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Clinical-Bladder cancer

Development and external validation of a nomogram predicting prognosis of upper tract urothelial carcinoma after radical nephroureterectomy

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Abstract

Objective: To create multivariable models with readily available clinicopathologic variables for predicting the prognosis of upper tract urothelial carcinomas (UTUC).

Patients and methods: We retrospectively analyzed patients diagnosed as UTUC and underwent radical nephroureterectomy in 2 high volumes, tertiary care centers. A total of 445 patients and 227 patients met the inclusion criteria were included for constructing the prediction model and external validation, respectively. Univariable and multivariable Cox regression models were used to analyze independent risk factors, and nomogram and calibration curve were constructed by R project.

Results: The median follow-up for the development and external validation cohorts were 33.5 and 32.5 months, respectively. Multivariable analysis detected older age (≥65 years), with concurrent bladder cancer at diagnosis, with both ureter and renal pelvic tumor, lymphovascular invasion, urothelial carcinoma with divergent differentiation, higher pathological grade and stage, and positive lymph node were significantly associated with poorer outcome of UTUC. The *c*-index of the nomogram with these above-mentioned independent risk factors to predict the cancer specific survival was 0.74 (95% CI, 0.64–0.84) and 0.73 (95%CI, 0.59–0.87) for the development cohort and external validation cohort, respectively.

Conclusions: We developed and externally validated a novel and accurate nomogram with readily available clinicopathological information for predicting the cancer specific survival of UTUC. This nomogram could help clinicians stratify patients with UTUC into different risk groups with distinct prognosis by the total scores obtained from the prediction tool, thus facilitate decision-making and clinical trial designing.

Keywords: Nomogram; Predictors; Prognosis; Upper tract urothelial carcinoma

1. Introduction

Upper tract urothelial carcinoma (UTUC) is relatively uncommon and only accounts for about 5% to 10% of urothelial carcinomas. The gold standard for treatment of UTUC remains radical nephroureterectomy (RNU), since it eliminates the risk of ipsilateral recurrence [1]. The cisplatin-based chemotherapy is currently offered for

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nonorgan confined UTUC the same as those used for bladder cancer [1,2]. The ongoing POUT trial offers the opportunity to standardized postoperative management in this issue [3]. However, whether adjuvant chemotherapy could improve the prognosis of patients with nonorgan confined UTUC is still in controversy [2,4]. Meanwhile, the outcomes of UTUC have not significantly improved over the past 2 decades, thus the treatment protocol for UTUC needs a radical rethink [5,6].

With the advent of immunotherapy, the therapeutic paradigm of metastatic bladder cancer has been updated by including immunotherapy in the first-line treatment for cisplatin ineligible patients in the latest guidelines of European Association of Urology (http://uroweb.org/guideline). The US Food and Drug Administration recently approved 5 immune checkpoint inhibitors for treatment of urothelial carcinoma in both upper and lower urinary tract [7]. Therefore, the immunotherapy may also revolutionize the current management of advanced UTUC. Improved risk stratification and accurate prediction of postoperative prognosis of UTUC would be of great help to urologists and oncologists in daily practice, because they could identify patients with poorer outcome, decide follow-up scheduling, and choose multimodal treatment including administration of adjuvant chemotherapy or immunotherapy for patients with poorer prognosis [8,9]. Cha et al. [8] developed a prognostic model for prediction the prognosis of UTUC with the following variables: age, tumor architecture, stage, grade, lymph node status, carcinoma in situ (CIS) and lymphovascular invasion (LVI). Most of these predictors were obtained from pathologic evaluation, but several other clinicopathologic characteristics that were previous reported to be associated with adverse outcome of UTUC were not included in their analysis, such as urinary cytology, hydronephrosis, serum creatinine, and urothelial carcinoma with divergent histological differentiation [10–12].

Therefore, a novel prognostic model by taking these clinicopathologic variables into account is necessary to predict the prognosis of UTUC more accurately. The aim of this study was to identify independent clinicopathologic predictors of UTUC, then construct and externally validate a nomogram to facilitate the prediction of UTUC prognosis in clinical practice.

2. Patients and methods

From January 2008 to February 2018, 530 patients were diagnosed as UTUC in Changhai Hospital, a high volume, tertiary care center. Patients who received neoadjuvant or adjuvant chemotherapies, with incomplete perioperative or follow-up information, metastatic UTUC at diagnosis or had renal sparing treatment for UTUC were excluded. In total, 445 patients underwent RNU were then available for constructing the nomogram (development cohort). Meanwhile, a total of 227 patients from March 2005 to August 2015 with full data from the First Affiliated Hospital of Wenzhou Medical University were included for external validation (external validation cohort) [13]. The study protocol was designed in accordance with the ethical guidelines outlined in the Declaration of Helsinki and approved by the ethical board of Changhai Hospital and the ethical committee of The First Affiliated Hospital of Wenzhou Medical University.

The demographic and clinical parameters were retrospectively collected from medical records: age, sex, tumor location (ureter, renal pelvis, or both), bladder cancer history, examinations (urinary cytology, cystoscopy, serum creatinine, ultrasonography, computed tomography, or magnetic resonance imaging) and pathological outcomes (tumor histology, stage, grade, LVI, and lymph node). Hydronephrosis were classified as presence or absence by assessment of radiographic or ultrasonography reports. Tumor histology were classified as pure urothelial carcinoma or mixed type (with CIS, or sarcomatoid, adenocarcinoma, squamous differentiations, or other divergent differentiation). As concomitant CIS will not affect treatment strategies, the final pathological report from pathologists usually only included the invasive urothelial carcinoma without CIS. Therefore, there were few concomitant CIS reported in the present study, and CIS were included in the mixed type for analysis due to few samples. The pathological grade and stage of tumor were assessed by pathologists according to the 2004 WHO classification system and the tumor, node, metastasis (TNM) classification [1]. Follow-up of patients were performed by 2 experienced nurses according to the institutional protocols. Cystoscopy and urine cytology were performed every 3 months for 2 years after the surgery, every 6 months for the next 3 years, and annually thereafter. CT of abdomen was carried out every 6 months for 2 years after RUN, and annually thereafter. Postoperative imaging reports and laboratory data were provided by patients or family members who had access to the records of these materials.

Univariable and multivariable Cox proportional hazards models were performed in patients from development cohort. A backward step-down wald selection method was applied to select predictors (the entry and removal criteria were $P < 0.05$ and $P < 0.10$, respectively). A nomogram predicting the 3-year and 5-year cancer specific survival (CSS) was developed based on the results of multivariable Cox analyses by R 3.3.2 (http://www.r-project.org) with the Regression Modeling Strategies (RMS) packages. The CSS was defined as the length of time from the diagnosis of UTUC to the date of death from UTUC. The predictive accuracy of nomogram was quantified using Harrell's concordance index (*c*-index) using 1,000 bootstrap resamples [14,15]. The generalizability of the nomogram was examined in the external validation cohort. The performance of the nomogram on the development and external validation cohort was further explored by calibration plots.

Continuous parametric data were compared using *t* tests. Categorical and nonparametric variables were compared using Pearson chi-square test and Mann-Whitney *U* test, respectively. Statistical significance *P* value was set at 0.05 with 2 sides. The statistical tests were performed with the R software and SPSS 19.0 (IBM Inc.).

3. Results

In total, 445 and 227 patients from the development and external validation cohorts were included for analyses, and the demographic and clinicopathological characteristics of the 2 cohorts were shown in Table 1. The median follow-up for the development and external validation cohorts were 33.5 and 32.5 months, respectively. The 3-year and 5-year CSS were 78.7% and 70.9% for the development cohort, and 71.7% and 64.3% for the validation cohort. There were significant differences in terms of tumor location and pathological stage between the 2 cohorts, which represented common heterogeneities in difference centers and areas.

Detailed results of univariable and multivariable Cox regression analysis of predicative variables from development cohort were summarized in Table 2. Multivariable Cox analysis revealed independent inferior prognostic factors of UTUC included older age, with concurrent bladder cancer at diagnosis, with both ureter and renal pelvic tumor, higher pathological grade and stage, LVI, mixed type of histology and positive lymph node.

Table 1
Patient characteristics.

Variables	Development cohort ($n = 445$)	External validation cohort ($n = 227$)	*P* value
Age, mean(SD)	66.3 ± 10.6	67.4 ± 10.27	0.18
Gender, male/female	293/152	165/62	0.47
Median follow-up (IQR)	33.5 (16.9–57.4)	32.5 (14.5–58.9)	0.63
Tumor location			<0.01
Ureter	214	71	
Renal pelvis	194	146	
Ureter and renal pelvis	37	10	
Bladder cancer history			0.57
No	403	209	
Yes	42	18	
Concurrent bladder cancer			0.17
No	355	191	
Yes	90	36	
Urinary cytology			NA
Negative or NA	250	NA	
Positive	195	NA	
Hydronephrosis			0.93
No	151	78	
Yes	294	149	
Serum creatinine level			0.58
Normal	322	134	
Elevated	123	93	
Multifocality			0.24
No	339	183	
Yes	106	44	
Histology			0.05
Pure urothelial carcinoma	399	215	
Mixed type	46	12	
Lymphovascular invasion			0.44
No	374	187	
Yes	71	40	
Pathological stage			<0.01
Ta-1	215	68	
T2	82	81	
T3	112	50	
T4	36	28	
Pathological grade			0.27
Low	127	55	
High	318	172	
Lymph node			0.04
Negative or NA	420	204	
Positive	25	23	

IQR = interquartile range; NA = not available; SD = standard deviation.

Table 2
Univariable and multivariable Cox regression model for predicting cancer specific survival in development cohort.

	Univariable			Multivariable		
Variables	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (<65 y as referent)						
≥65 y	1.18	0.78–1.78	0.43	1.46	0.96–2.24	0.08
Gender (female as referent)						
Male	0.89	0.59–1.35	0.59	0.87	0.56–1.36	0.55
Tumor location (renal pelvis as referent)						
Ureter	1.53	0.98–2.39	0.06	1.59	0.99–2.56	0.06
Both	3.58	2.04–6.28	<0.01	3.16	1.76–5.68	<0.01
Bladder cancer history (no as referent)						
Yes	1.23	0.67–2.26	0.50	0.98	0.42–2.28	0.97
Concurrent bladder cancer (no as referent)						
Yes	1.20	0.76–1.91	0.43	1.52	0.95–2.46	0.08
Hydronephrosis (no as referent)						
Yes	1.32	0.85–2.03	0.22	1.15	0.69–1.93	0.60
Serum creatinine (normal as referent)						
Elevated	1.68	0.89–3.18	0.11	0.79	0.49–1.28	0.34
Urine cytology (negative or NA as referent)						
Positive	1.29	0.87–1.92	0.21	1.31	0.87–1.98	0.20
Multifocality (no as referent)						
Yes	1.30	0.84–2.01	0.23	1.06	0.66–1.71	0.80
Histology (pure urothelial as referent)						
Mixed type	1.73	1.00–3.00	0.05	1.65	0.94–2.90	0.08
Lymphovascular invasion (no as referent)						
Yes	1.85	1.15–2.97	0.01	1.83	1.18–3.17	0.01
Pathological stage (Ta as referent)						
T1	1.49	0.68–3.30	0.32	1.33	0.58–3.04	0.50
T2	2.05	0.91–4.65	0.08	1.53	0.63–3.72	0.35
T3	4.83	2.35–9.91	<0.01	3.24	1.48–7.80	<0.01
T4	4.53	1.97–10.96	<0.01	2.62	1.01–6.82	0.05
Pathological grade (low as referent)						
High	2.36	1.42–3.95	<0.01	1.64	0.93–2.90	0.09
Lymph node (negative or NA as referent)						
Positive	4.58	2.59–8.10	<0.01	2.20	1.17–4.11	0.01

CI = confidence interval; HR = hazard ratio; NA = not available.

The resulting coefficients of independent predictors from the multivariable Cox regression model were used to establish the nomogram for CSS (Fig. 1A). Each subtype of the independent factors was assigned a score, and the total score projected to the probability of the outcomes. In the development cohort, the nomogram for the CSS had a bootstrap-corrected *c*-index of 0.74 (95% CI, 0.64–0.84). In the external validation cohort, the *c*-index was 0.73 (95%CI, 0.59–0.87). As shown in the calibration plots (Fig 1B and C), the nomogram had fair agreements between the prediction and actual observation in the development cohort, and slightly underestimated the actual probability in the external validation cohort. We further classified the patients into 3 different risk groups according to the nomogram generated scores, and the cutoff values were depended on the interquartile scores. As shown in Fig. 2, each risk group represented a distinct prognosis.

4. Discussion

Improved risk stratification and prediction of postoperative prognosis are important to guide patient counseling, administration of adjuvant therapies, surveillance scheduling, and design of clinical trials [8]. Currently, the EORTC scoring system has been widely used for predicting the recurrence and progression of nonmuscle invasive bladder cancer, and stratified bladder cancer into different risk groups [16,17]. More recently, comprehensive molecular characterization identified 5 expression subtypes of muscle invasive bladder cancer that may stratify prognosis and response to different treatments [18]. However, the UTUC remains an understudied malignancy due to its low incidence, and the management of UTUC is mostly based on the data extrapolation from bladder cancer and the prognosis prediction tools of UTUC are few [7].

Several studies have investigated clinical and pathologic variables on predicting the UTUC prognosis. Jeldres et al.[19] developed a nomogram including age, pT and pN stages combined with tumor grade for predicting the CSS of UTUC with an accuracy of 75.4%. Cha et al. [8] further incorporated LVI, tumor architecture and CIS into the nomogram developed by Jeldres et al.[19], and enabled higher prediction accuracy of CSS with the *c*-index of 0.82. We tested this prognostic model

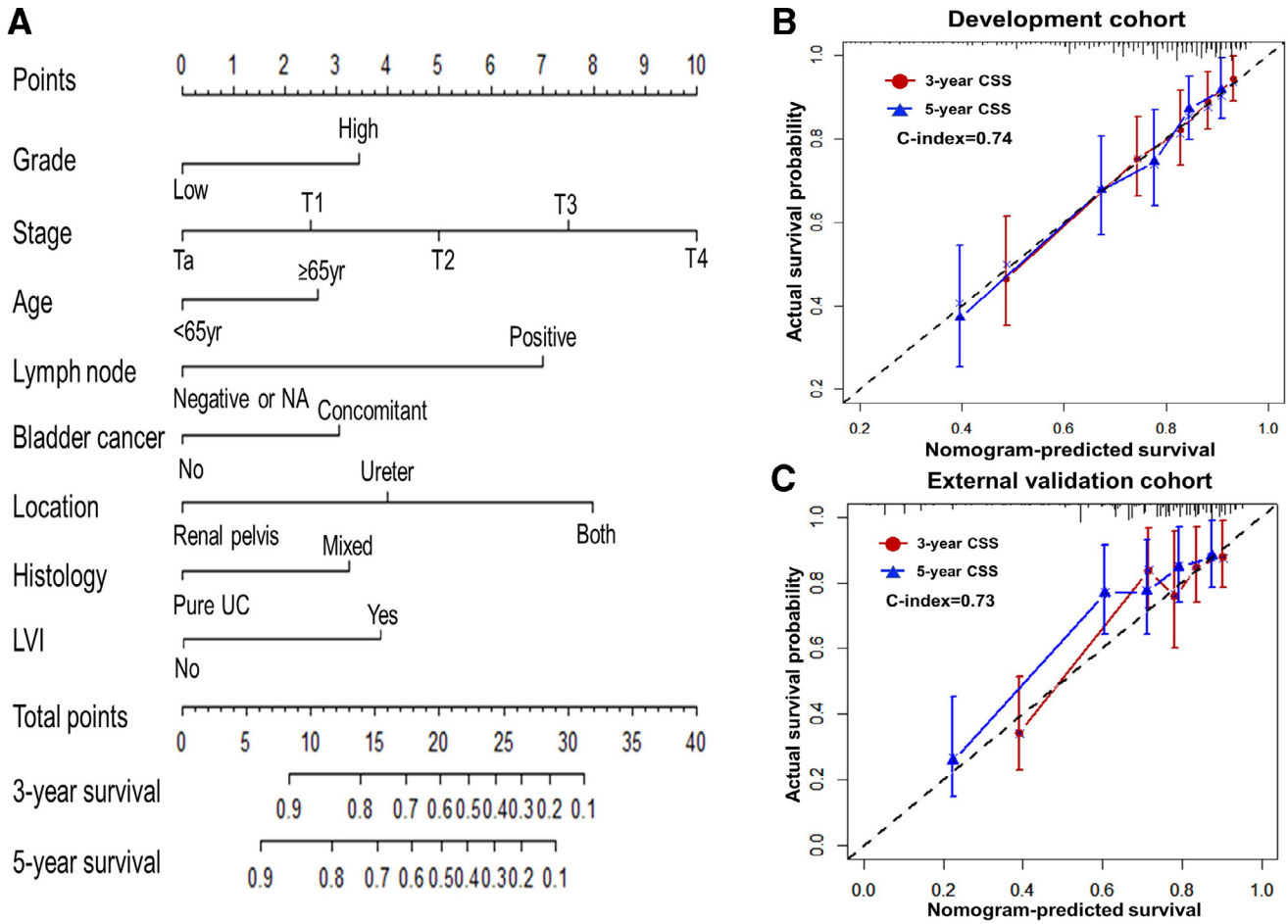

Fig. 1. (A) Nomogram for prediction of cancer specific survival of UTUC. (B) Calibration plot of cancer specific survival at 3 and 5 years in the development cohort. (C) Calibration plot of cancer specific survival at 3 and 5 years in the external validation cohort. LVI = lymphovascular invasion; UC = urothelial carcinoma; UTUC = upper tract urothelial carcinoma.

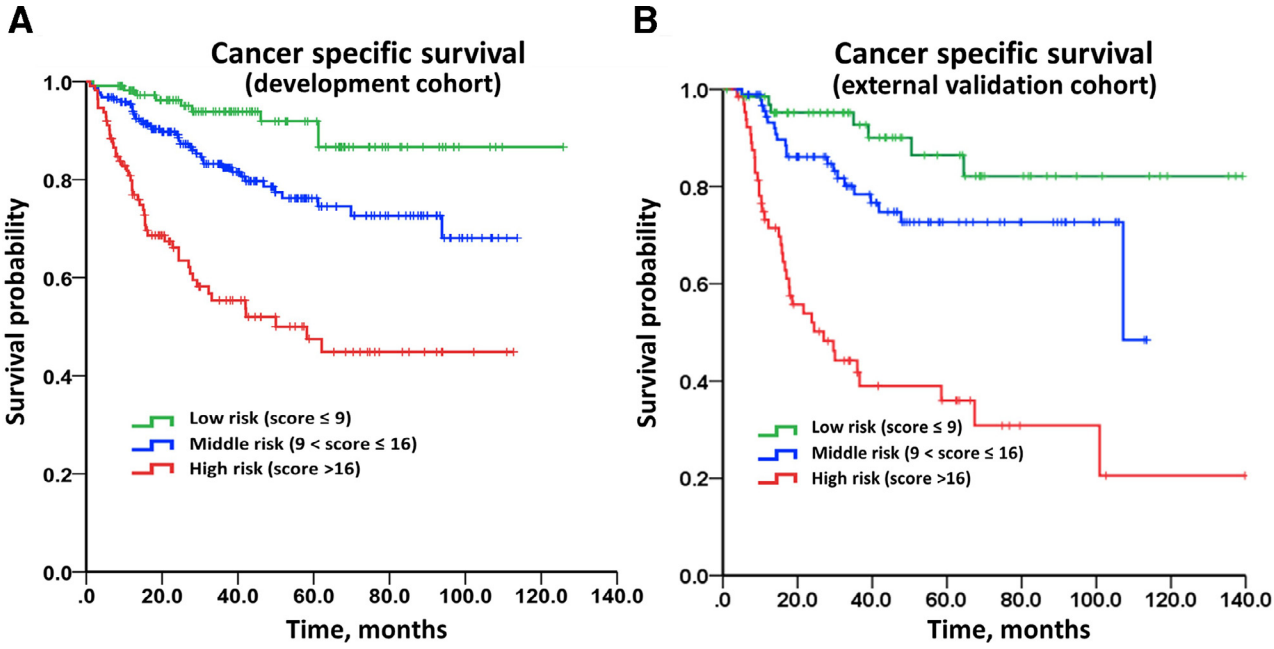

Fig. 2. (A) Kaplan-Meier curves of different risk groups stratified by the nomogram in the development cohort ($P < 0.001$); (B) Kaplan-Meier curves of different risk groups stratified by the nomogram in the external validation cohort ($P < 0.001$).

utilizing data from development cohort and validation cohort in the present study and come to *c*-index of 0.70 and 0.69, respectively. Nevertheless, tumor architecture was not included for analysis, because this information was not routinely reported in the pathological evaluation report or surgery record in our center. The inconsistent result may be also due to geographic or racial differences in UTUC, as the nomograms of Cha et al.[8] were derived from western regions and non-Asian populations. Singla et al. [20] suggested that there might be unique population-based predictors that profoundly influence the accuracy of nomograms in certain populations. Meanwhile, Chinese patients with UTUC appeared relatively healthier at diagnosis but more often with adverse pathological features [21]. The correlation between LVI, sessile tumor architecture, and tumor aggressiveness has been proved in multiple reports, and they could serve as independent predictors of recurrence free survival and CSS [8,22,23]. Although CIS has been revealed as an independent risk factor in bladder cancer, its role in UTUC was understudied and in controversy. Cao et al.[24] showed that concomitant CIS was an independent predictor of intravesical recurrence rather than CSS after RNU. Elawdy et al. [25] found CIS has no effect on survival of UTUC. Several other clinicopathological variables were also revealed as independent predictors of UTUC, such as C-reactive protein [26], neutrophil-to-lymphocytes ratio [27], HER2 overexpression [28], tumor location [29], and urothelial carcinoma with divergent differentiation [30].

In the present study, we developed a nomogram with significant predicators obtained from our readily available clinicopathological information. The nomogram enabled accurate prediction of CSS of UTUC with *c*-index of 0.74 and 0.73 in the development and external validation cohort, respectively. Except for the predictors identified by Cha et al. [8], this study further suggested that patients with both renal pelvic and ureteral cancer, urothelial carcinoma with divergent differentiation histology and concurrent bladder cancer might have poorer outcome. Incorporating these 3 variables further improved the prediction accuracy of prognostic model developed by Cha et al. [8]. Divergent differentiation of urothelial carcinoma, e.g., squamous, sarcomatoid, glandular differentiation, were indicative of aggressive tumor biology, and had been shown correlated with worse postoperative outcomes in multiple reports [12,30–32]. However, the impact of tumor location of UTUC on the prognosis is in controversy [33,34]. Wu et al. [29] performed a meta-analysis including 12,094 patients with UTUC from 17 studies, and demonstrated that ureteral tumors had worse CSS than renal pelvic tumors. Meanwhile, patients with urothelial carcinoma involving both renal pelvis and ureter had the worst outcome [7,29]. Patients with tumors in ureter as well as renal pelvis, or with concurrent bladder cancer implicated that they were likely remained asymptomatic for a longer time or presented themselves late at hospital after first gross hematuria. It has been shown that delay from diagnosis to RNU may impose patients with UTUC with worse outcome [35,36].

We stratified patients into different risk groups with distinct prognosis by the total scores obtained from nomogram. This may will help clinicians to determine postoperative follow-up strategies and adjuvant treatment based on the stratified risks of patients. Currently, the cisplatin-based adjuvant chemotherapy used for UTUC are the same as those offered for bladder cancer, and the ongoing POUT trial offers the opportunity to standardized postoperative management in this issue [3]. However, cisplatin-based regimens were not safe for patients with declined renal function after RNU, and have led to contradictory results in terms of overall survival [2,4]. Meanwhile, there is a large ongoing multicenter prospective trials (NCT02412670) exploring the role of neoadjuvant chemotherapy in UTUC. Immune checkpoint inhibitors have shed light on the treatment of urothelial carcinoma recently [37–39]. Patients stratified as high risk with poor outcome can receive immune checkpoint inhibitors as adjuvant therapy and probably benefit from immunotherapy. Thus, more accurate risk stratification of UTUC may help clinicians in counseling, treatment planning and clinical trial designing [7,8]. Robertson et al. [18] proposed that muscle invasive bladder cancer with luminal-infiltrated type and basal/squamous type may benefit from immunotherapy. However, few studies focused on comprehensive molecular classification of UTUC and their response to therapies. Incorporating novel molecular biomarkers into risk assessment tools may further improve the accuracy of prognostication of UTUC and predict the response to adjuvant therapies, thereby potentially improving their outcomes. Furthermore, Singla et al. [20] suggested that there may be unique population-based markers that suitable for certain populations, and population differences should be considered when applying predictive tools in clinical practice.

Several limitations of the current study should be noted. First, the present study is a retrospective cohort study, and the intrinsic biases must be acknowledged. For example, some variables of interest, e.g., tumor architecture, were not available for most of patients in the medical records. Second, patients underwent RNU by multiple surgeons in this study, and the criteria of performing lymphadenectomy varied among different surgeons. Third, central pathological review for UTUC specimens was neither performed in development nor validation cohort. However, pathological evaluation of each specimen was performed at least by 2 experienced specialized genitourinary cancer pathologists in daily clinical practice. Fourth, small number of patients were included in this study with relative shorter follow-up period compared to previous studies both in development and validation cohort. Fifth, the present study excluded patients receiving neoadjuvant or adjuvant chemotherapy, this may further introduce selection bias in this setting.

5. Conclusions

The present study developed and externally validated a novel and accurate nomogram for predicting the CSS using readily available clinicopathological information. This

nomogram could help clinicians stratify patients with UTUC into different risk groups with distinct prognosis by the total scores obtained from the prediction tool, thus facilitate decision-making and clinical trial designing.

Conflict of interest

None declared.

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