Original Article

A population-based study to predict distant metastasis in patients with renal cell carcinoma

Yong Li[1], Peng Chen[2], Zhi Chen[2]

[1]Department of Urology, The Second Affiliated Hospital, University of South China, Hengyang, China; [2]Department of Urology, Xiangya Hospital, Central South University, Changsha, China

Contributions: (I) Conception and design: Z Chen, Y Li; (II) Administrative support: Z Chen; (III) Provision of study materials or patients: Z Chen, Y Li; (IV) Collection and assembly of data: Y Li, P Chen; (V) Data analysis and interpretation: Y Li, P Chen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Zhi Chen. Department of Urology, Xiangya Hospital, Central South University, No. 87 Xiangya Road, Changsha 410008, China. Email: czhi1011@126.com.

Background: Nomogram is potentially applied for quantitatively evaluating the probability of distant metastasis. The objective of our research was to establish a nomogram to predict distant metastasis in renal cell carcinoma (RCC) patients.

Methods: We conducted a retrospective analysis on 37,190 RCC cases diagnosed between 2010 and 2015 in the Surveillance Epidemiology and End Results (SEER) database. A multivariate logistic regression model-based nomogram was applied for predicting the risk factors concerning distant metastasis of RCC individuals. The concordance index (C-index) and calibration curves were utilized to internally validate the discrimination of nomogram. Decision curve analysis (DCA) was applied for comparing the predictive performance and clinically practical values between nomogram and conventional clinicopathologic risk factors.

Results: The nomogram incorporated seven clinical variables and achieved a predictive accuracy with a C-index of 0.863. The calibration plots illustrated optimal accordance between model prediction and practical observation. The DCA indicated the nomogram-based clinical utility. Receiver operating characteristic (ROC) curves also demonstrated an area under the curve (AUC) of 0.901 [95% confidence interval (CI): 0.894–0.908] in the training cohort and 0.892 (95% CI: 0.881–0.903) in the testing cohort.

Conclusions: Our proposed novel nomogram potentially serves as an accurate and user-friendly clinical tool to predict occurrence of distant metastases in RCC patients.

Keywords: Distant metastasis; nomogram; renal cell carcinoma (RCC); risk factors; Surveillance Epidemiology and End Results (SEER)

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Introduction

Kidney cancer represents the 7th most prevalent tumor in the developed countries (1,2), accounting for 3.7% of the global cancer burden (3). There were an estimated 63,990 newly diagnosed patients with kidney cancer in USA in 2017 (3). Renal cell carcinoma (RCC), the most frequent histopathological subtype, accounts for approximately 85% of kidney cancer and is one of malignancies derived from renal tubular cells (2,3). RCC is the 6th most commonly diagnosed cancer in men and the 10th in women (4) and the ratio of male to female morbidity is 1.7:1, with a mean age of 64 years (3,5). RCC primarily comprises three histopathologic subtypes, including clear cell RCC (ccRCC) (70%), papillary RCC (pRCC) (15%) and chromophobe RCC (chRCC) (5%) (6-8). The survival of RCC patients

has been improving owing to significant progress in the surgical management and the use of novel immunotherapy agents (8,9). Nevertheless, a large proportion of RCC patients present with high-stage disease, with unsatisfactory prognosis because of the occurrence of distant metastases (3,10).

Although the majority of detected renal neoplasms are small lesions, up to 17% of RCC patients are initially diagnosed with distant metastases (11-13). One-third of the localized RCC patients are treated by curative surgery and demonstrate a relapse at distant locations (10). In a retrospective study of 338 pathologic T1a (pT1a) RCC patients, 9 patients (2.7%) were reported with metastatic lesions (14). The regional lymph nodes are potentially the most common metastatic site, followed by the lung, brain, bone and soft tissue (15,16). Among metastatic RCC cases, approximately 75% demonstrate three or more metastatic locations (17). Distant metastasis adversely impacts the prognosis of the patients (18). The 5-year relative survivals of RCC of TNM stages I and II are 81% and 74%, respectively, and the overall 5-year survival of RCCs stage III and IV sharply diminishes to 53% and 10%, respectively, mostly due to distant metastases (19-21). Therefore, it is crucial to elucidate the clinicopathological risk factors promoting distant metastatic disease in RCC.

Nomograms represent user-friendly graphical mathematical models that generate a single numerical estimate of a clinical event of interest, thus helping physicians predict occurrence of a given event based on specific clinical and pathological variables (22-24). A growing number of nomogram models have been developed to improve clinical decision making during, such as hepatocellular carcinoma (23), breast carcinoma (25) and lung carcinoma (26) as well as colon carcinoma (27). To our knowledge, a promising nomogram model has not been established for predicting distant metastasis of RCC patients, using the Surveillance Epidemiology and End Results (SEER) database. Herein, we sought to design a robust nomogram by incorporating clinicopathological parameters extracted from the SEER database, to predicting presence of distant metastases in RCC patients that would be potentially clinically useful (23).

We present the following article in accordance with the TRIPOD Checklist (available at http://dx.doi.org/10.21037/apm-20-2481).

Methods

Data source

Original clinical data were extracted from the SEER public national database that incorporates 18 population-based tumor registries and covers approximately 28% of America population (http://seer.cancer.gov/) (23,28). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The clinical data in the SEER database, including patient demographics, tumor characteristics and survival status, are publicly accessible and anonymized. Therefore, our study did not require a separate ethical review or the patient consent (23). The study methods also conformed to the rules and regulations of this database.

Patient data extraction

The data of RCC patients diagnosed between 2010 and 2015 were identified from the SEER database through the SEER*Stat 8.3.2 software. A total of 37,190 eligible RCC individuals that have undergone a cancer-directed surgery were retrieved, and were further divided into a training set (n=24,793) and a testing set (n=12,397). Using the International Classification of Diseases for Oncology, third edition (ICD-O-3) categories, we searched the RCC-associated codes 8310/3, 8312/3, 8317/3 and 8318/3. The collected data included patient demographics (age at diagnosis, sex, ethnicity), tumor characteristics (laterality, pathological differentiation, T stage, lymph node status, metastasis status, TNM stage, tumor size, histological type, status of invasion beyond the capsule, Fuhrman nuclear grade), surgery type and survival status. The exclusion criteria included: (I) the age of patient at diagnosis less than 18 years; (II) individuals lacking sufficient information regarding the pathological differentiation, TNM stage, distant metastasis, cause of death and complete survival data. The flow diagram describing the patient selection is shown in *Figure 1*.

Nomogram construction and validation

The univariate and multivariable Cox regression analyses were utilized to investigate significantly independent risk factors associated with distant metastasis in RCC patients. The significant parameters identified on the multivariate

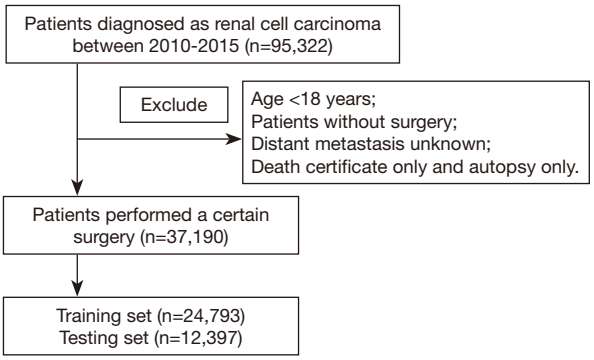


Figure 1 The flow chart of patient selection.

analysis were incorporated into a nomogram to predicting distant metastasis. The predictive reliability and accuracy of the nomogram was evaluated through the SEER internal testing group. A bootstrapping method with 2,000 resamples was used to internally validate the nomogram. The receiver operating characteristic (ROC) and calibration curves were applied to measure the predictive efficiency and reliability of the nomogram.

Clinical utility

Decision curve analysis (DCA) represents a novel algorithm that was used to evaluate the clinical application value of the predictive nomogram, through estimating the net benefits at every risk threshold possibility (29). Based on the DCA, the curves were formulated to estimate the clinical effect and to identify the number of high-risk RCC subjects with distant metastasis under the condition of different threshold probabilities, thus assisting physicians to more visually conclude its significant performance (30). The most desirable model demonstrated greater net benefits throughout a range of threshold probabilities (31). DCA was applied to compare the clinical benefit of the nomogram model versus the other clinicopathological factors in the training set.

Statistical analysis

The R software version 3.3.4 was applied for our statistical analyses. We compared classification variables and continuous variables using the Chi-squared test and Student's *t*-test (22). The nomogram was constructed and validated using the "rms" R package. The "survivalROC" R package was used to formulate ROC curve. The "rmda" R package was used to establish DCA (22). On the basis of the maximum Youden index in the training group, we estimated the cutoff values of the risk scores in the predictive nomogram. All RCC individuals were stratified into low- and high-risk sets. Statistically significant result was considered when P value was less than 0.05.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All information from the SEER program is available and free for public, so the agreement of the medical ethics committee board was not necessary.

Results

Clinical features

The clinicopathological features of the RCC cases are shown in *Table 1*. No statistically significant differences were found between the training set and testing set (P>0.05). Median patient age was 59 years and a large proportion of the patients were male (62.8%) in both cohorts. The ccRCC subtype was the most frequent histologic type in both cohorts. The rates of distant metastasis were 6.17% (1,530/24,793) and 6.04% (749/12,397) in the training and testing sets, respectively. Notably, patients administrated with nephrectomy displayed a higher rate (58.8%), compared with those performed by local excision (40.6%). In the correlative analysis (*Table 2*), 11 parameters were significantly associated with distant metastasis in both sets (P<0.001), including gender, pathological differentiation, T stage, lymph node status, TNM stage, tumor size, histological type, invasion beyond the capsule, Fuhrman nuclear grade, surgery type, overall survival (OS).

Predictive parameters associated with distant metastasis

The following parameters were associated with the occurrence of distant metastasis on univariate regression analysis: gender, race, pathological differentiation, T stage, lymph node status, tumor size, histological type, status of invasion beyond the capsule, Fuhrman nuclear grade and surgery type (P<0.05) (*Table 3*). These parameters were incorporated into a multivariate Cox proportional hazard regression model (*Table 4*). Seven parameters were considered as significantly independent risk factors

Table 1 Clinical characteristics of RCC cases

Variables	Total	Training set	Testing set	P value
Total	37,190	24,793	12,397	
Age (years), mean ± SD	59.4±12.4	59.3±12.4	59.3±12.3	0.74
Gender				0.94
Female	13,825	9,213	4,612	
Male	23,365	15,580	7,785	
Race				0.23
White	30,250	20,186	10,064	
Black	3,985	2,614	1,371	
Unknown	2,955	1,993	962	
Laterality				0.11
Right	18,909	12,702	6,207	
Left	18,255	12,076	6,179	
Bilateral	18	11	7	
Unknown	8	4	4	
Pathological differentiation				0.12
Well; I	4,133	2,790	1,343	
Moderately; II	19,391	12,924	6,467	
Poorly; III	11,066	7,307	3,759	
Undifferentiated; IV	2,600	1,772	828	
T stage				0.53
T1	25,176	16,808	8,368	
T2	4,004	2,630	1,374	
T3	7,527	5,027	2,500	
T4	439	301	138	
Unknown	44	27	17	
Lymph node status				0.94
N0	35,653	23,773	11,880	
N1	1,124	744	380	
Unknown	413	276	137	
Metastasis status				0.64
M0	34,911	23,263	11,648	
M1	2,279	1,530	749	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Total	Training set	Testing set	P value
TNM stage				0.82
I	24,606	16,428	8,178	
II	3,563	2,346	1,217	
III	6,263	4,168	2,095	
IV	2,473	1,659	814	
Unknown	285	192	93	
Tumor size				0.26
≤30 mm	11,593	7,776	3,817	
>30 mm	25,597	17,017	8,580	
Histological type				0.57
Clear cell	26,097	17,389	8,708	
Papillary	4,502	2,971	1,531	
Chromophobe	1,790	1,202	588	
Others	4,801	3,231	1,570	
Invasion beyond the capsule				0.95
No invasion	30,686	20,465	10,221	
Invasion	4,583	3,046	1,537	
Unknown	1,921	1,282	639	
Fuhrman nuclear grade				0.57
1	3,758	2,530	1,228	
2	18,494	12,331	6,163	
3	10,558	6,990	3,568	
4	2,581	1,746	835	
Unknown	1,799	1,196	603	
Surgery type				0.11
Local excision	15,098	10,106	4,992	
Nephrectomy	21,877	14,557	7,320	
Surgery (NOS)	215	130	85	
Overall survival				0.78
Alive	34,230	22,827	11,403	
Death	2,960	1,966	994	

RCC, renal cell carcinoma; SD, standard deviation; NOS, not otherwise specific.

Table 2 Correlations between distant metastasis and clinicopathologic factors of RCC patients in the two sets

Variables	Training			Testing		
	Negative	Positive	P value	Negative	Positive	P value
Total	23,262	1,530	–	11,648	749	–
Age (years), mean ± SD	59.3±12.5	60.3±10.1	<0.001	59.3±12.4	59.7±11.1	0.30
Gender			<0.001			<0.001
Female	8,747	466		4,412	200	
Male	14,516	1,064		7,236	549	
Race			<0.001			0.003
White	18,911	1,275		9,438	626	
Black	2,498	116		1,315	56	
Unknown	1,854	139		895	67	
Laterality			<0.001			0.13
Right	12,004	698		5,837	370	
Left	11,246	830		5,802	377	
Bilateral	9	2		5	2	
Unknown	4	–		4	–	
Pathological differentiation			<0.001			<0.001
Well; I	2,768	22		1,331	12	
Moderately; II	12,625	299		6,320	147	
Poorly; III	6,639	668		3,407	352	
Undifferentiated; IV	1,231	541		590	238	
T stage			<0.001			<0.001
T1	16,617	191		8,267	101	
T2	2,422	208		1,257	117	
T3	4,071	956		2,043	457	
T4	129	172		65	73	
Unknown	24	3		16	1	
Lymph node status			<0.001			<0.001
N0	22,685	1,088		11,351	529	
N1	346	398		188	192	
Unknown	232	44		109	28	
TNM stage			<0.001			<0.001
I	16,428	–		8,178	–	
II	2,346	–		1,217	–	
III	4,168	–		2,095	–	
IV	129	1,530		65	749	
Unknown	192	–		93	–	

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Training			Testing		
	Negative	Positive	P value	Negative	Positive	P value
Tumor size			<0.001			<0.001
≤30 mm	7,729	47		3,794	23	
>30 mm	15,534	1,483		7,854	726	
Histological type			<0.001			<0.001
Clear cell	16,220	1,169		8,136	572	
Papillary	2,881	90		1,478	53	
Chromophobe	1,188	14		576	12	
Others	2,974	257		1,458	112	
Invasion beyond the capsule			<0.001			<0.001
No invasion	19,826	639		9,895	326	
Invasion	2,346	700		1,190	347	
Unknown	1,091	191		563	76	
Fuhrman nuclear grade			<0.001			<0.001
1	2,511	19		1,218	10	
2	12,045	286		6,025	138	
3	6,375	615		3,252	316	
4	1,211	535		596	239	
Unknown	1,121	75		557	46	
Surgery type			<0.001			<0.001
Local excision	10,048	58		4,962	30	
Nephrectomy	13,097	1,460		6,608	712	
Surgery (NOS)	118	12		78	7	
Overall survival			<0.001			<0.001
Alive	22,190	637		11,078	325	
Death	1,073	893		570	424	

RCC, renal cell carcinoma; SD, standard deviation; NOS, not otherwise specific.

associated with distant metastasis. Compared with the ccRCC subtype, papillary subtype [odds ratio (OR) =0.55, 95% confidence interval (CI): 0.42–0.70, P<0.001] and chromophobe subtype (OR =0.18, 95% CI: 0.10–0.30, P<0.001) had a lower rate of distant metastasis. The status of lymph node involvement N1 (OR =5.47, 95% CI: 4.56–6.57, P<0.001), larger tumor size (>30 mm, OR =2.49, 95% CI: 1.82–3.49, P<0.001) and the invasion beyond the capsule (OR =1.48, 95% CI: 1.25–1.75, P<0.001) were related to the presence of distant metastasis. Patients undergoing radical nephrectomy were associated with higher risk of distant metastasis than patients undergoing local excision (OR =4.17, 95% CI: 3.15–5.61, P<0.001). Notably, RCC patients with more advanced T stage had a higher rate of distant metastasis (T2: OR =2.85, 95% CI: 2.30–3.54; T3: OR =3.96, 95% CI: 3.21–4.89; T4: OR =11.94, 95% CI: 8.56–16.68; P<0.001 for all). Regarding pathological differentiation grade, compared with well differentiated RCC, poorly differentiated RCC (OR =2.76, 95% CI: 1.17–7.43, P=0.03) and undifferentiated RCC (OR

Table 3 Risk factors for distant metastasis in RCC patients through univariate analysis in the training group

Variables	Distant metastasis		
	OR	95% CI	P value
Age (years)			
≤65	1.00	–	–
>65	0.94	0.84–1.05	0.26
Gender			
Female	1.00	–	–
Male	1.38	1.23–1.54	<0.001
Race			
White	1.00	–	–
Black	0.69	0.56–0.83	<0.001
Laterality			
Right	1.00	–	–
Left	1.27	1.14–1.41	<0.001
Bilateral	3.82	0.58–14.86	0.08
Pathological differentiation			
Well; I	1.00	–	–
Moderately; II	2.98	1.98–4.74	<0.001
Poorly; III	12.66	8.48–19.99	<0.001
Undifferentiated; IV	55.29	36.84–87.68	<0.001
T stage			
T1	1.00	–	–
T2	7.47	6.11–9.14	<0.001
T3	20.43	17.47–24.02	<0.001
T4	116	88.77–152.13	<0.001
Lymph node status			
N0	1.00	–	–
N1	23.98	20.52–28.05	<0.001
Tumor size			
≤30 mm	1.00	–	–
>30 mm	15.7	11.87–21.31	<0.001
Histological type			
Clear cell	1.00	–	–
Papillary	0.43	0.35–0.54	<0.001
Chromophobe	0.16	0.09–0.27	<0.001
Others	1.2	1.04–1.38	0.012

Table 3 (*continued*)

Table 3 (*continued*)

Variables	Distant metastasis		
	OR	95% CI	P value
Invasion beyond the capsule			
No invasion	1.00	–	–
Invasion	9.26	8.25–10.39	<0.001
Fuhrman nuclear grade			
1	1.00	–	–
2	3.14	2.03–5.18	<0.001
3	12.75	8.3–20.89	<0.001
4	58.39	37.86–96	<0.001
Surgery type			
Local excision	1.00	–	–
Nephrectomy	19.31	14.99–25.42	<0.001

RCC, renal cell carcinoma; OR, odds ratio; CI, confidence interval.

=4.06, 95% CI: 1.69–11.16, P=0.003) were characterized with a higher possibility of distant metastasis.

Construction and validation of predictive nomogram for distant metastasis

A nomogram model was constructed by incorporating seven significant risk factors identified on multivariate Cox regression analysis based on the training set (*Figure 2A*). Additionally, each parameter had a corresponding score in the nomogram. As revealed in Table S1, we estimated the point distributions and predictive scores for every parameter in our nomogram. As shown in *Figure 2A*, T stage made the largest contribution to the presence of distant metastasis, followed by pathological differentiation, histological type, the status of lymph node involvement, surgery type, tumor size and the status of invasion beyond the capsule in descending order. The discriminatory capacity of our nomogram model was satisfactory, and demonstrated a concordance index (C-index) of 0.863. The calibration plots to predict distant metastasis in the training group (*Figure 2B*) and in the testing group (*Figure 2C*) demonstrated the desirable concordance between model predictions and the actual observations.

Additionally, we performed a comparison of the predictive nomogram with the conventional clinicopathologic risk variables through ROC analysis. The AUCs of the predictive nomogram were 0.901 (95% CI: 0.894–0.908) in the training set (*Figure 3A*) and 0.892 (95% CI: 0.881–0.903) in the testing set (*Figure 3B*), respectively, which were dramatically greater than the other clinical factors (such as pathological differentiation, histological type, lymph node status, invasion beyond the capsule and Fuhrman nuclear grade). These results highlighted the fact that the predictive nomogram achieved remarkable superiority over these additional risk factors.

In accordance with the nomogram risk score, bar diagrams were formulated to assess the discriminatory performance. We further calculated the cutoff value of 238 for the distant metastasis nomogram via the maximum Youden index. All RCC individuals were stratified into low- and high-risk subgroups. Indeed, the RCC patients in the high-risk group exhibited a higher probability of distant metastasis than did those in the low-risk group in the training and testing cohorts (*Figure 4A*,*B*).

Clinical application of the nomogram

RCC patients in the high-risk group were characterized by significantly shorter OS, compared with those in the low-risk group in the two cohorts (P<0.0001) (*Figure 4C*,*D*). DCAs further demonstrated that the clinical utility and the benefits of the nomogram were the superior to the conventional clinicopathological variables (including

Table 4 Risk factors for distant metastasis in RCC patients on multivariate analysis in the training set

Variables	Distant metastasis		
	OR	95% CI	P value
Gender			
Female	1.00	–	–
Male	0.97	0.85–1.11	0.64
Laterality			
Right	1.00	–	–
Left	1.12	0.99–1.26	0.07
Bilateral	1.58	0.15–11.27	0.67
Pathological differentiation			
Well; I	1.00	–	–
Moderately; II	1.45	0.61–3.88	0.43
Poorly; III	2.76	1.17–7.43	0.03
Undifferentiated; IV	4.06	1.69–11.16	0.003
T stage			
T1	1.00	–	–
T2	2.85	2.30–3.54	<0.001
T3	3.96	3.21–4.89	<0.001
T4	11.94	8.56–16.68	<0.001
Lymph node status			
N0	1.00	–	–
N1	5.47	4.56–6.57	<0.001
Tumor size			
≤30 mm	1.00	–	–
>30 mm	2.49	1.82–3.49	<0.001
Histological type			
Clear cell	1.00	–	–
Papillary	0.55	0.42–0.70	<0.001
Chromophobe	0.18	0.10–0.30	<0.001
Others	0.96	0.8–1.13	0.61
Invasion beyond the capsule			
No invasion	1.00	–	–
Invasion	1.48	1.25–1.75	<0.001

Table 4 (*continued*)

Table 4 (*continued*)

Variables	Distant metastasis		
	OR	95% CI	P value
Fuhrman nuclear grade			
1	1.00	–	–
2	1.42	0.51–3.72	0.49
3	1.48	0.53–3.85	0.44
4	2.02	0.71–5.37	0.17
Surgery			
Local excision	1.00	–	–
Nephrectomy	4.17	3.15–5.61	<0.001

RCC, renal cell carcinoma; OR, odds ratio; CI, confidence interval.

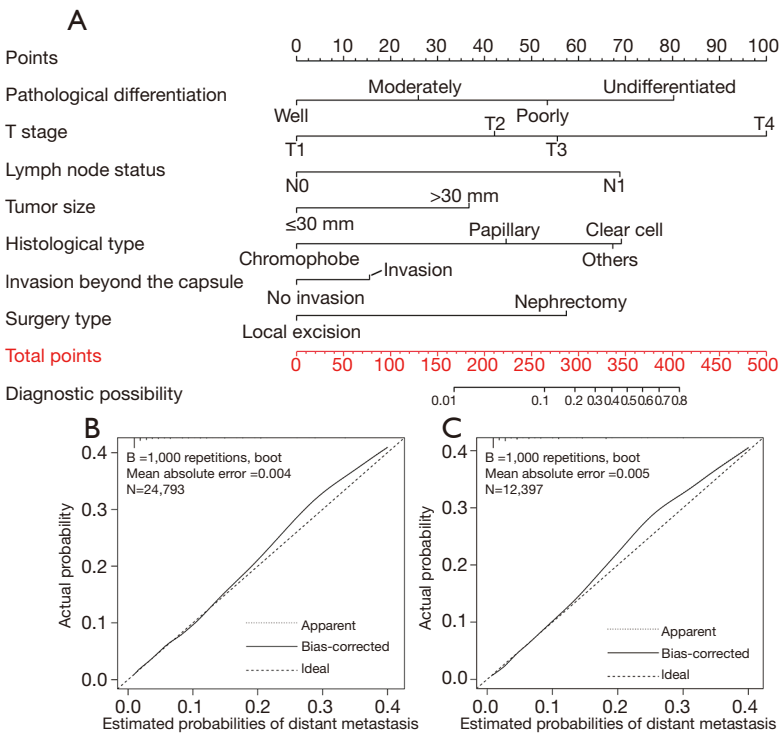
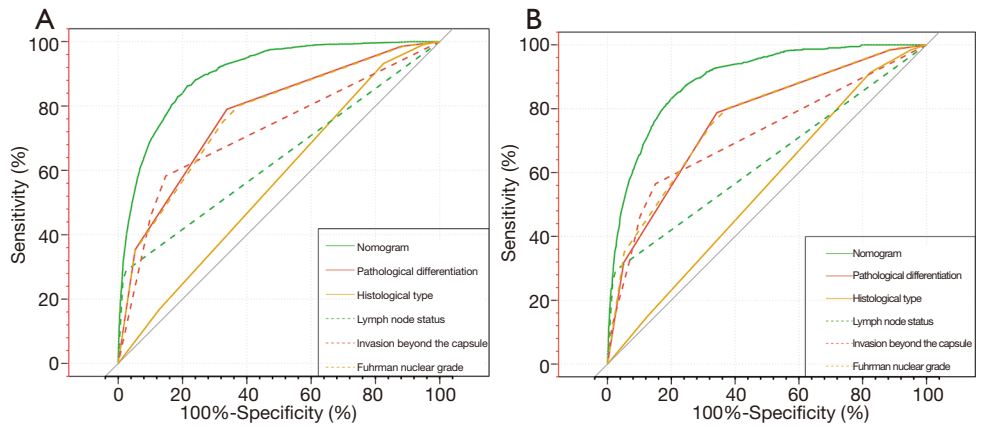


Figure 2 Nomogram and calibration curves for predicting distant metastasis in patients with RCC. (A) Predictive nomogram for the presence of distant metastasis in RCC patients. (B,C) Calibration plots for evaluating the predictive efficiency of nomogram in (B) training and (C) testing group, respectively. RCC, renal cell carcinoma.

pathological differentiation, histological type, lymph node status, invasion beyond the capsule, and Fuhrman nuclear grade), both in the training cohort (*Figure 5A*) and in the validation cohort (*Figure 5B*). The threshold probabilities of 0–0.4 were the most beneficial in predicting distant metastasis using the nomogram. The clinical impact plots of the nomogram in the training set (*Figure 5C*) and in the testing set (*Figure 5D*) demonstrated that the model



Distant metastasis (Train)			
Variable	AUC	95%CI	P value
Nomogram	0.901	0.894–0.908	
Pathological differentiation	0.773	0.761–0.784	<0.001
Histological type	0.564	0.554–0.575	<0.001
Lymph node status	0.633	0.622–0.645	<0.001
Invasion beyond the capsule	0.722	0.701–0.734	<0.001
Fuhrman nuclear grade	0.768	0.756–0.779	<0.001

Distant metastasis (Test)			
Variable	AUC	95%CI	P value
Nomogram	0.892	0.881–0.903	
Pathological differentiation	0.764	0.747–0.781	<0.001
Histological type	0.551	0.535–0.565	<0.001
Lymph node status	0.635	0.618–0.652	<0.001
Invasion beyond the capsule	0.713	0.695–0.732	<0.001
Fuhrman nuclear grade	0.769	0.743–0.776	<0.001

Figure 3 ROC curves for comparing the predictive value between the distant metastasis nomogram and clinicopathological risk factors in the (A) training and (B) testing cohort, respectively. ROC, receiver operating characteristic; AUC, area under the curve; 95% CI, 95% confidence interval.

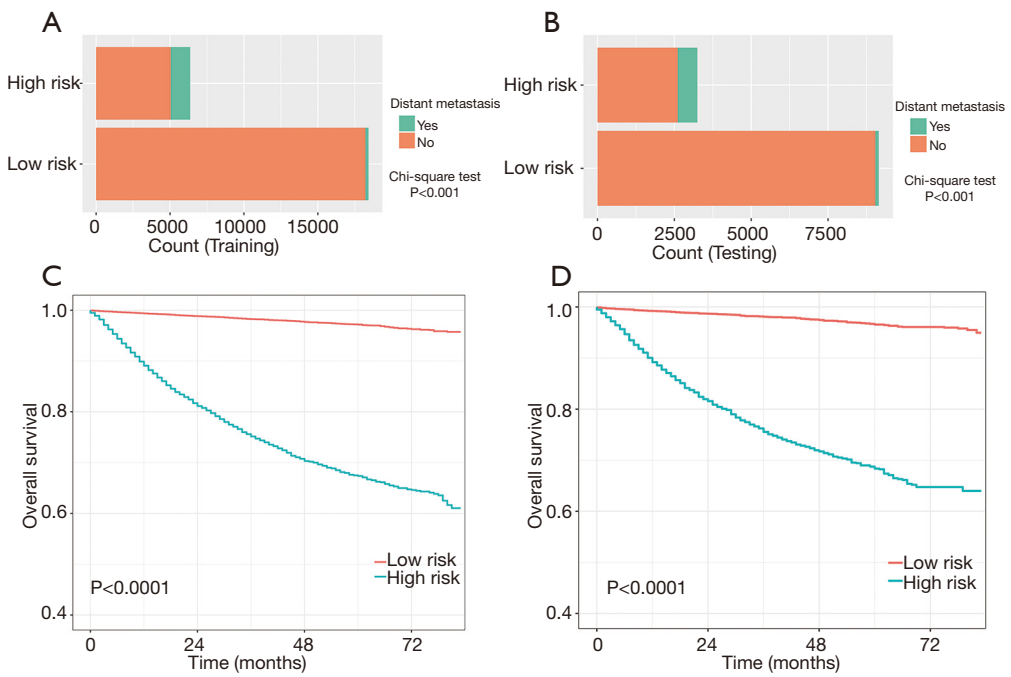


Figure 4 Risk classification and Kaplan-Meier survival curves for RCC patients. (A,B) The bar graphs for evaluating the discriminatory performance of the nomogram for distant metastasis in the training (A) and testing (B) cohort, respectively. (C,D) Survival plots for evaluating the OS of RCC patients with distant metastasis in the training (C) and testing (D) group, respectively. OS, overall survival; RCC, renal cell carcinoma.

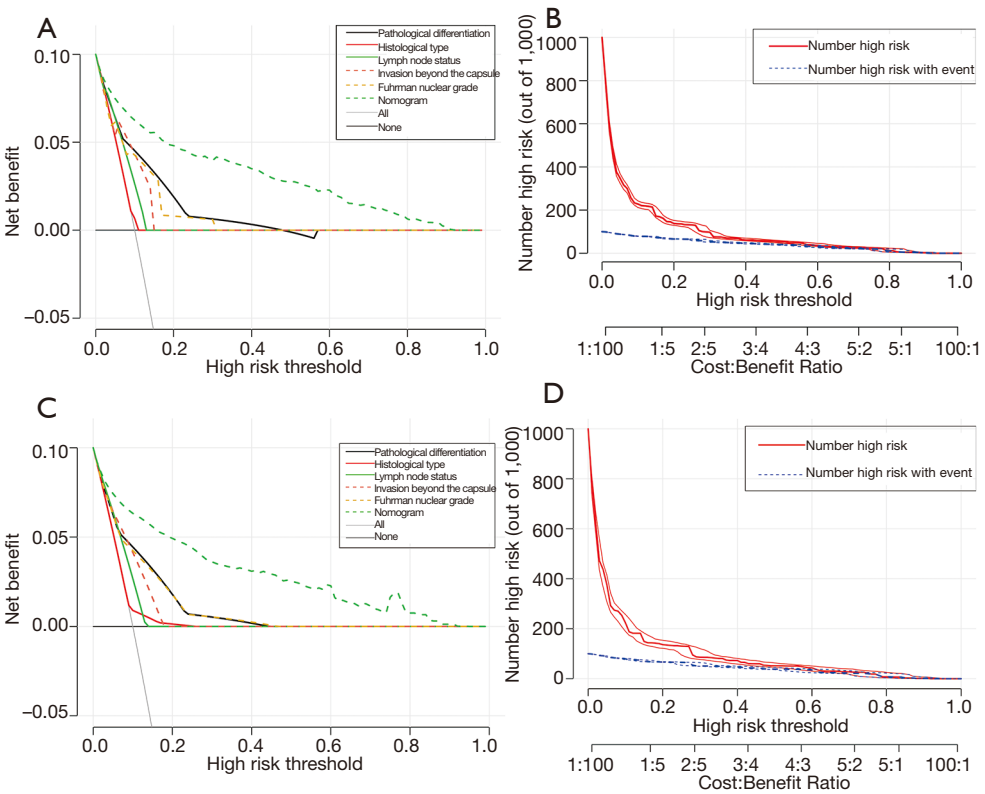


Figure 5 The decision curves and clinical impact curves of the nomogram for predicting distant metastasis for RCC patients. (A,B) DCAs of nomogram and additional clinical risk factors in the training (A) and testing (B) cohort, respectively. (C,D) Clinical impact curves of the predictive nomogram in the training (C) and testing (D) cohort. DCA, decision curve analysis; RCC, renal cell carcinoma.

displayed a desirable predictive performance.

Discussion

Distant metastatic disease is a conventional symbol of advanced stage and indicates unfavorable prognosis for RCC patients (32). It has been demonstrated that cancer-targeted surgical intervention provides an enhanced survival in RCC patients with metastatic disease (33,34). Immune checkpoint inhibitors (ICIs) and multitarget tyrosine kinase inhibitors (TKIs) such as cabozantinib can be used as the second-line drugs to improve prognosis (35,36). Therefore, timely and accurate detection of distant metastasis is crucial, and may guide an optimal treatment decision. Computed tomography (CT) remains the first-line method of examination of suspected metastatic disease with a good staging accuracy. Nevertheless, there are limitations of CT examination in evaluating the nodal status (37,38). It is important to predict the risk of distant metastasis of RCC patients using a noninvasive method. In this report, we aimed to generate a predictive nomogram model associated with distant metastasis, utilizing the data from the SEER database. The nomogram demonstrated a desirable discrimination and can be used as a clinical tool for individualized evaluation to predict the occurrence of distant metastasis in RCC patients.

Our predictive nomogram model associated with distant RCC metastasis incorporated seven clinicopathological risk factors: T stage, pathological differentiation, histological type, lymph node status, surgery type, tumor size and the status of invasion beyond the capsule. Hutterer *et al.* collected data from 2,660 RCC patients from 11 centers and developed a nomogram to predict the risk of distant metastases. They found that there were 10.1% and 10.5% patients with distant metastases in the initial group and in the external validation group, respectively, which was higher

than in our data set with 6.17% and 6.04% in the training and testing groups, respectively (39). Multiple studies have also revealed that the tumor size was indeed significantly correlated with the presence of distant metastasis in RCC, while age was not an independent predictor, consistent with the findings in our study (39-41). They also demonstrated that the occurrence of metastatic lesions in RCC enhanced with increasing tumor size. Specifically, there was a statistically significant correlation between metastatic risk and the tumor size of less than 5 cm. In the current study, we found that renal neoplasms ≥3 cm in size had a higher risk of distant metastasis (42). When RCC was 23 mm (mean size), the proportion of metastatic tumor was approximately 2.0% (43). As shown in the current study, histologic RCC subtype had a crucial impact on the metastatic potential of tumors. Indeed, another study also found that ccRCC harbored the highest metastatic risk, followed by pRCC and chRCC (40). Additionally, the influence of regional lymph node involvement on the distant metastatic potential of RCC was also demonstrated in our finding. Another study found that regional lymph node involvement increased the occurrence of distant metastasis by 50% (44). Our nomogram highlighted the fact that the rate of distant metastasis increased with the RCC differentiation (from well to poorly differentiated). Other reports similarly showed that poor pathological differentiation of RCC was correlated with inferior prognosis (45-47). This is not surprising, as the pathological differentiation grade reflects the tumor biological behavior and represents an independent predictor for distant RCC metastasis.

In our report, we incorporated a large number of cases from the SEER database, arguably the best available source of clinical data. All cases were randomly stratified into a training and internal testing set to establish and validate a predictive nomogram, which makes the conclusion convincing. All variables included in our nomogram were readily available and prevalent in clinical practice, contributing to convenient evaluation of risk factors for physicians. Nevertheless, certain shortcomings should be acknowledged in our study. First, our report could not incorporate some potentially important indicators, such as BMI, family history of hypertension, smoking and drinking, genetic markers, vascular invasion, surgical margin status and the immunotherapeutic protocols, which were not available in the SEER database (23,48-50). Second, the training and validation groups in our study were both derived from the SEER database, and were not externally validated in an independent dataset or our hospital (51). Third, our study may have had some inherent bias because of the use of retrospective information from the SEER database. Prospective clinical trials with a large sample size are thus required to verify our predictive model in the general population (23,31).

Conclusions

In conclusion, a novel nomogram to predict distant metastasis in RCC patients was established, using a large population cohort from the SEER database. This tool may potentially help both physicians and RCC patients in make risk assessment of metastatic disease.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD Checklist. Available at http://dx.doi.org/10.21037/apm-20-2481

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-2481). 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All information from the SEER program is available and free for public, so the agreement of the medical ethics committee board was not necessary.

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Supplementary

Table S1 Point distributions and predictive scores for every parameter in the nomogram model

Variables	Nomogram score (distant metastasis)
Pathological differentiation	
Well; I	0
Moderately; II	26
Poorly; III	53
Undifferentiated; IV	80
T stage	
T1	0
T2	42
T3	55
T4	100
Lymph node status	
N0	0
N1	69
Tumor size	
≤30 mm	0
>30 mm	37
Histological type	
Clear cell	69
Papillary	45
Chromophobe	0
Others	67
Invasion beyond the capsule	
No invasion	0
Invasion	15
Surgery type	
Local excision	0
Nephrectomy	57

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