)	3.64	2.43–5.44	<0.0001***
Undifferentiated, anaplastic, Grade IV	188 (15.33)	2.90	1.87–4.52	<0.0001***
Histologic type				
Adenocarcinoma NOS	664 (54.16)	Reference		
Mucinous adenocarcinoma	243 (19.82)	0.95	0.75–1.19	0.6277
Signet ring cell adenocarcinoma	149 (12.15)	2.12	1.68–2.68	<0.0001***
Other adenocarcinoma subtypes	170 (13.87)	0.98	0.75–1.28	0.8662
SEER historic stage A				
Localized	344 (28.06)	Reference		
Regional	882 (71.94)	2.13	1.71–2.64	<0.0001***
Radiation				
No/unknow	145 (11.83)	Reference		
Yes	1,081 (88.17)	1.74	1.38–2.18	<0.0001***
Chemotherapy				
No/unknow	250 (20.39)	Reference		
Yes	976 (79.61)	1.56	1.28–1.90	<0.0001***
Surgery				
No cancer-direct surgery	39 (3.18)	Reference		
Transurethral resection	452 (36.87)	0.28	0.19–0.40	<0.0001***
Partial cystectomy	317 (25.86)	0.13	0.09–0.20	<0.0001***
Cystectomy	376 (30.67)	0.28	0.19–0.41	<0.0001***
Other surgery type	42 (3.43)	0.23	0.12–0.42	<0.0001***

Data are presented as median (IQR) or n (%). **, P<0.01; ***, P<0.001. ACB, adenocarcinoma of the bladder; CI, confidence interval; HR, hazard ratio.

Table 3 Multivariate Cox regression analysis of prognostic factors for cancer specific survival in ACB

Variable	Level	HR	95% CI	P value
Age at diagnosis (years)	65 (55 to 75)	1.02	1.01–1.03	<0.0001***
Sex				
Male	787 (64.19)	Reference		
Female	439 (35.81)	1.17	0.89–1.82	0.0905
Primary site				
Urachus	151 (12.32)	Reference		
Non-urachus	1,075 (87.68)	1.27	0.89–1.82	0.1839
Grade				
Well differentiated; Grade I	117 (9.54)	Reference		
Moderately differentiated; Grade II	397 (32.38)	1.86	1.21–2.87	0.0047**
Poorly differentiated; Grade III	524 (42.74)	2.53	1.65–3.87	<0.0001***
Undifferentiated; anaplastic; Grade IV	188 (15.33)	2.01	1.26–3.20	0.0035**
Histologic type				
Adenocarcinoma NOS	664 (54.16)	Reference		
Mucinous adenocarcinoma	243 (19.82)	1.36	1.06–1.73	0.0138*
Signet ring cell adenocarcinoma	149 (12.15)	1.80	1.39–2.33	<0.0001***
Other adenocarcinoma subtypes	170 (13.87)	0.96	0.73–1.27	0.7817
SEER historic stage A				
Localized	344 (28.06)	Reference		
Regional	882 (71.94)	2.59	2.02–3.32	<0.0001***
Radiation				
No/unknow	145 (11.83)	Reference		
Yes	1,081 (88.17)	1.07	0.83–1.38	0.6124
Chemotherapy				
No/unknow	250 (20.39)	Reference		
Yes	976 (79.61)	1.20	0.96–1.50	0.1139
Surgery				
No cancer-direct surgery	39 (3.18)	Reference		
Transurethral resection	452 (36.87)	0.38	0.25–0.56	<0.0001***
Partial cystectomy	317 (25.86)	0.15	0.10–0.24	<0.0001***
Cystectomy	376 (30.67)	0.24	0.16–0.36	<0.0001***
Other surgery type	42 (3.43)	0.33	0.17–0.62	0.0006***

Data are presented as median (IQR) or n (%). *, P<0.05; **, P<0.01; ***, P<0.001. Multivariable Cox regression hazards models were also adjusted for diagnosis year and race. ACB, adenocarcinoma of the bladder; CI, confidence interval; HR, hazard ratio.

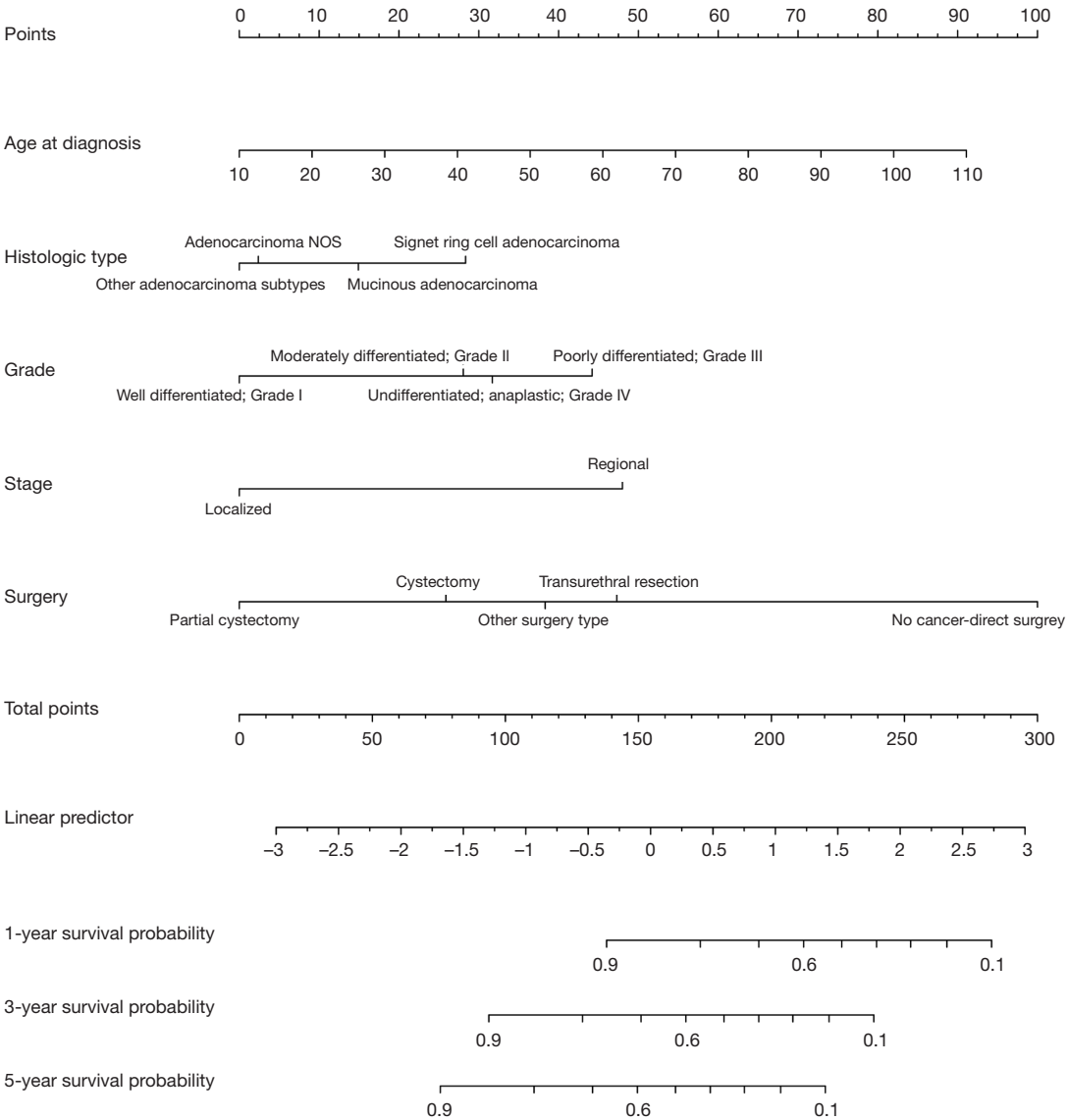

Figure 2 Nomogram predicting 1-, 3- and 5-year CSS of patients with primary adenocarcinoma of the bladder. CSS, cancer-specific survival.

Harrel's C indices for CSS were 0.729 (95% CI, 0.707–0.751) in the training cohort and 0.716 (95% CI, 0.678–0.754) in the validation cohort. The AUC values were 0.769, 0.735 and 0.724 for 1, 3 and 5-year CSS in the training cohort, and 0.738, 0.727 and 0.713 for 1, 3 and 5-year in the validation cohort, respectively. These values indicated that the nomogram had good discriminative capability, as shown in *Figure 3*. Calibration plots indicated that the predicted 1, 3 and 5-year CSS rates were close to actual observations, as shown in *Figure 4*.

Discussion

Primary adenocarcinoma of the urinary bladder (ACB) is a rare malignant tumor with a wide range of clinical outcomes. Accurate prediction of disease prognosis plays an important role in disease management. Nomograms are considered reliable visualization models and have been widely used to predict individual risks of particular events, such as metastatic progression, survival and recurrence *etc*. (10).

In the present study, using data from a large, nationwide, population-based database, independent prognostic factors

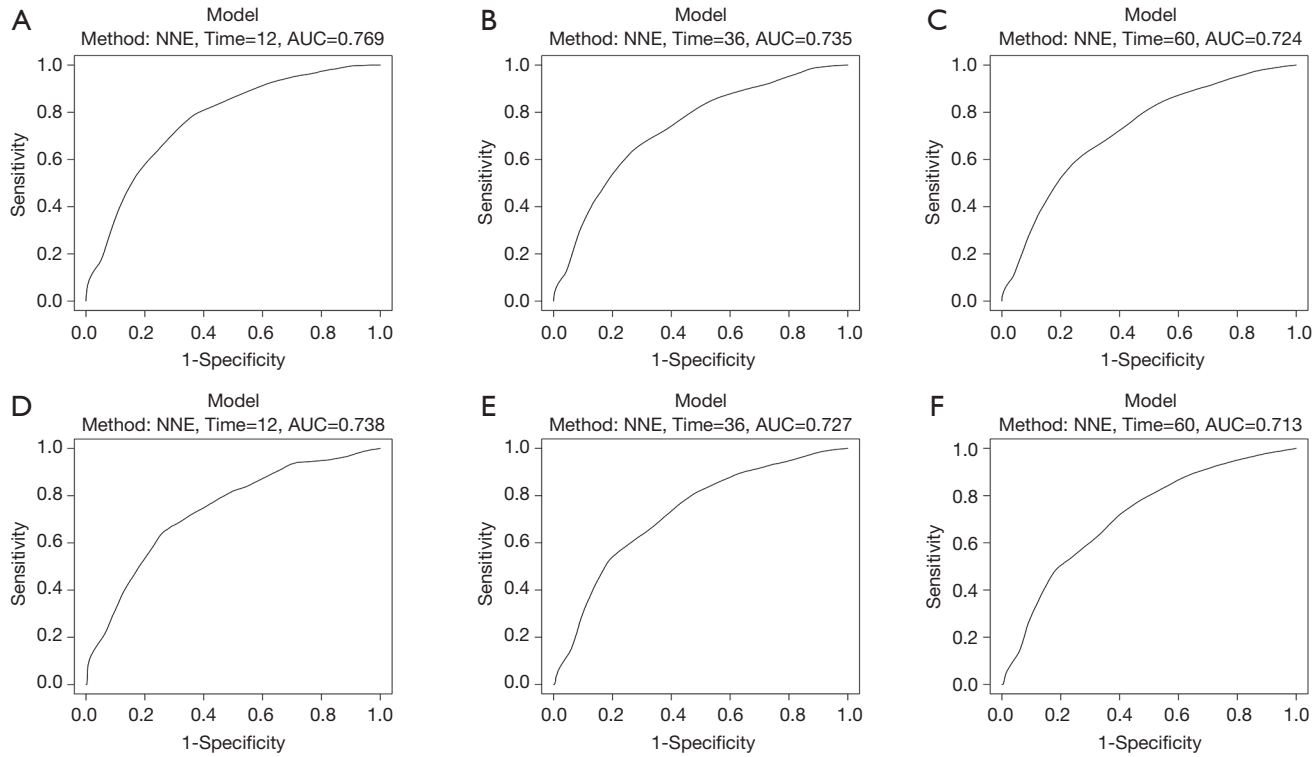

Figure 3 ROC curves. The ability of the Nomogram to be measured by the AUC. (A) 1-year, (B) 3-year and (C) 5-year ROC curves in the training cohort; (D) 1-year, (E) 3-year and (F) 5-year ROC curves in the validation cohort. ROC, receiver operating characteristics curve; AUC, the area under the receiver operating characteristics curve.

were identified for patients with NMACB and thus a nomogram was established to predict personalized CSS. The nomogram used the following prognostic factors previously demonstrated to be associated with survival of ACB patients: age at diagnosis (16), histological type (17,18), grade (19), stage (16,19,20) and surgery (17,19).

Using these independent prognostic factors, we constructed a nomogram that combined treatment with particular clinical parameters. The nomogram demonstrated that age and surgery are the most important factors affecting prognosis, while histological subtypes have limited influence. One interesting finding was that patients with undifferentiated or anaplastic tumors had better survival outcomes than those with a poorly differentiated tumor grade.

Wright *et al*. (21) and Natale *et al*. (17) demonstrated that compared with patients with non-urachal tumors, individuals with urachal adenocarcinoma had better CSS, even if patients with urachal adenocarcinoma were more likely to have a higher tumor stage than those with non-urachal adenocarcinoma. The reported 5-year cancer specific survival rates were 48% and 35% for urachal and non-urachal adenocarcinoma, respectively (21). In the present study, primary tumor site was found not to be an independent prognostic factor. This inconsistency may be due to our focus on non-metastatic patients. An additional analysis was later performed that included metastatic patients, the results of which matched those observed in earlier studies (data not presented in the article) (17,21).

Surgery with or without adjuvant radiation or chemotherapy is the principal form of treatment for patients with ACB. The most commonly used surgical procedure is radical or partial cystectomy with or without node dissection (22). The role of chemotherapy and radiotherapy in primary adenocarcinoma of the bladder is controversial. No specific recommendations exist for the use or type of chemotherapy or radiotherapy (4,23). Szarvas *et al*. (24) and Tatli *et al*. (25) believed that chemotherapy regimens containing 5-FU can improve the prognosis of ACB, while others have indicated that radiotherapy, or neo-adjuvant

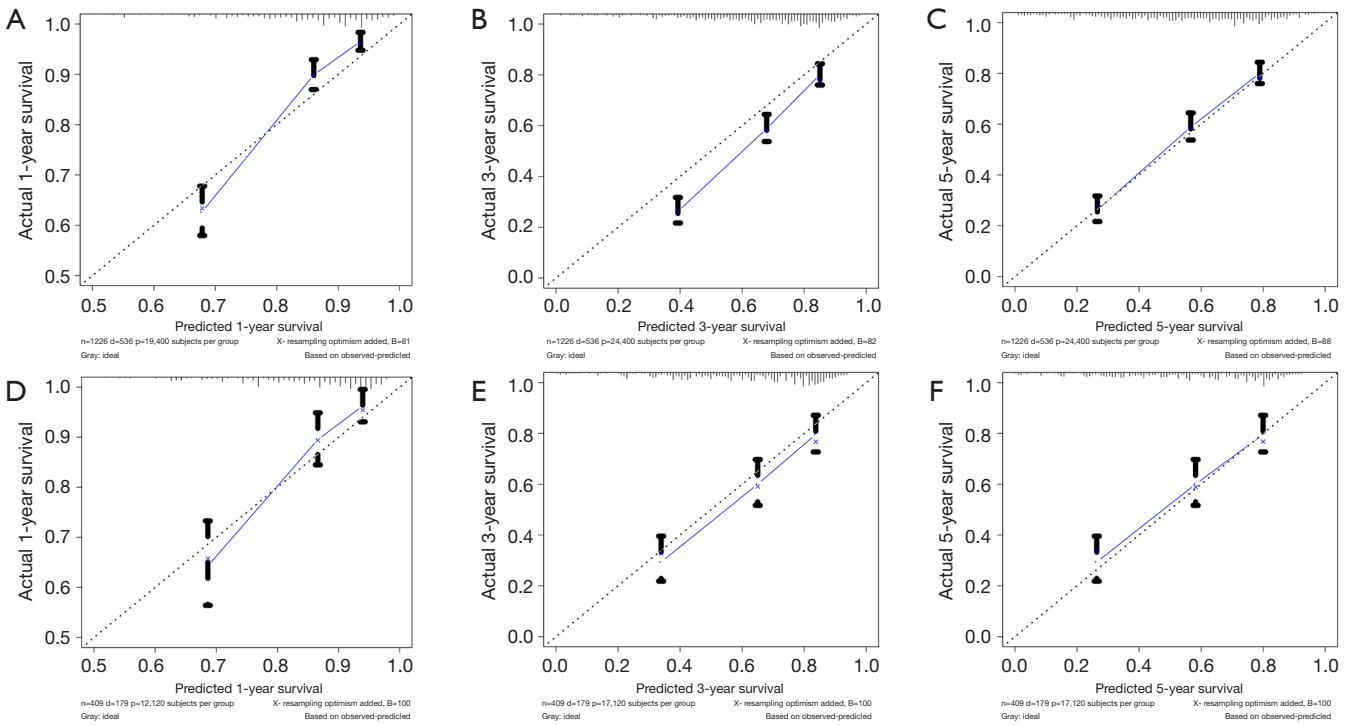

Figure 4 CSS calibration plots. The relationship between the predicted survival probabilities and actual values. (A) 1-year, (B) 3-year and (C) 5-year calibration plots in the training cohort; (D) 1-year, (E) 3-year and (F) 5-year calibration plots in the validation cohort. CSS, cancer-specific survival.

or adjuvant chemotherapy have not proved efficacious in adenocarcinoma of the bladder (22,26). Conversely, in the present study, chemotherapy or radiotherapy were found not to be independent prognostic factors.

Previous studies have shown that ACB patients have a higher risk of suffering from non-organ-confined disease (3). In this study, 1,156 (70.70%) patients had regional tumor stage. This may due to its intramural growth leading to late-onset hematuria, urinary tract irritation, or other symptoms, leading to a late stage when diagnosed (27).

Generally speaking, the TNM staging system is strongly related to survival outcomes. However, different survival outcomes were also observed among patients at the same stage. These differences may because of the lack of other prognostic factors such as age and grade, etc. For this reason, a more accurate method of predicting individualized survival outcomes in ACB patients is required and a nomogram is a suitable method for this purpose. In the present study, we developed a nomogram capable of predicting CSS in ACB. The AUC values for 1, 3, and 5-year CSS indicated good discriminative capability of the nomogram. Calibration plots indicated that the predicted 1, 3, and 5-year CSS rates were close to actual observations, confirming the validity and reliability of the nomogram.

We should note that there are a number of limitations to this study. Firstly, our research was retrospective which inevitably resulted in selection bias. Secondly, the distinction between urachal and non-urachal primary adenocarcinoma has always been difficult to ascertain, both in clinic and by pathology (20,28,29), resulting in potential misclassification bias. Consequently, we performed the analysis again after excluding the primary site of dome lesion. There was no significant change to the results (data not shown in the article). Thirdly, the SEER database lacks information about treatment strategies, family history, occupation, comorbid conditions, tumor markers or biochemical or immunological factors, which may cause confounding or selection bias. Fourthly, we used the SEER historic stage A (localized, regional, distant and unstaged) classification, which is not widely accepted, because it is the only staging system used continuously throughout the study period from 1973 to 2015. A nomogram based on the TNM staging system was also constructed (not shown in the article), but it did not significantly improve the performance of the prediction. Lastly, but not least, external validation and prospective clinical trials are essential to establish the

accuracy and clinical utility of the models. However, this is a real-world study based on a large sample, and these limitations do not weaken our conclusions.

Conclusions

In summary, age, grade, stage, histologic type, and surgery were found to be independent prognostic factors for CSS. We developed an effective nomogram for predicting 1, 3 and 5-year CSS of NMACB patients, which can help clinicians accurately predict risk of mortality and allow them to propose a personalized treatment modality.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/tcr-20-354

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-354). 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. This study was conducted in accordance with standard guidelines and was approved by the local Ethics Committee. We also got permission from the National Cancer Institute USA to access the SEER dataset for research purposes only (reference number: 18015-Nov2017). All the data from the SEER database were de-identified, and the extracted data did not require informed consent.

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