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Nomogram for predicting cancer-specific survival of patients with clear-cell renal cell carcinoma: a SEER-based population study

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Abstract. This study was aimed to develop a nomogram for predicting the cancer-specific survival (CSS) of patients with clear-cell renal cell carcinoma (ccRCC). Based on the Surveillance, Epidemiology, and End Results (SEER) database, 24,477 patients diagnosed with ccRCC between 2010 and 2015 were collected. They were randomly divided into a training cohort (n = 17,133) and a validation cohort (n = 7,344). Univariate and multivariate Cox regression analyses were performed in the training cohort to identify independent prognostic factors for construction of nomogram. Then, the nomogram was used to predict the 3- and 5-year CSS. The performance of nomogram was evaluated by using concordance index (C-index), net reclassification improvement (NRI), integrated discrimination improvement (IDI), calibration curve, and decision curve analysis (DCA). Moreover, the nomogram and tumor node metastasis (TNM) staging system (AJCC 7th edition) were compared. Eleven variables were screened to develop the nomogram. The area under the receiver operating characteristic (ROC) curve (AUC) and the calibration plots indicated satisfactory ability of the nomogram. Compared with the AJCC 7th edition of TNM stage, C-index, NRI, and IDI showed that the nomogram had improved performance. Furthermore, the 3- and 5-year DCA curves of nomogram yielded more net benefits than the AJCC 7th edition of TNM stage in both the training and validation sets. We developed and validated a nomogram for predicting the CSS of patients with ccRCC, which was more precise than the AJCC 7th edition of TNM staging system.

Key words: Clear-cell renal cell carcinoma — Cancer-specific survival — Nomogram — SEER database — AJCC 7th edition of TNM staging system

Introduction

Renal cell carcinoma (RCC) is a common malignant tumor of the urinary system, second to prostate cancer and bladder cancer. In recent years, its incidence has continued to rise, accounting for 3% of all newly diagnosed cancer cases (Siegel et al. 2020). Clear-cell renal cell carcinoma (ccRCC) is the most common subtypes of RCC and comprises approximately 80–90% of RCC-related deaths (Linehan et al. 2019). The ccRCC usually does not present any early clinical symptoms and about 30% of patients are already in a metastatic state at the time of diagnosis (Lin et al. 2020). Despite surgery provides long-term survival opportunities for patients with ccRCC, 30–40% patients undergone surgery are still found to have metastatic recurrence during follow-up (Ghatalia et al. 2019). In addition, ccRCC is refractory to chemotherapy and radiation (Tumkur et al.

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2021). Hence, the prognosis of the patients with advanced and metastatic cancers is extremely poor. Taken together, it is necessary to establish an effective model to predict the prognosis of patients with ccRCC, which may assist clinicians to perform personalized survival predictions and risk identification.

The American Joint Committee on Cancer (AJCC) staging system is a classification system that describes the course of cancer progression (Meng et al. 2017). AJCC-based tumor node metastasis (TNM) stage is generally considered to be the most powerful prognostic indicator for ccRCC, which is also the most commonly used tool in clinical practice. It is both important to predict the prognosis of ccRCC and propose a reasonable treatment plan for clinicians. However, due to the impact of prognostic diversity and genetic heterogeneity, it has become a challenge by using a single parameter to predict the overall survival (OS) of patients with ccRCC (Sankin et al. 2014). Despite several nomograms have been developed for predicting the prognosis of patients with ccRCC (Zhang et al. 2018; Peng et al. 2020; Wu Z et al. 2020), there is still a lack of models for predicting the cancer-specific survival (CSS) of ccRCC. Moreover, TNM stage system only considered the tumor invasion range (T stage), lymph node involvement (N stage) and tumor metastasis (M), and other prognostic factors such as tumor characteristics and treatment-related factors may be neglected. Therefore, a comprehensive prognostic model containing the complete clinicopathological and demographic variables is needed to be constructed.

Nomogram is a reliable and convenient tool for evaluating the prognosis of tumors, which has been widely used as a predictor for oncology (Iasonos et al. 2008; Chen et al. 2020). In this study, a cohort of patients with ccRCC was collected from the Surveillance, Epidemiology, and End Results (SEER) database. The univariate and multivariate Cox regression analyses were used to select significant prognostic factors, and then these factors were utilized to construct a nomogram for predicting the CSS rates of patients with ccRCC.

Materials and Methods

Study population

The clinical information of patients with ccRCC diagnosed between 2010 and 2015 was collected from the SEER database (https://seer.cancer.gov/, latest version). The inclusion criteria were as follows: (1) patients were confirmed with ccRCC (histological type code 8312/3) according to the International Classification of Diseases-Oncology (third edition) or WHO classification (8^{th} edition); (2) patients were diagnosed as ccRCC with histological confirmation; (3) patients with clear survival status and cause of death (thyroid carcinoma); and (4) patients diagnosed at 19 to 85 years old. The excluded criteria were as follows: (1) patients with incomplete information; (2) patients with unclear survival time; and (3) patients diagnosed by autopsy or death certificate.

Collection of clinical information

Nineteen clinical variables of each case were collected from SEER database, including five categories: baseline information (age, gender, race, marital status, insurance state, and CSS time), tumor characteristics (grade, size, site, TNM stage, and Mayo Clinic stage), metastases states (lymph node, bone, brain, liver, and lung), surgery status, and adjuvant therapy (radiation or chemotherapy). In this study, the clinical outcome was defined as cancer-specific death.

Development and validation of nomogram

After screening eligible cases, total patients were randomly assigned to a validation cohort and a training cohort with a ratio of 3:7 using the R function "create Data Partition". Among these, the training set was used to develop nomogram and the validation set was applied to verify the precision of established model. Univariate and multivariate Cox regression analyses were conducted to assess the association between clinical characteristics and CSS time, and the hazard ratios (HRs) and its 95% confidence intervals (CIs) were calculated. Variable with p less than 0.05 was considered to be significantly associated with CSS time. Next, the variable with $p < 0.05$ in the multivariate analysis was selected to establish a nomogram model for predicting 3- and 5-year CSS rate of patients with ccRCC.

Moreover, the predicted performance of this nomogram was evaluated by using the training and validation sets. First, the receiver operating characteristic (ROC) curves were generated, followed by calculation of corresponding area under the curve (AUC) values, which could reflect the predictive ability of model (Hanley et al. 1982). Notably, the AUC value > 0.7 was considered ideal (Wu J et al. 2020). Second, calibration curve was plotted to access the consistency between the the actual and predicted probability of 3- and 5-year CSS time. Meanwhile, the concordance index (C-index) was calculated through bootstrapping with 500 resamples (Royston et al. 2013) to estimate the predictive performance. Furthermore, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were used to compare the discriminative performance of the constructed nomogram and AJCC 7^{th} model (Pencina et al. 2011). As described previously (Vickers et al. 2006),

the net benefit of these two models was also estimated using decision curve analysis (DCA).

Statistical analysis

All data were statistically analyzed using SPSS (version 21.0, IBM Corp., Armonk, NY) and R software (version 3.5.2, http://www.r-project.org/). p values < 0.05 obtained *via* two-tailed test were regarded as significant difference.

Results

Clinical features of patients with ccRCC

According to the inclusion and exclusion criteria, 24,477 ccRCC patients were collected; among these, 17,133 cases were assigned in the training cohort and 7,344 cases were assigned in the validation cohort. The clinical characteristics of all patients are listed in Table 1. In the whole population, the median age at diagnosis was 60 (51–68) years. Of these patients, 20,952 patients were white ethnicity (85.6%), 15,144 patients were male (61.9%), and 16,171 patients were married (66.1%). Most of the patients had insurance (84.9%). More than half of the patients had stage II (53.4%), TNM stage I (65.5%), and localized stage (74.8%). The tumor size of 18,644 patients (76.2%) was less than 70 mm. With regard to treatment, almost all patients were undergone surgery (99.9%) and only a small number of patients were treated with radiotherapy (1.8%) and chemotherapy (4.6%). Most patients did not present metastatic, including lymph nodes (97.6%), bone (98.3%), brain (99.5%), liver (99.4%), and lung (96.2%). The median of CSS time was 27 months (range 11 to 47 months). Meanwhile, there were 1,610 patients with ccRCC-specific death, accounting for 6.6% of all cases. No significant difference in all clinical variables was observed between the training and validation cohorts (all $p > 0.05$).

Prognostic factors for CSS time in the training cohort

Based on the 19 variables, a series of Cox regression analysis was performed to identify the variables that significantly related to CSS time. After univariate and multivariate Cox analyses, 11 factors included age, marital status, tumor size, grade, TNM stage, surgery treatment, radiation, lymph node metastasis, liver metastasis, lung metastasis, and bone metastases were observably associated with CSS time (all $p < 0.01$, Table 2).

Table 1. Clinical characteristics of patients included in this analysis

	Whole population (n = 24477) No. (%)	Training cohort (n = 17133) No. (%)	Validation cohort (n = 7344) No. (%)	p
Age at diagnosis (years)	60 (51–68)	60 (51–68)	60 (51–68)	0.062
Sex				0.145
Male	15144 (61.9)	10651 (62.2)	4493 (61.2)	
Female	9333 (38.1)	6482 (37.8)	2851 (38.8)	
Race				0.793
White	20952 (85.6)	14666 (85.6)	6286 (85.6)	
Black	1675 (6.8)	1163 (6.8)	512 (7.0)	
Other[a]	1850 (7.6)	1304 (7.6)	546 (7.4)	
Marital status				0.594
Married	16171 (66.1)	11301 (66.0)	4870 (66.3)	
Unmarrie[d]b	8306 (33.9)	5832 (34.0)	2474 (33.7)	
Insurance recode				0.383
Uninsurance	775 (3.2)	584 (3.4)	191 (2.6)	
Insurance	20773 (84.9)	14481 (84.5)	6292 (85.7)	
Any medical	2929 (12.0)	2068 (12.1)	861 (11.7)	
Grade				0.950
I	2549 (10.4)	1797 (10.5)	752 (10.2)	
II	13063 (53.4)	9133 (53.3)	3930 (53.5)	
III	7117 (29.1)	4979 (29.1)	2138 (29.1)	
IV	1748 (7.1)	1224 (7.1)	524 (7.1)	

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Table 1. (continued)

	Whole population (n = 24477) No. (%)	Training cohort (n = 17133) No. (%)	Validation cohort (n = 7344) No. (%)	p
Tumor size				0.798
≤70 mm	18644 (76.2)	13033 (76.1)	5611 (76.4)	
70–100 mm	3626 (14.8)	2555 (14.9)	1071 (14.6)	
>100 mm	2207 (9.0)	1545 (9.0)	662 (9.0)	
Site				0.656
Left	12052 (49.2)	8420 (49.1)	3632 (49.5)	
Right	12425 (50.8)	8713 (50.9)	3712(50.5)	
TNM stage				0.588
I	16037 (65.5)	11188 (65.3)	4849 (66.0)	
II	2271 (9.3)	1612 (9.4)	659 (9.0)	
III	4497 (18.4)	3150 (18.4)	1347 (18.3)	
IV	1672 (6.8)	1183(6.9)	489 (6.7)	
Stage				0.891
Localized	18308 (74.8)	12800 (74.7)	5508 (75.0)	
Regional	4651 (19.0)	3267 (19.1)	1384 (18.8)	
Distant	1518 (6.2)	1066 (6.2)	452 (6.2)	
Surgery				0.827
Yes	24452 (99.9)	17116 (99.9)	7336 (99.9)	
No	25 (0.1)	17 (0.1)	8 (0.1)	
Radiotherapy				0.308
Yes	432 (1.8)	312 (1.8)	120 (1.6)	
None/Unknown	24045 (98.2)	16821 (98.2)	7224 (98.4)	
Chemotherapy				0.715
Yes	1115 (4.6)	775 (4.5)	340 (4.6)	
No	23362 (95.4)	16358 (95.5)	7004 (95.4)	
Lymph nodes metastasis				0.485
No	23886 (97.6)	16727 (97.6)	7159 (97.5)	
Yes	591 (2.4)	406 (2.4)	185 (2.5)	
Metastasis at bone				0.282
No	24057 (98.3)	16829 (98.2)	7228 (98.4)	
Yes	420 (1.7)	304 (1.8)	116 (1.6)	
Metastasis at brain				0.601
No	24359 (99.5)	17053 (99.5)	7306 (99.5)	
Yes	118 (0.5)	80 (0.5)	38 (0.5)	
Metastasis at liver				0.928
No	24332 (99.4)	17032 (99.4)	7300 (99.4)	
Yes	145 (0.6)	101 (0.6)	44(0.6)	
Metastasis at lung				0.920
No	23555 (96.2)	16489 (96.2)	7066 (96.2)	
Yes	922 (3.8)	644 (3.8)	278 (3.8)	
CSS (months)	27 (11–47)	27 (11–47)	28 (12–47)	0.710
Cancer-specific mortality	1610 (6.6)	1113 (6.5)	497 (6.8)	0.433

[a] American Indian, AK native, Asian and Pacific islander; [b] single, separated, divorced, widowed and unmarried or domestic partner; CSS, cancer-specific survival; p, Training cohort *vs.* Validation cohort.

Establishment and validation of the nomogram for ccRCC

The selected prognosis-related factors were utilized to establish a nomogram for predicting the 3- and 5-year CSS of patients with ccRCC (Fig. 1). This model revealed that TNM stage was the most important factor responsible for the CSS time, followed by age, grade, and surgical treatment.

Next, we validated the accuracy and predictive ability of this model by using the training and validation cohorts. As for the 3-year CSS time, in the training cohort, the AUC of the nomogram and AJCC 7th edition of TNM stage were 0.901 and 0.862 (Fig. 2A); in the validation cohort, the AUCs were 0.893 and 0.841, respectively (Fig. 2B). Meanwhile, AUC of the nomogram was higher than that of AJCC 7th edition of TNM stage in predicting the 5-year CSS time in both the training cohort (0.920 *vs.* 0.874, Fig. 2C) and validation cohort (0.906 *vs.* 0.846, Fig. 2D). Together, these findings suggested that the nomogram had better prediction accuracy for the 3- and 5-year CSS time compared to AJCC 7th edition of TNM stage. Calibration plots of the nomogram revealed that excellent consistency was observed both in the training and validation cohorts between predicted results and actual observations for 3-year (Fig. 3A, B) and 5-year CSS (Fig. 3C, D).

We also compared the difference in NRI, IDI, and C-index between the established model and AJCC 7th edition of TNM stage. The specific results are listed in Table 3. While using the nomogram in the training cohort, the NRI values for the 3- and 5-year CSS were 0.276 (95% CI = 0.214–0.328, $p < 0.001$) and 0.284 (95% CI = 0.230–0.352, $p < 0.001$), and the IDI values for the 3- and 5-year CSS were 0.060 (95% CI = 0.049–0.070, $p < 0.001$) and 0.052 (95% CI = 0.042–0.062, $p < 0.001$). These results were also observed in the validation cohort. In addition, the C-index for the nomogram was calculated to be 0.898 in the training set and 0.905 in the validation set, which were all higher than AJCC 7th edition of TNM stage in the same groups, respectively. Together, the constructed nomogram model had greater accuracy in predicting the CSS of patients with ccRCC than the AJCC 7th edition of TNM stage.

Furthermore, the clinical benefits of the nomogram and AJCC 7th edition of TNM stage were compared. DCA curves showed that despite the nomogram had several overlaps with AJCC 7th edition of TNM stage in both the training and validation cohorts, it still added more net benefits, indicating that the nomogram could better predict the 3 (Fig. 4A, B) and 5 years CSS (Fig. 4C, D).

Discussion

As the most common kidney malignancy in adults, clinical and pathological heterogeneity of metastatic RCC highly

Table 2. Univariate and multivariate Cox regression analysis of CSS rates in training cohort

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*p*	HR (95%CI)	*p*
Age at diagnosis	1.02 (1.02–1.03)	<0.001	1.02 (1.02–1.03)	<0.001
Marital status				
Married	Reference		Reference	
Unmarried	1.06 (0.94–1.20)	0.358	1.15 (1.02–1.30)	<0.01
Grade				
I	Reference		Reference	
II	2.44 (1.55–3.85)	<0.001	1.76 (1.11–2.79)	<0.01
III	9.78 (6.25–15.30)	<0.001	3.36 (2.13–5.32)	<0.001
IV	42.48 (27.10–66.60)	<0.001	6.63 (4.15–10.57)	<0.001
Tumor size				
≤70mm	Reference		Reference	
70–100mm	5.44 (4.69–6.30)	<0.001	1.46 (1.22–1.75)	<0.001
>100mm	11.71 (10.16–13.50)	<0.001	1.83 (1.53–2.19)	<0.001
TNM stage				
I	Reference		Reference	
II	4.17 (3.18–5.46)	<0.001	2.08 (1.52–2.86)	<0.001
III	9.26 (7.61–11.27)	<0.001	4.33 (3.45–5.44)	<0.001
IV	57.01 (47.32–68.67)	<0.001	10.26 (7.79–13.52)	<0.001

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Table 2. (continued)

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*p*	HR (95%CI)	*p*
Surgery				
Yes	Reference		Reference	
No	6.74 (2.80–16.22)	<0.001	5.00 (2.04–12.25)	<0.001
Radiation				
Yes	Reference		Reference	
None/unknown	0.07 (0.06–0.08)	<0.001	0.65 (0.53–0.80)	<0.001
Lymph nodes metastasis				
No	Reference		Reference	
Yes	14.55 (12.48–16.97)	<0.001	1.74 (1.47–2.06)	<0.001
Metastasis at bone				
No	Reference		Reference	
Yes	14.52 (12.29–17.17)	<0.001	1.77 (1.42–2.22)	<0.001
Metastasis at liver				
No	Reference		Reference	
Yes	16.38 (12.69–21.13)	<0.001	1.71 (1.31–2.23)	<0.001
Metastasis at lung				
No	Reference		Reference	
Yes	18.08 (15.88–20.58)	<0.001	1.62 (1.35–1.94)	<0.001
Sex			excluded	
Male	Reference			
Female	0.65 (0.58–0.75)	<0.001		
Race			excluded	
White	Reference			
Black	0.72 (0.55–0.95)	0.019		
Other	0.99 (0.79–1.24)	0.955		
Insurance recode			excluded	
Uninsurance	Reference			
Insurance	1.03 (0.74–1.43)	0.851		
Any medical	1.18 (0.82–1.69)	0.377		
Site			excluded	
Left – origin of primary	Reference			
Right – origin of primary	0.90 (0.80–1.02)	0.089		
Stage			excluded	
Localized	Reference			
Regional	7.07 (6.00–8.35)	<0.001		
Distant	42.63 (36.41–49.91)	<0.001		
Chemotherapy			excluded	
Yes	Reference			
No	0.08 (0.07–0.09)	<0.001		
Metastasis at brain			excluded	
No	Reference			
Yes	17.73 (13.30–23.64)	<0.001		

CSS, cancer-specific survival; HR, hazard ratio; TNM, tumor node metastasis.

influences the prognosis of patients with the cancer (Margulis et al. 2013). The clear cell subtype is the most aggressive subtype, accounting for 80% of all RCC cases (Delahunt et al. 2007). Unfortunately, there is still lack an accurate prognostic prediction tool for patients with ccRCC. Thus, our study aims to establish and evaluate a practical nomogram for predicting the CSS of patients with ccRCC based on the complete clinical characteristics. Result showed that 11 variables were selected by the multivariate Cox regression analysis and then merged into the nomogram model. Among these, TNM stage was the most significant factor responsible for CSS time, followed by age, grade, and surgical treatment. We observed that the nomogram showed good accuracy and discriminative ability in predicting 3- and 5-year CSS. Meanwhile, the prediction performance of the novel model was superior compared to the traditional AJCC 7th edition of TNM stage.

In the present study, we fully considered a range of clinical factors that might influence the prognosis of ccRCC. Univariate and multivariate Cox regression analyses revealed that prognostic factors such as age, marital status, tumor grade as well as size, TNM stage, surgery status, bone metastasis, lymph node metastases, lung metastasis, and liver metastasis were independent predictors for CSS in patients with ccRCC. Previous studies have highlighted the important role of TNM staging in the diagnosis and prognosis of ccRCC. TNM stage proved to be an independent CSS predictor for RCC *via* multivariate analysis (Neuzillet et al. 2011). In addition, Xu et al. (2020) suggested that genes related to the clinical TNM stage might provide guidance for early diagnosis and individualized therapy of patients with ccRCC. In addition, the prognostic value of other clinical characteristics has also been confirmed in other studies. For example, Wu et al. (Wu G et al. 2020) observed that age at diagnosis, grade, and stage were independent risk factors connected with the OS time of patients with ccRCC. Meanwhile, Zhang et al. (2018) suggested that clinicopathological parameters, such as marital status and surgical status, were significantly associated with the OS and CSS of patients with ccRCC; other study also indicated that unmarried patients

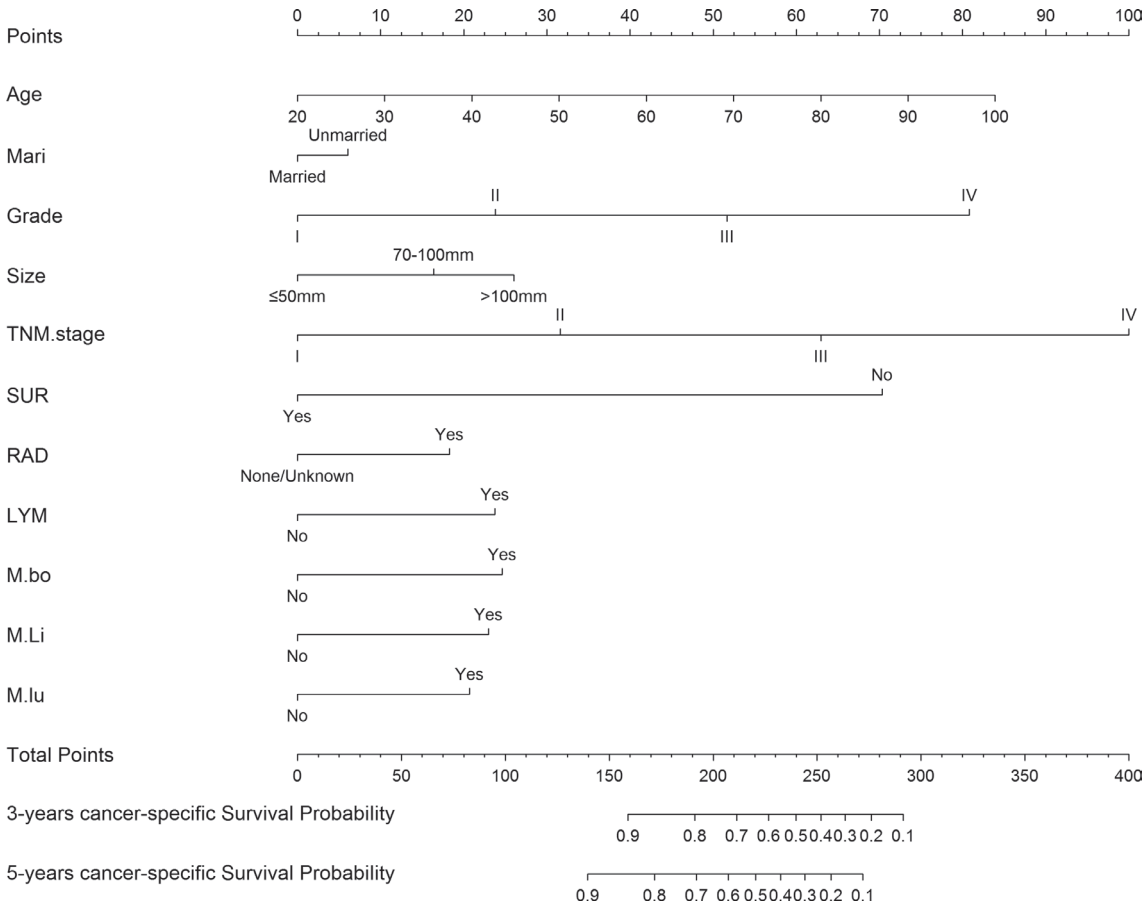

Figure 1. Nomogram for predicting the 3-year and 5-year cancer-specific survival (CSS) of patients with ccRCC. Mari, marital status; SUR, surgery; RAD, radiation; LYM, lymph nodes metastases; M.bo, metastases at bone; M.Li, metastases at liver; M.lu, metastases at lung.

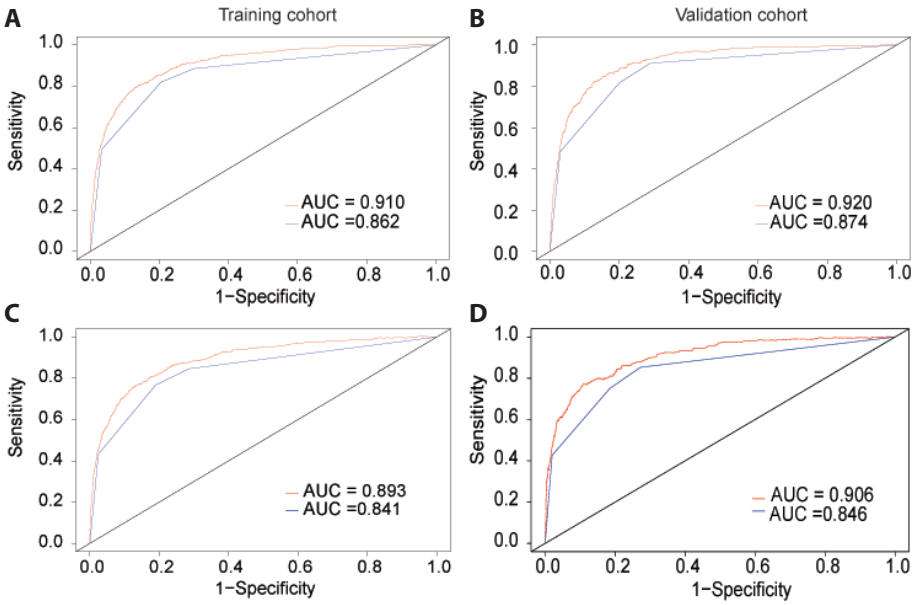

Figure 2. Receiver operating characteristic (ROC) curves of the nomogram in the training and validation cohorts. The 3-year CSS in the training (**A**) and validation sets (**B**). The 5-year CSS in the training (**C**) and validation sets (**D**). Red line: ROC of nomogram; blue line: ROC of TNM stage AJCC, 7th edition. (See online version for color figure.)

with ccRCC experienced worse survival than their married counterparts (Zhang et al. 2019), and these evidences further confirmed our findings. Interestingly, we revealed some metastases state, including bone, lymph node, lung, and liver, were responsible for the CSS of ccRCC. Evidences demonstrated that tumor size was positively associated with the risk of lymph node metastases in ccRCC (Zhi et al. 2020); in addition, age and tumor size were independent risk clinical indicators of brain metastasis in patients with RCC (Ke et al. 2020). However, there was no direct evidence that these metastases contributed to CSS of patients with ccRCC. Meanwhile, the patients with metastases accounted for a minority of included patients, a large-scale patient needed to be enrolled to confirm these findings.

These prognostic-related variables were used to generate a novel nomogram to predict the CSS time of ccRCC patients. Then, the precision and predictive ability of this model were adequate assessed in both training and validation cohorts by using the following indices: AUC, C-index, NRI, IDI, and DCA plot. AUC and C-index are typically

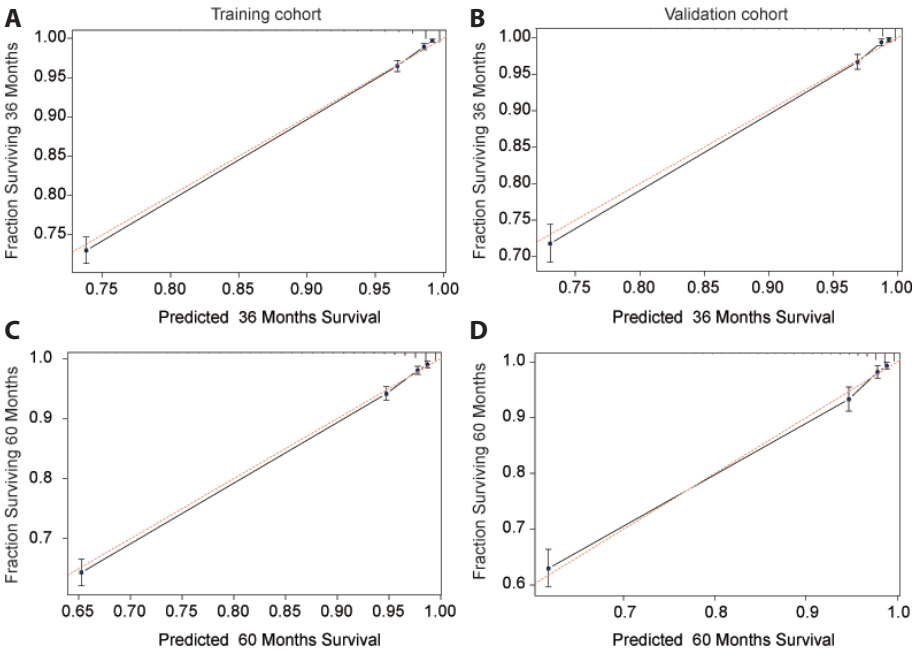

Figure 3. Calibration plots of the nomogram and AJCC 7th of TNM stage for prediction of CSS at 3 and 5 years. Calibration curve of 3-year CSS in the training (**A**) and validation sets (**B**). Calibration curve of 5-year CSS in the training set (**C**) and validation sets (**D**). X-axis is predicted probability based nomogram and y-axis is observed cumulative incidence.

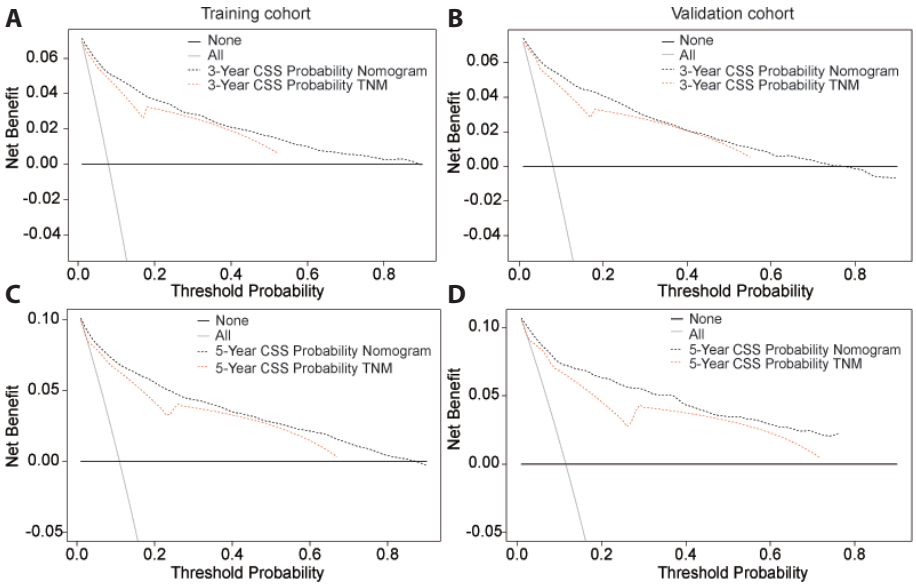

Figure 4. Decision curve analysis (DCA) of the nomogram and AJCC 7th of TNM stage for the survival prediction of patients with ccRCC. DCA of 3-year CSS in the training (**A**) and validation sets (**B**). DCA of 5-year CSS in the training (**C**) and validation sets (**D**).

utilized to assess the discriminative ability of models (Hanley et al. 1982; Pencina et al. 2015). Similarly, the NRI and IDI can also be applied to evaluate and quantify the risk prediction of the novel constructed models (Pencina et al. 2008). These results indicated that our model has better discriminative performance for predicting the 3-year and 5-year CSS of ccRCC than the AJCC 7th edition of staging system. Furthermore, DCA is an approach suitable for evaluating alternative diagnostic and prognostic strategies, which can be employed for assessing clinical effectiveness (Vickers and Elkin 2006). In this study, DCA curves indicated that the net benefit generated by our model was greater than the AJCC TNM staging system in both the training set and validation set.

Although some articles have constructed a nomogram predicting OS of patients with ccRCC (Wu X et al. 2020; Zhang et al. 2020), these models have defects more or less. For example, nomogram generated by Zhang et al. (2018) did not include radiotherapy, which has been linked to cancer resistant and has been shown to impact the prognosis of ccRCC (Qian et al. 2009). Moreover, the model constructed by Karakiewicz et al. (2007) lacked demographic variables of patients with ccRCC, which could affect the accuracy of the predictions. Thus, our study constructed a nomogram for predicting CSS of patients with ccRCC based on a large population and incorporating complete demographic variables. Our research has certain advantages. The constructed nomogram is more helpful for clinicians to predict the prog-

Table 3. Comparison of NRI, IDI, and C-index between nomogram and AJCC of TNM stage in ccRCC patients

Index	Training cohort			Validation cohort		
	Estimate	95%CI	*p*	Estimate	95%CI	*p*
NRI (*vs.* TNM stage)						
3-year CSS	0.276	0.214–0.328	<0.001	0.263	0.161–0.350	<0.001
5-year CSS	0.284	0.230–0.352	<0.001	0.339	0.234–0.408	<0.001
IDI (*vs.* TNM stage)						
3-year CSS	0.060	0.049–0.070	<0.001	0.046	0.031–0.060	<0.001
5-year CSS	0.052	0.042–0.062	<0.001	0.054	0.040–0.069	<0.001
C-index						
The nomogram	0.898	0.888–0.908		0.905	0.893–0.917	
TNM stage	0.856	0.845–0.867		0.862	0.845–0.879	
Change	0.042	0.027–0.057	<0.001	0.043	0.022–0.064	<0.001

AJCC, American Joint Committee on Cancer; ccRCC, clear-cell renal cell carcinoma; C-index, concordance index; CSS, cancer-specific survival; IDI, integrated discrimination improvement; NRI, net reclassification improvement; TNM, tumor node metastasis.

nosis of ccRCC patients than a single clinical parameter. In addition, the novel nomogram is mainly to predict the CSS of ccRCC patients, while other studies may focus more attention on OS. Importantly, we observed that our nomogram had improved discriminant power compared to AJCC 7th edition of TNM stage. However, some limitations still need to be acknowledged. First, clinical characteristics showed that the patients included in this analysis were mainly white, thus the obtained findings might not be applicable to other racial groups. Second, our study was retrospective; meanwhile, clinical information as well as follow-up data were extracted from the SEER database, so there was a certain inherent bias in this research. Third, the included variables were incomplete. For instance, the expression level of some key genes (VEGF, HIF-2α, and Ki-67) related to the pathogenesis of ccRCC (Fan et al. 2015; Ebru et al. 2017) were not considered in this analysis. Finally, although the nomogram fitted well, it had not been validated by additional external data and was devoid of prospective research.

Conclusion

In short, our study established and validated a nomogram to predict the CSS of patients with ccRCC based on the SEER population cohort. Eleven independent prognostic factors were eventually incorporated the nomogram; among these, TNM stage was the most significant factor responsible for CSS time, followed by age and grade. The nomogram showed improved performance in predicting 3- and 5-year CSS compared to the AJCC 7th TNM stage. This new nomogram may help to improve the predictive accuracy of survival outcomes, thereby assisting doctors to perform personalized survival prediction in patients with ccRCC.

Data Availability Statement. All data generated and analyzed in this study were available from the SEER database (https://seer.cancer.gov/).

Ethics approval and consent to participate. Not applicable. Our study was exempted from insitutional review board approval because of using the de-identified data in the SEER database.

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Conflict of interests. The authors declare that they have no competing interests.

Authors' contributions. JW carried out the Conception and design of the research. YL and QW participated in the Acquisition of data. JY carried out the Analysis and interpretation of data. ChL and KZ participated in the design of the study and performed the statistical analysis. XW and XL and QW conceived of the study, and participated in its design and coordination and helped to draft the manuscript and revision of manuscript for important intellectual content. All authors read and approved the final manuscript.

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