Original Article

Nomograms for predicting overall and cancer-specific survival in patients with papillary renal cell carcinoma: a population-based study using SEER database

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Background: To establish and validate nomograms for predicting the overall survival (OS) and cancer-specific survival (CSS) in patients with papillary renal cell carcinoma (pRCC).

Methods: Patients diagnosed with pRCC between 2010 and 2014 in the Surveillance, Epidemiology, and End Results (SEER) database were retrospectively included in this study and divided into training and validation groups randomly. Uni- and multivariate Cox regression analyses were used to identify significant variables related to OS and CSS in the training group. Based on results of multivariate Cox regression analysis, nomograms for 3- and 5-year CSS and OS were established, respectively. Additionally, Kaplan-Meier (KM) survival curves were produced to learn the actual effects of different variables. Finally, the nomograms were evaluated both in the training group and the validation group using the area under the receiver operating characteristic (ROC) curve, the concordance index (C-index) and calibration curves.

Results: A total of 4,859 eligible patients were enrolled, with 3,403 categorized into the training group and 1,456 into the validation group. Seven factors [age, T stage, N stage, M stage, use of surgery/lymph node removal (LNR) and insurance status] were significantly related to OS and seven factors (age, T stage, N stage, M stage and use of surgery/chemotherapy/LNR) were significantly associated with CSS. These factors were eventually included in the predictive nomograms. The C-indexes for OS in the training and validation groups were 0.764 and 0.723 respectively, and 0.859 and 0.824 for CSS. The 3- and 5-year AUCs for OS were 0.779 and 0.752 in the training cohort, and 0.749 and 0.722 in the validation cohort. Similarly, 3- and 5-year AUCs for OS were 0.871 and 0.844 in the training cohort, and 0.853 and 0.822 in the validation group. Finally, the calibration curves suggested that the predictive nomograms had a good consistency between the observed and the predicted survival.

Conclusions: It was the first time to develop nomograms to predict the survival outcomes of pRCC patients. The prognostic nomograms were reliable with high accuracy, which might have guiding significance for clinical practice.

Keywords: Prognostic model; nomogram; papillary renal cell carcinoma (pRCC); Surveillance, Epidemiology, and End Results (SEER) database

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Introduction

Renal cell carcinoma (RCC), as the most common type of kidney cancers, is mainly classified into clear cell RCC (ccRCC) and non-ccRCC according to the histology (1). ccRCC was the most common subtype of RCC, accounting for 75–80% of the total diagnosed cases, while papillary RCC (pRCC) ranked the second, accounting for approximately 10–15% of the total diseases (2,3). Further, pRCC could be divided into two major subtypes according to histopathological features. Type I tumors are usually with thin basophilic papillary cells, while type II pRCCs are composed of thicker nipples and eosinophilic cytoplasm (4).

Currently, the prognosis of pRCC remained poor, and there were still no effective methods for the treatment of advanced pRCC (5). Therefore, it was essential to identify related prognostic factors for improving the survival of pRCC at early stage. Traditionally, TNM stage was regarded as one of the most important prognostic factors in various cancers (6). However, it was not sufficient to cover the biological characteristics of cancer and predict survival outcomes (7). In addition, other clinical variables such as age, gender, ethnicity, grade, surgical treatment, adjuvant therapy, and molecular characteristics may generate influence on the prognosis of cancer patients (8). Nevertheless, the prognostic value of these parameters in pRCC remained inconsistent and even doubtful.

In recent years, there have been a lot of tools used to predict the survival outcomes in numerous cancers (9-11). Of the available tools, nomogram is currently one of the most effective and accurate methods for predicting the prognosis of cancer patients (12). The aim of this retrospective study was to explore the clinicopathological features associated with the prognosis of pRCC and to construct nomograms to predict survival on account of these features.

Methods

Patients

Primary data of patients with pRCC were obtained from the Surveillance, Epidemiology, and End Results (SEER) database (http://seer.cancer.gov/) utilizing the SEER*Stat software [Version 8.3.6; National Cancer Institute, Bethesda, United States (US)]. It is a public and population-based database which covers approximately 30% of the US population. The inclusion criteria of this study were as follows: (I) diagnosed as pRCC (International Classification of Diseases for Oncology: 8260/3) with positive histology, (II) year at diagnosis was from 2010 to 2014 to ensure a relatively long follow-up period, (III) complete data were available with active follow-up. Additionally, the exclusion criteria were as follows: (I) missing/unknown data in following variables: age, sex, race, American Joint Committee on Cancer (AJCC) 7th edition TNM stage, tumor laterality (bilateral tumors also been excluded), surgery, radiation, chemotherapy, follow-up time, insurance status, marital status, survival outcomes and so on, (II) pRCC was not the first primary malignancy, (III) type of reporting source was autopsy only or death certificate only.

Primary data were reviewed respectively by two independent investigators (Haicui Yan and Xiyi Wei) to extract the clinical characteristics and survival outcomes of the enrolled patients. Variables included age, sex, race, tumor laterality, AJCC 7th edition TNM stage, the use of radiation, chemotherapy, surgery, lymph node removal (LNR), survival months, survival status, insurance status and marital status. The primary endpoints were overall survival (OS) and cancer-specific survival (CSS). Survival time was calculated from the date of diagnosis to the date of death from pRCC (defined as CSS) or any disease cause (defined as OS). Lastly, use of SEER was exempt from Institutional Review Board (IRB).

Training and validation group

In order to develop the prognostic nomograms and undergo further external validation, all of the enrolled patients were divided into training group and validation group randomly at a ratio of 7:3 by using random-number generation method. Finally, chi-square test was utilized to make comparisons in basic characteristics between two groups.

Statistical analysis

Uni- and multivariate Cox regression analyses were conducted to explore the prognostic factors which affect OS and CSS significantly. Additionally, hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) of selected factors were calculated. According to the results of multivariate Cox regression analysis, predictive nomograms for 3- and 5-year CSS and OS were developed. In the training group, survival curves for different variables were produced by Kaplan-Meier (KM) analyses and were compared utilizing the log-rank test.

To assess the predictive ability and accuracy of the

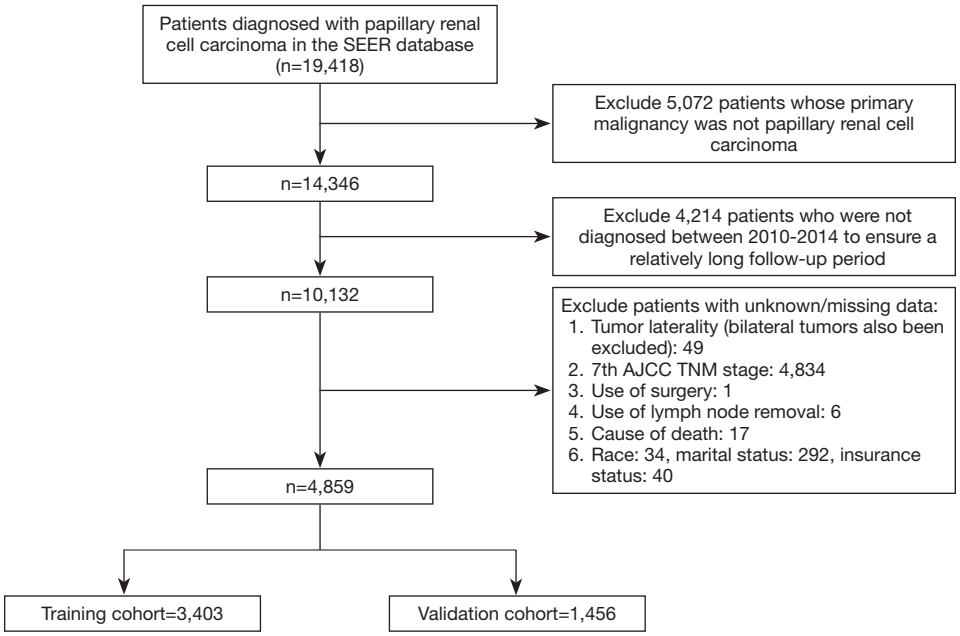

Figure 1 The study flow diagram of the selection process.

nomograms, discrimination and calibration of the nomograms were measured in two groups. The area under receiver operating characteristic (ROC) curve (defined as AUC) (13,14) and Harrell's concordance index (C-index) (15) were applied to assess the discrimination. The AUC and C-index range from 0.5 to 1.0, with 0.5 suggesting the total chance and 1.0 suggesting a perfect discrimination ability (16). Calibration curves were performed to identify the consistency between the observed survival and the predicted survival.

The Cox analysis and chi-square test were conducted via SPSS 23.0 software (SPSS Inc, Chicago, IL, US). Survival and RMS package were used to develop and validate the predictive nomograms via RStudio software (Version 1.2.5001). Two-sided P<0.05 was considered to be statistically significant during the whole analysis process.

Results

Basic characteristics

A total of 4,859 patients with pRCC diagnosed between 2010 and 2014 were included in this study (selection flow chart was in *Figure 1*. After randomly grouping, 3,403 patients were included in the training cohort and the remaining 1,456 patients were in the validation cohort. The training group was used for the development and internal validation of the predictive nomograms while the validation group was assigned for the external validation.

In the total cohort, most of the patients were male (75.06%), white (66.99%), and had a tumor in early T stage (76.29%) and without metastasis (95.76%). In terms of tumor laterality, no significant difference was detected between these two groups. Most patients had undergone surgery (95.93%) and a small number of patients had received chemotherapy (3.25%) and radiotherapy (1.29%). Detailed clinical information and comparisons between two groups was summarized in *Table 1*. There were no significant differences in race, age, sex, tumor laterality, TNM stage, insurance status, marital status, or use of surgery/chemotherapy/radiotherapy/LNR (all P>0.05). However, patients with radiotherapy in the training group were more than those in the validation group significantly (P=0.038).

Cox analyses, KM analyses and nomograms construction

As shown in *Table 2* and *Table 3*, in univariate Cox analysis, 13 variables were enrolled including age, race, sex, tumor laterality, T stage, N stage, M stage, use of surgery/chemotherapy/radiotherapy/LNR, insurance status and marital status. Eventually, seven factors (age, T stage, N stage, M stage, the use of surgery, LNR and insurance status) were significantly related to OS and seven factors (age,

Table 1 Clinical characteristics of included patients in the study

Variables	Total (n=4,859)	Training group (n=3,403)	Validation group (n=1,456)	P*
Age (year)				0.360
<40	197	134	63	
40–59	1,880	1,344	536	
60–79	2,527	1,749	778	
≥80	255	176	79	
Race				0.734
White	3,255	2,280	975	
Black	1,422	991	431	
Other	182	132	50	
Sex				0.173
Male	3,647	2,573	1,074	
Female	1,212	830	382	
Laterality				
Left	2,398	1,675	723	0.781
Right	2,461	1,728	733	
T stage				
T1	3,707	2,609	1,098	0.353
T2	568	383	185	
T3–T4	584	411	173	
N stage				
N0	4,627	3,246	1,381	0.421
N1	232	157	75	
M stage				
M0	4,653	3,252	1,401	0.296
M1	206	151	55	
Surgery				
No	198	133	65	0.369
Yes	4,661	3,270	1,391	
LNR				
No	4,428	3,110	1,318	0.330
Yes	431	293	138	
Radiation				0.038
No	4,806	3,359	1,447	
Yes	53	44	9	
Chemotherapy				
No/unknown	4,701	3,285	1,416	0.195
Yes	158	118	40	

Table 1 *(continued)*

Table 1 *(continued)*

Variables	Total (n=4,859)	Training group (n=3,403)	Validation group (n=1,456)	P*
Marital status				
Married	3,031	2,123	908	0.991
Previously married	893	624	269	
Never married	935	656	279	
Insurance status				
Any medicaid	525	371	154	0.764
Insured	4,196	2,932	1,264	
Uninsured	138	100	38	

LNR, Lymph node removal. *, P values of comparisons between the training group and the validation group.

Table 2 Uni- and multivariate analysis of the training group for OS

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age (year)			0.000			0.000
<40		Reference			Reference	
40–59	1.220	0.693–2.148	0.491	1.862	1.040–3.336	0.037
60–79	2.030	1.166–3.534	0.012	3.494	1.961–6.225	0.000
≥80	5.211	2.888–9.403	0.000	7.896	4.242–14.699	0.000
Sex			0.156			
Male		Reference				
Female	0.867	0.711–1.056	0.156			
Laterality			0.312			
Left		Reference				
Right	0.919	0.780–1.083	0.312			
Race			0.290			
White		Reference				
Black	0.931	0.774–1.119	0.445			
Other	1.284	0.869–1.897	0.209			
T stage			0.000			0.000
T1		Reference			Reference	
T2	1.996	1.574–2.530	0.000	1.521	1.190–1.945	0.001
T3–T4	4.037	3.574–5.190	0.000	1.971	1.569–2.477	0.000
N stage			0.000			0.000
N0		Reference			Reference	
N1	10.157	8.259–12.490	0.000	1.928	1.402–2.650	0.000

Table 2 *(continued)*

Table 2 *(continued)*

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
M stage			0.000			0.000
M0		Reference			Reference	
M1	16.256	13.246–19.923	0.000	5.235	3.754–7.301	0.000
Surgery			0.000			0.000
No		Reference			Reference	
Yes	0.165	0.129–0.210	0.000	0.409	0.303–0.551	0.000
LNR			0.000			0.000
No		Reference			Reference	
Yes	3.264	2.658–4.010	0.000	1.604	1.240–2.075	0.000
Radiation			0.000			0.646
No		Reference			Reference	
Yes	10.260	7.300–14.421	0.000	0.912	0.614–1.353	0.646
Chemotherapy			0.000			0.091
No/unknown		Reference			Reference	
Yes	13.375	10.691–16.734	0.000	1.337	0.955–1.871	0.091
Marital status			0.000			0.247
Married		Reference			Reference	
Previously married	1.572	1.253–1.860	0.000	1.183	0.964–1.451	0.107
Never married	1.041	0.834–1.298	0.724	1.110	0.878–1.405	0.383
Insurance status			0.000			0.000
Any medicaid		Reference			Reference	
Insured	0.626	0.499–0.786	0.000	0.597	0.469–0.761	0.000
Uninsured	0.470	0.257–0.859	0.014	0.610	0.330–1.128	0.115

OS, overall survival; HR, hazard ratio; CI, confidence interval; LNR, lymph node removal.

Table 3 Uni- and multivariate analysis of the training group for CSS

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age (year)			0.000			0.000
<40	Reference			Reference		
40-59	0.962	0.501–1.846	0.907	1.945	0.969–3.905	0.061
60-79	1.328	0.702–2.514	0.383	2.862	1.439–5.689	0.003
≥80	3.127	1.548–6.315	0.001	5.206	2.428–11.160	0.000
Sex			0.943			
Male	Reference					
Female	0.991	0.764–1.285	0.943			

Table 3 *(continued)*

Table 3 *(continued)*

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Laterality			0.597			
Left	Reference					
Right	0.942	0.753–1.177	0.597			
Race			0.018			0.199
White	Reference			Reference		
Black	0.793	0.609–1.031	0.083	0.783	0.595–1.031	0.081
Other	1.601	1.002–2.560	0.049	0.845	0.519–1.376	0.498
T stage			0.000			0.000
T1	Reference			Reference		
T2	3.575	2.580–4.954	0.000	2.326	1.652–3.275	0.000
T3–T4	10.258	8.000–13.154	0.000	3.536	2.617–4.778	0.000
N stage			0.000			0.001
N0	Reference			Reference		
N1	18.858	14.836–23.971	0.000	1.855	1.304–2.638	0.001
M stage			0.000			0.000
M0	Reference			Reference		
M1	32.313	25.445–41.035	0.000	6.952	4.758–10.156	0.000
Surgery			0.000			0.000
No	Reference			Reference		
Yes	0.121	0.090–0.162	0.000	0.345	0.237–0.501	0.000
LNR			0.000			0.000
No	Reference			Reference		
Yes	5.682	4.462–7.234	0.000	2.111	1.540–2.894	0.000
Radiation			0.000			0.658
No	Reference			Reference		
Yes	17.441	12.216–24.901	0.000	0.911	0.603–1.377	0.658
Chemotherapy			0.000			0.043
No/unknown	Reference			Reference		
Yes	23.700	18.392–30.541	0.000	1.447	1.011–2.072	0.043
Marital status			0.012			0.629
Married	Reference			Reference		
Previously married	1.444	1.104–1.890	0.007	1.148	0.866–1.522	0.336
Never married	0.918	0.673–1.252	0.918	1.051	0.756–1.462	0.766
Insurance status			0.080			
Any medicaid	Reference					
Insured	0.720	0.521–0.994	0.046			
Uninsured	0.492	0.210–1.157	0.104			

CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval; LNR, lymph node removal.

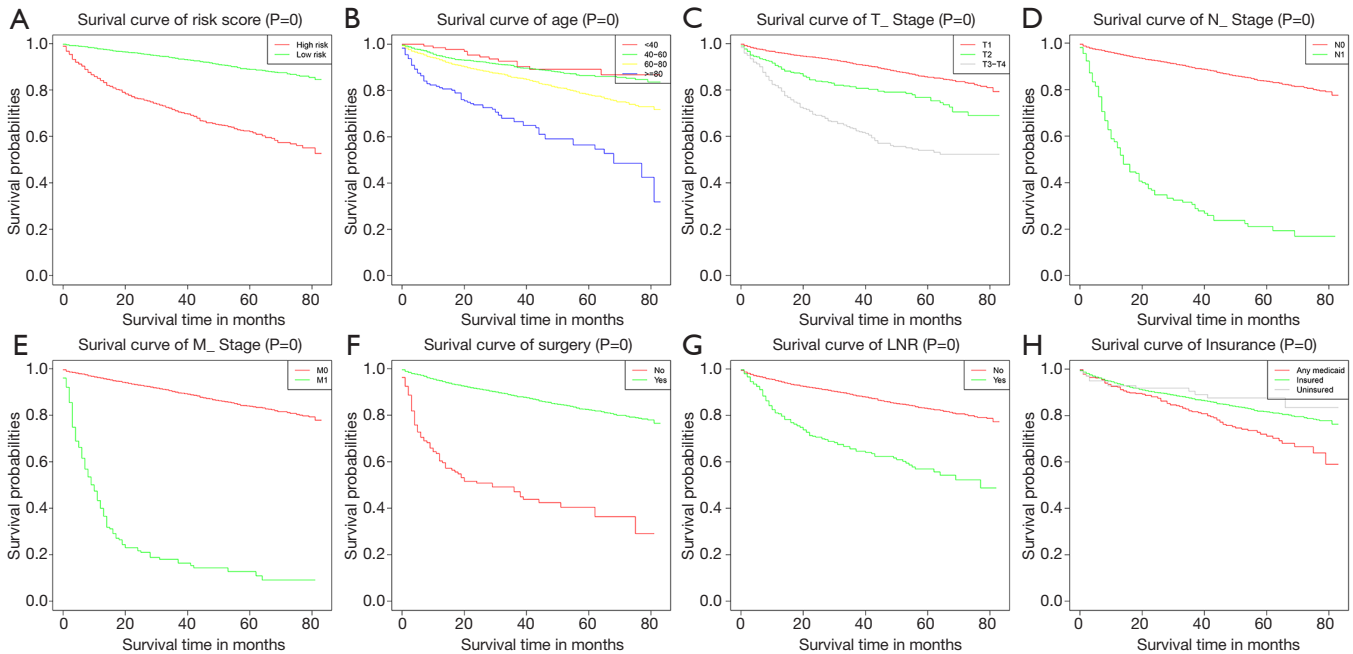

Figure 2 Kaplan-Meier curves of OS for risk stratification by risk score (A), age (B), T stage (C), N stage (D), M stage (E), the use of surgery (F), the use of lymph node removal (G) and insurance status (H).

T stage, N stage, M stage, the use of surgery, chemotherapy and LNR) were significantly associated with CSS. Finally, KM survival curves for OS and CSS were generated to learn the actual effect of different variables (*Figures 2*,*3*).

Based on the results of multivariate Cox analysis, nomograms to predict 3- and 5-year OS and CSS were conducted (*Figure 4*). A total point can be obtained by adding the score of each variable and the total point had its corresponding OS/CSS probabilities by the nomograms.

Nomogram validation

The C-index of the OS predictive model was 0.764 in the training group and 0.723 in the validation group. As to the CSS nomogram, it was 0.859 in the training group and 0.824 in the validation group, respectively. For OS, the 3- and 5-year AUCs were 0.779 and 0.752 in the training group and 0.749 and 0.722 in the validation group (*Figure 5*). For CSS, the 3- and 5-year AUCs were 0.871 and 0.844 in the training group and 0.853 and 0.822 in the validation group (*Figure 6*). These results suggested the predictive nomograms were with good discrimination performance. Furthermore, calibration curves for 3- and 5-year indicated a good consistency between the observed survival and the predicted survival in both in OS (*Figure 7*) and CSS (*Figure 8*).

Discussion

As mentioned above, RCC accounts for approximately 90% of kidney cancer (17). As one of the prominent subtypes of RCC, pRCC accounts for approximately 6–18% of renal tumors (17,18) and is the dominant histological subtype in pediatric RCC patients. Unfortunately, approximately 20% of pRCCs were found to be incidental, and with specific symptoms and prognostic factors (19,20). Therefore, it was crucial to determine related prognostic factors to improve the prognosis of patients with pRCC. Because the nomogram can predict survival risk by combining and quantifying the relative importance of various prognostic factors, it has been widely applied for clinical oncology assessment.

Our study demonstrated that age, T stage, N stage, M stage, surgery, LNR and insurance status were prognostic factors for OS. Moreover, age, T stage, N stage, M stage, use of surgery, chemotherapy and LNR were significantly associated with CSS. Nomograms were then developed based on these prognostic factors to predict 3- and 5-year OS and CSS rate in patients with pRCC. Both in the

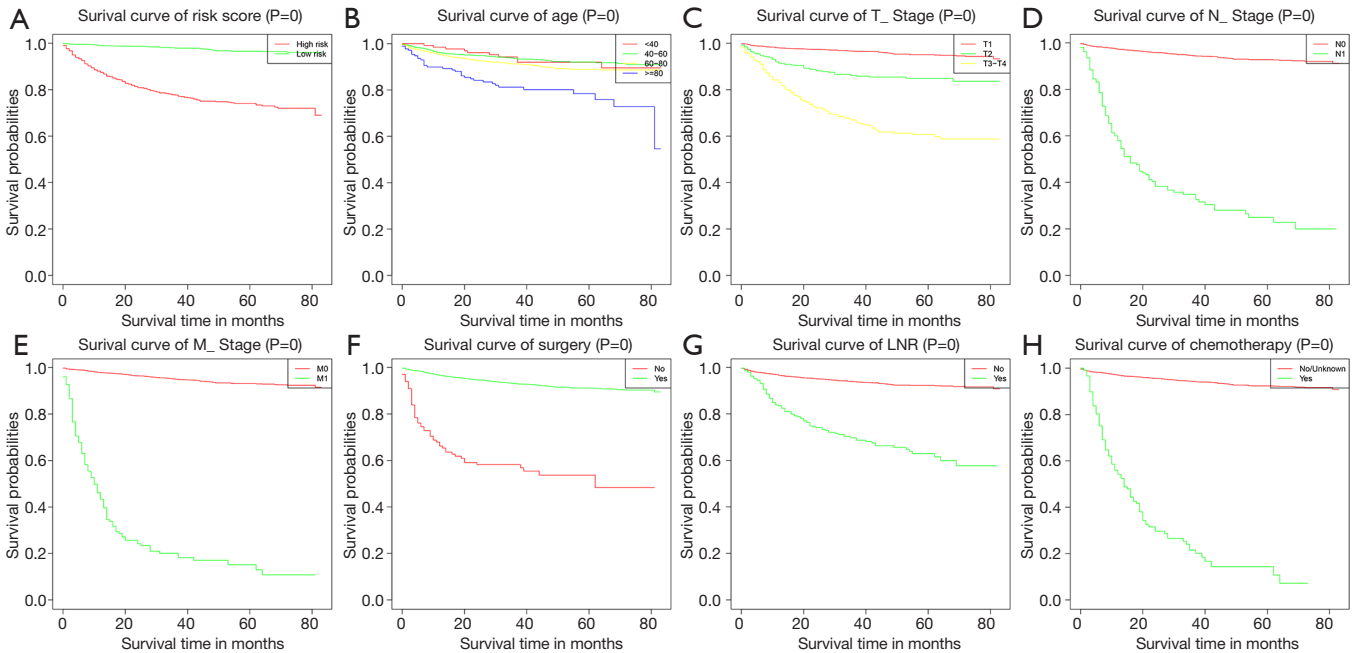

Figure 3 Kaplan-Meier curves of CSS for risk stratification by risk score (A), age (B), T stage (C), N stage (D), M stage (E), the use of surgery (F), the use of lymph node removal (G) and the use of chemotherapy (H).

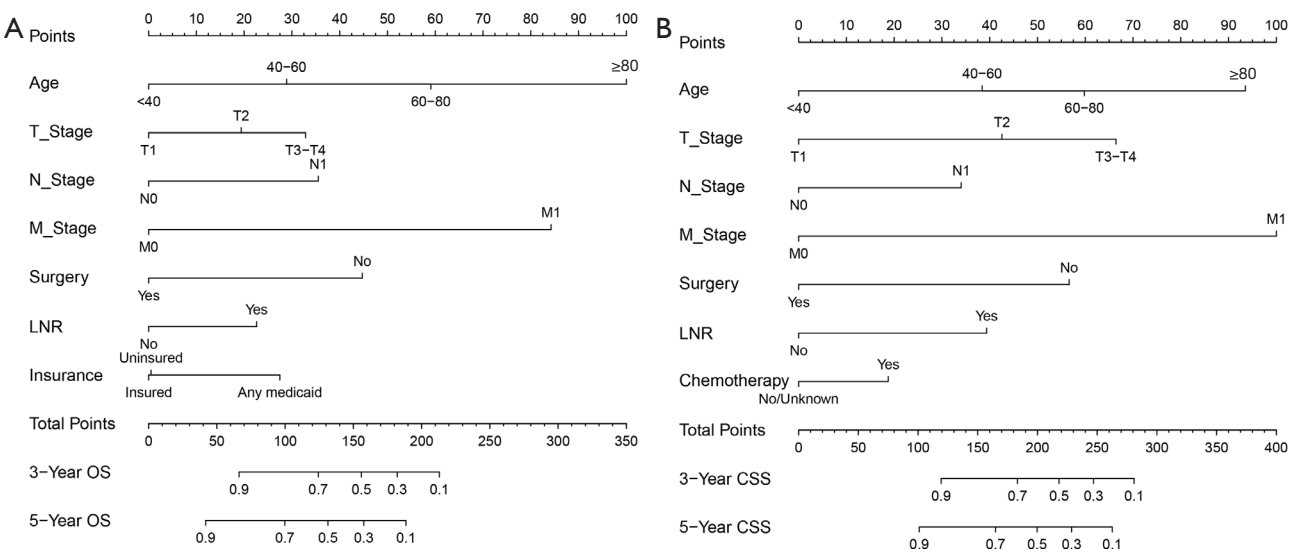

Figure 4 Prognostic nomograms of 3- and 5-year OS (A) and CSS (B).

training and validation cohorts, the nomograms showed good predictive ability.

Chai *et al.* (21) demonstrated that age, T stage, N stage, M stage, and the use of surgery/chemotherapy played an important role in the prognosis of cancer patients, which was consistent with our results. In our study, patients over 80 years old and patients with higher TNM stages appeared to have lower OS and CSS rates. Moreover, the use of surgery may effectively reduce the risk of recurrence and death. In addition, we found that chemotherapy was a negative prognostic factor in our model. Conversely, various multi-center clinical trials have shown that patients with non-

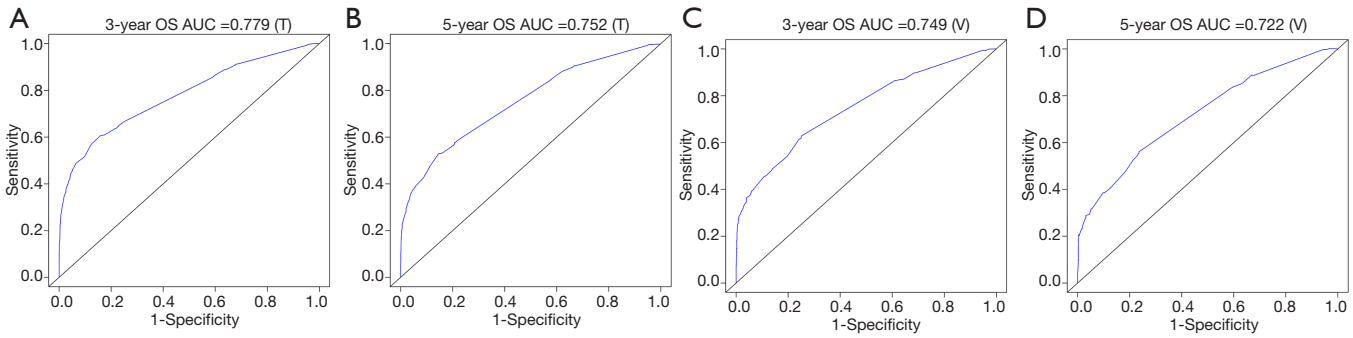

Figure 5 Three- and 5-years ROC curves of OS in training (A,B) and validation (C,D) groups for validating nomogram model.

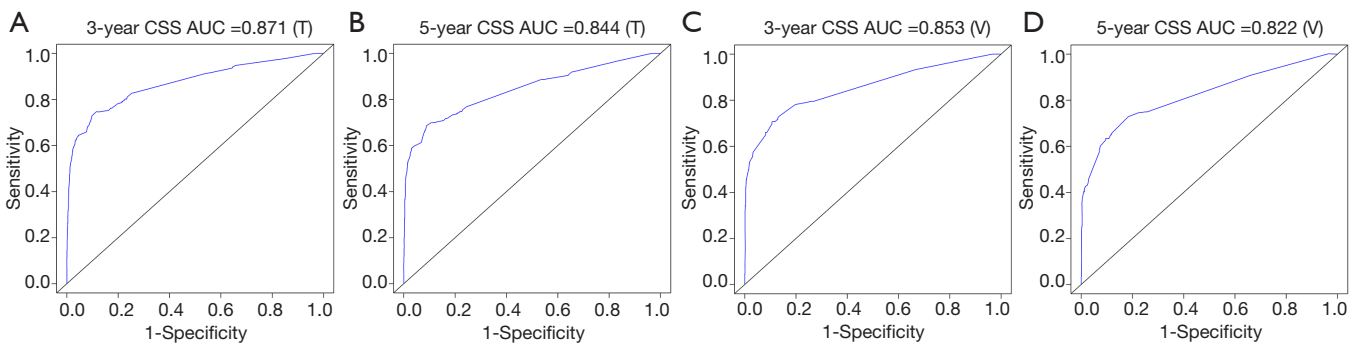

Figure 6 Three- and 5-years ROC curves of CSS in training (A,B) and validation (C,D) groups for validating nomogram model.

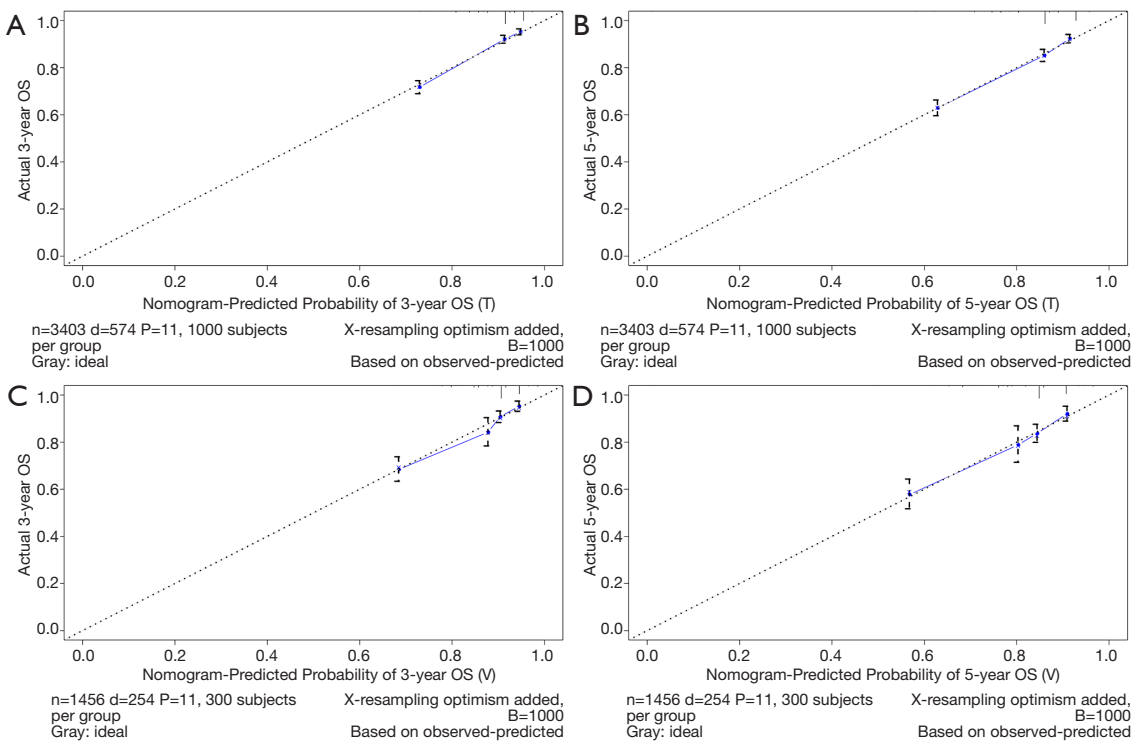

Figure 7 Three- and 5-years calibration curves of OS in training (A,B) and validation (C,D) groups for validating nomogram model.

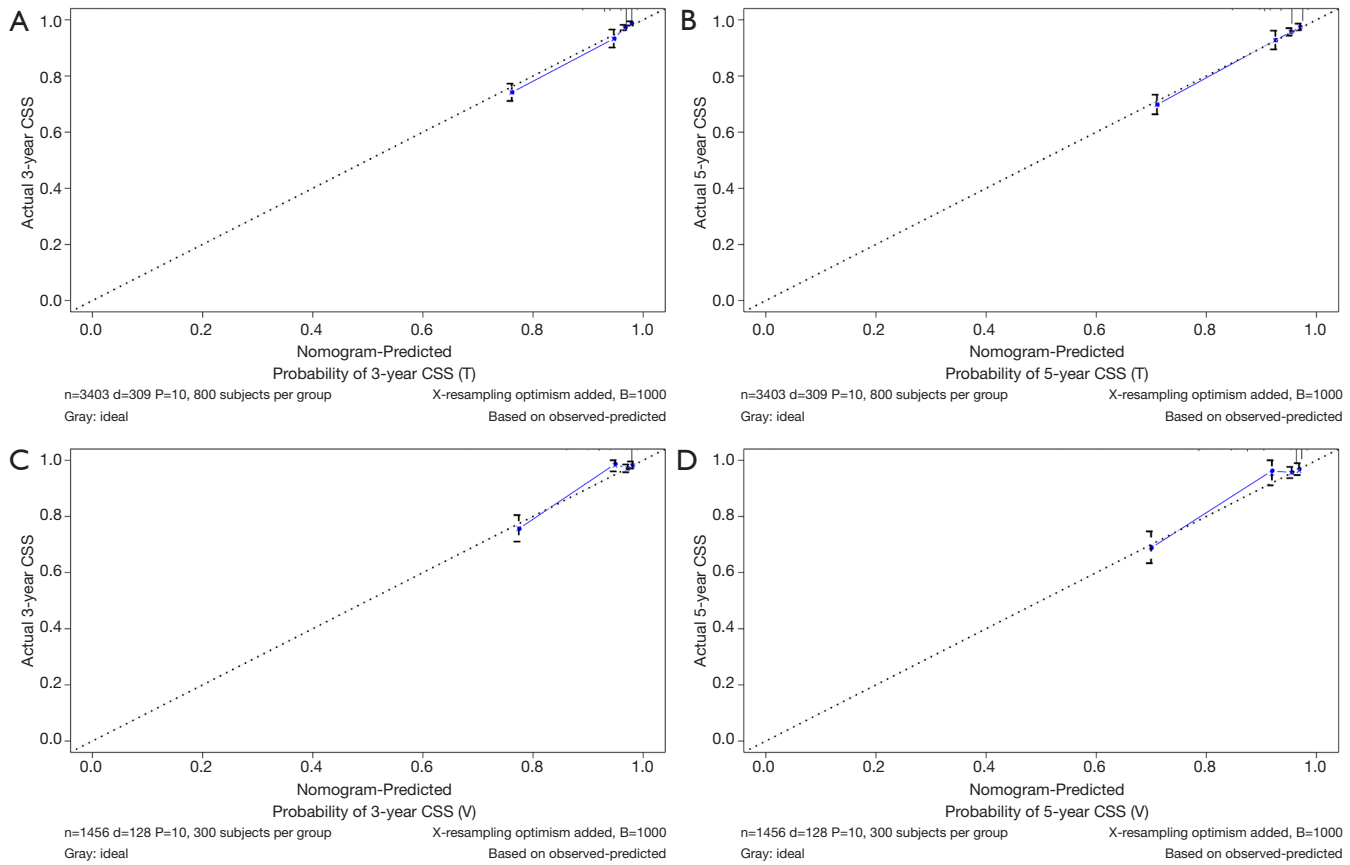

Figure 8 Three- and 5-years calibration curves of CSS in training (A,B) and validation (C,D) groups for validating nomogram model.

ccRCC had a good response rate to chemotherapy and had considerable efficacy (22-24). The adjuvant chemotherapy seemed to be a protective prognostic factor in their study. This might be attributed to the fact that considerable proportion of patients receiving chemotherapy were diagnosed with metastatic or advanced papillary cancer.

Furthermore, with regard to LNR, it seemed that lymph node ratio had become the primary prognostic factor for tumor outcomes and showed significant advantages in breast cancer, ovarian cancer, and cervical cancer (25-27). LNR might significantly reduce the risk of survival in tumor patients. Interestingly, our results provided different opinions, where LNR was a risk factor in our model. Meanwhile, several other studies also suggested that the role of lymph node dissection in RCC remains controversial (28-30). The most recent systematic review (28) concluded that although LNR could provide independent prognostic information, the current literature failed to recognize the therapeutic benefit in non-metastatic or metastatic RCC. We attributed the adverse value of LNR in our model to the truth that the lymph node metastasis may have occurred in these patients before the dissection, and thus showing a poor prognosis. Nevertheless, LNR may still play a role in some high-risk non-metastatic patients and a further prospective study was completely substantial.

Overall, our research had the following advantages. First, our research was based on the population-based cancer database (SEER database), which collected cancer cases from 18 regions of the US, effectively avoiding selection bias in single-center and small-sample studies. Secondly, our study was the first attempt to establish prognostic nomograms of pRCC, and further tested its effectiveness by modest validation and good calibration. However, some limitations should not be ignored. First, difference was detected in the use of LNR between two groups, which probably due to the poor number of people with LNR. Second, the cases included in the study were from retrospective cohorts. Larger prospective randomized controlled trials were needed to verify the accuracy of the model.

In conclusion, prognostic factors for pRCC patients were

identified and further survival nomograms were developed to predict the 3- and 5-year OS and CSS probabilities, providing an effective tool to assess individualized survival rate of pRCC patients.

Acknowledgments

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Footnote

Conflict of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tau-19-807). XL serves as an unpaid Section Editor of *Translational Andrology and Urology* from Oct 2019 to Dec 2021. The other 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. Use of SEER is exempt from Institutional Review Board.

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