Original Article

Establishment of predictive model for patients with kidney cancer bone metastasis: a study based on SEER database

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Background: Bone is a common metastatic tissue of kidney cancer. Accurate prediction of the prognosis of patients with kidney cancer bone metastasis (KCBM) can help doctors and patients choose a further appropriate treatment.

Methods: During the period from January 1, 2010 to December 31, 2015, screening patients with kidney cancer diagnosed with bone metastases from the SEER database. Summary of demographic, pathology, number of other metastatic organs, and treatment for KCBM patients. All prognostic factors were plotted for Kaplan-Meier survival curves and log-rank test. Prognostic factors of P<0.001 in the log-rank test were chosen and used to establish nomograms of OS and KCSS. We used C-index, ROC curve, and calibration plot to test the prediction accuracy of two nomograms.

Results: A total of 4,234 KCBM patients were included in the study, and patients were diagnosed between January 1, 2010 and December 31, 2015. The model establishment group included 2,966 KCBM patients and the validation group included 1,268 KCBM patients. We have established nomograms for OS and KCSS respectively. These two nomograms included factors such as age, marital status, insurance status, histological type, grade, T stage, N stage, number of extra-bone metastatic organs, surgery, RT, and CT. The C-index of nomograms of OS and KCSS was 0.733 and 0.752, respectively. In all ROC curves, all AUC values were greater than 0.7, proving that the nomograms of both OS and KCSS have achieved medium prediction accuracy. The calibration plots of the model establishment group and the validation group showed good consistency between the predicted nomograms of OS and KCSS.

Conclusions: In this study, nomograms of OS and KCSS were established based on the published data of KCBM patients in the SEER database, and the model was validated internally and externally. The prediction accuracy of nomograms of OS and KCSS achieved satisfactory results. At present, this model has the ability to predict the prognosis of KCBM patients and can be used in clinical work.

Keywords: Kidney cancer bone metastasis (KCBM); SEER; nomogram

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Introduction

Kidney cancer is a malignant tumor originating from the renal tubule and collecting tubular epithelial system, and the incidence rate is 2% to 3% of adult malignant tumors (1). In 2018, the incidence of renal cancer in the United States had ranked 6th in male malignant tumors and 10th in female malignant tumors (2). According to the data, since 1950, the incidence and mortality of renal malignancies in the United States have been increasing year by year. By 2001, the incidence rate had increased by 126%, and the mortality rate had increased by 36.5%, while the 5-year survival rate

had only increased by about 9% (3,4). In China, this upward trend is also very obvious. In 2015, the number of new and death cases was about 66,800 and 23,400, respectively (1).

In recent years, advances in imaging diagnostic techniques and surgical techniques have enabled earlier resection of early-stage kidney cancer, but there are still some patients with kidney cancer who have distant metastases at the initial diagnosis or after undergoing radical surgery (5). In addition to the lungs, bone is the second most common site of metastasis of kidney cancer (6). Bone metastases often occur in the mid-shaft bone, of which 71% are osteolytic lesions, 18% are osteogenic lesions, and 11% are mixed lesions. Kidney cancer bone metastasis (KCBM) is a catastrophic event that can lead to pain and pathology in patients (7,8). The incidence of skeletal-related events (SRE) after bone metastasis in patients with kidney cancer is higher (74%) than in breast cancer (64%), myeloma (51%), and prostate cancer (44%) (9). SRE such as fractures, spinal cord compression, and hypercalcemia seriously affect the quality of life.

Accurate prediction of the prognosis of patients with KCBM can help doctors and patients choose a further appropriate treatment. The Surveillance, Epidemiology, and End Results (SEER) database is the US's leading cancer statistics database that records information on morbidity, mortality, and disease in millions of malignancies in some states and counties (10). We collected the data of patients with KCBM from this database for analysis and proposed to establish a clinical prediction model to provide a convenient and effective tool for predicting the prognosis and to evaluate its prediction accuracy.

Methods

Data collection

The National Cancer Institute's SEER database covers about 28% of the population of the United States and collects data on cancer patients from 18 tumor registration centers (11). The latest data for the (1973–2016 varying) database released in November 2018 was obtained using SEER stat special software (version 8.3.6), and data acquisition was done in client-server mode. During the period from January 1, 2010 to December 31, 2015, screening patients with kidney cancer diagnosed with bone metastases. Exclusion criteria include: no/unknown kidney cancer patients with bone metastases, unknown survival time and vital status.

Inclusion codes and criteria

The main endpoints were overall survival (OS) and kidney cancer-special survival (KCSS). In this study, we classified patients according to the following factors, such as age (<50, 50–70, >70), gender (female, male), race (White, Black, others), marital status (Married, Unmarried), insurance status (Insured, Uninsured).

For the tumor pathology, the patients were classified according to histological type (clear cell carcinoma, other), grade (I, II, III, IV, unknown), T stage (T0, T1, T2, T3, T4, TX), N stage (N0, N1, NX).

For the number of other metastatic organs and treatment, the patients were classified according to number of extra-bone (brain, liver, and lung) metastatic organs (0, 1, 2, 3), surgery (yes, no), radiotherapy (RT) (yes, no) and chemotherapy (CT) (yes, no).

Patients grouping

In order to establish an effective prognostic prediction model, all patients were divided into a model establishment group and validation group according to a random assignment method (ratio 7:3). Among them, the model establishment group included a total of 2,966 patients, and the validation group included 1,268 patients.

Statistical analysis

Demographic information about KCBM patients using a method of descriptive statistics. The chi-square test was used to analyze the dead/live of categorical variables of prognostic factors in KCBM patients. The survival time of each prognostic factor was expressed as the median and interquartile ranges. Kaplan-Meier survival curves and log-rank tests were used to analyze the OS and KCSS for each prognostic factor. Multivariate cox regression analysis was used to analyze all-cause mortality (ACM) and kidney cancer-special mortality (KCSM) for each prognostic factor and categorical variable. Moreover, the hazard ratios (HR) and 95% confidence intervals (CIs) for all strata of each factor were also calculated. The P value <0.05 was considered statistically significant.

Kaplan-Meier survival curves and construction of nomograms

Kaplan-Meier survival curves were plotted for all prognostic

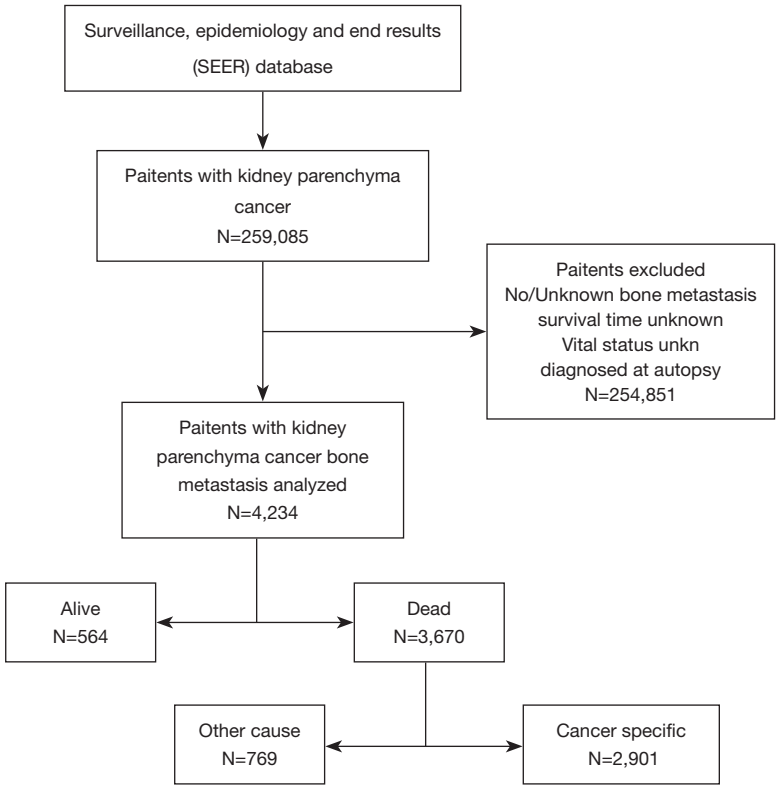

Figure 1 Flowchart of patients identification and selection.

factors. Based on the results of the multivariate Cox regression analysis, the prognostic predictors of P<0.001 in the log-rank test were included in the nomograms. The model was used to model establishment group data for internal verification of the nomograms, and the validation group data is used for external verification of the nomograms. The concordance index (C-index), receiver operating characteristic (ROC) curve and calibration curve were used to evaluate the accuracy of the model. The C-index was between 0.5 and 1, 0.5 was completely inconsistent, indicating that the model had no predictive effect, and 1 was completely consistent, indicating that the model's prediction results were completely consistent with the actual. In general, the C-index was less accurate at 0.50–0.70, moderate accuracy between 0.71 and 0.90, and high accuracy above 0.90 (12,13). The area under the ROC curve (AUC) referred to the area around the ROC curve and the x-axis, (1,0)-(1,1). Similar to the C-index, the AUC was less accurate at 0.50–0.70, moderate accuracy between 0.71 and 0.90, and high accuracy above 0.90 (14,15). The predicted probability of the nomograms of the OS and KCSS for 1, 3 and 5 years were compared with the observed survival probability to obtain calibration plots (16,17). All statistical analysis, model establishment group and validation group generation and construction of nomograms were performed by the R project (Version 3.6.1).

Results

Demographic, pathological, number of other metastatic organs, and treatment features of KCBM patients

The screening process for patients included in the study was shown in *Figure 1*. The number and proportion of patients with various prognostic factors were shown in *Table 1*, and the median survival was shown in *Table 2*. The mean age and median age of 4,234 patients were 65.63 and 65 years, respectively. In entire group, the majority of the categorical variables were 50–70 years old (56.3%), male (68.9%), White (83.1%), married (57.9%), insured (80.0%), clear cell carcinoma (78.5%), grade unknown (66.7%), T3 (25.7%), N0 (54.8%), number of extra-bone metastatic organs was

Table 1 Demographic information, pathology, number of other metastatic organs, and treatment information of KCBM patients

Characteristics	Entire group		Model establishment group		Validation group	
	No.	%	No.	%	No.	%
Total	4,234	100.0	2,966	100.0	1,268	100.0
Age at diagnosis						
<50	380	9.0	259	8.7	121	9.5
50–70	2,384	56.3	1,682	56.7	702	55.4
>70	1,470	34.7	1,022	34.5	448	35.3
Gender						
Female	1,317	31.1	898	30.3	419	33.0
Male	2,917	68.9	2,068	69.7	849	67.0
Race						
White	3,519	83.1	2,448	82.5	1,071	84.5
Black	434	10.3	308	10.4	126	9.9
Other	281	6.6	210	7.1	71	5.6
Marital status						
Married	2,450	57.9	1,712	57.7	738	58.2
Unmarried	1,784	42.1	1,254	42.3	530	41.8
Insurance status						
Insured	3,386	80.0	2,363	79.7	1,023	80.7
Uninsured	848	20.0	603	20.3	245	19.3
Histological type						
Clear cell carcinoma	3,324	78.5	2,319	78.2	1,005	79.3
Other	910	21.5	647	21.8	263	20.7
Grade						
I	61	1.4	46	1.6	15	1.2
II	286	6.8	201	6.8	85	6.7
III	663	15.7	469	15.8	194	15.3
IV	400	9.4	272	9.2	128	10.1
Unknown	2,824	66.7	1,979	66.7	845	66.6
Stage_T						
T0	57	1.3	41	1.4	16	1.3
T1	1,013	23.9	709	23.9	304	24.0
T2	668	15.8	473	15.9	195	15.4
T3	1,088	25.7	759	25.6	329	25.9
T4	424	10.0	290	9.8	134	10.6
TX	984	23.2	694	23.4	290	22.9

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Entire group		Model establishment group		Validation group	
	No.	%	No.	%	No.	%
Stage_N						
N0	2,320	54.8	1,636	55.2	684	53.9
N1	1,266	29.9	883	29.8	383	30.2
NX	648	15.3	447	15.1	201	15.9
Other metastases*						
0	1,822	43.0	1,280	43.2	542	42.7
1	1,595	37.7	1,113	37.5	482	38.0
2	725	17.1	506	17.1	219	17.3
3	92	2.2	67	2.3	25	2.0
Surgery						
Yes	1,144	27.0	815	27.5	329	25.9
No	3,090	73.0	2,151	72.5	939	74.1
RT						
Yes	2,133	50.4	1,496	50.4	637	50.2
No	2,101	49.6	1,470	49.6	631	49.8
CT						
Yes	2,119	50.0	1,479	49.9	640	50.5
No	2,115	50.0	1,487	50.1	628	49.5

*, number of extra-bone (brain, liver and lung) metastatic organs. KCBM, kidney cancer bone metastasis; CT, chemotherapy; RT, radiotherapy.

0 (43.0%), no surgery (73.0%), radiotherapy (50.4%), and chemotherapy (50.0%).

In model establishment group, the majority of the categorical variables were 50–70 years old (56.7%), male (69.7%), White (82.5%), married (57.7%), insured (79.7%), clear cell carcinoma (78.2%), grade unknown (66.7%), T3 (25.6%), N0 (55.2%), number of extra-bone metastatic organs was 0 (43.2%), no surgery (72.5%), radiotherapy (50.4%), and no chemotherapy (50.1%).

In validation group, the majority of the categorical variables were 50–70 years old (55.4%), male (67.0%), White (84.5%), married (58.2%), insured (80.7%), clear cell carcinoma (79.3%), grade unknown (66.6%), T3 (25.9%), N0 (53.9%), number of extra-bone metastatic organs was 0 (42.7%), no surgery (74.1%), radiotherapy (50.2%), and chemotherapy (50.5%).

The impact of different variables on ACM and KCSM

There were 3,670 patients with ACM and 2,901 patients with KCSM (*Figure 1*, *Table 3*). In the demographic data, >70 years patients had the highest ACM (91.7%) and KCSM (88.7%). Gender differences had no significant effect on ACM (87.2% *vs.* 86.4%, P=0.468) and KCSM (84.3% *vs.* 83.4%, P=0.508). Black patients had the highest ACM (88.9%) and KCSM (86.6%). Unmarried patients had the highest ACM (89.1%) and KCSM (86.7%). Uninsured patients had the highest ACM (88.7%) and KCSM (86.7%).

In tumour pathology data, patients with non-clear cell carcinoma had the highest ACM (91.5%) and KCSM (89.6%). Patients with grade II had the lowest ACM (68.2%) and KCSM (61.9%). Patients with T1 stage tumor had the lowest ACM (83.4%) and KCSM (78.6%). N0 stage tumor patients had the lowest ACM (81.5%) and KCSM (77.6%).

Table 2 Median survival and survival months of KCBM patients

Characteristics	Patients (N)	Median survival months
Total	4,234	6 [2–16]
Age at diagnosis		
<50	380	8 [3–19]
50–70	2,384	7 [2–17]
>70	1,470	4 [1–12]
Gender		
Female	1,317	5 [2–15]
Male	2,917	6 [2–16]
Race		
White	3,519	6 [2–16]
Black	434	5 [2–13]
Other	281	6 [2–16.5]
Marital status		
Married	2,450	7 [2–17]
Unmarried	1,784	5 [1–14]
Insurance status		
Insured	3,386	6 [2–16]
Uninsured	848	5 [2–13]
Histological type		
Clear cell carcinoma	3,324	6 [2–17]
Other	910	4 [1.75–11]
Grade		
I	61	7 [2.5–21]
II	286	17 [6–35]
III	663	9 [4–24]
IV	400	9 [3–17]
Unknown	2,824	4 [1–13]
Stage_T		
T0	57	5 [2–15.5]
T1	1,013	7 [2–19]
T2	668	6 [2–17]
T3	1,088	8 [3–19]
T4	424	4 [2–11]
TX	984	4 [1–11]
Stage_N		
N0	2,320	8 [3–21]
N1	1,266	4 [2–11]
NX	648	4 [1–11]
Other metastases*		
0	1,822	10 [3–24]
1	1,595	5 [2–13]
2	725	3 [1–8]
3	92	3 [1–6]
Surgery		
Yes	1,144	16 [7–32]
No	3,090	4 [1–11]
RT		
Yes	2,133	8 [3–18]
No	2,101	4 [1–13]
CT		
Yes	2,119	9 [4–19]
No	2,115	3 [1–11]

*, number of extra-bone (brain, liver and lung) metastatic organs. KCBM, kidney cancer bone metastasis; CT, chemotherapy; RT, radiotherapy.

The number of extra-bone metastatic organs was 0, ACM and KCSM were lowest, 80.1% and 75.3% respectively. Among the treatment data, patients who did not undergo surgery had significantly higher ACM (92.7% *vs.* 70.5%, P<0.001) and KCSM (90.8% *vs.* 66.3%, P<0.001) than patients who underwent surgery. Radiotherapy had no significant effect on ACM (85.9% *vs.* 87.5%, P=0.127) and KCSM (83.3% *vs.* 84.1%, P=0.517) in patients. Receiving chemotherapy could significantly reduce ACM (84.8% *vs.* 88.6%, P<0.001) and KCSM (82.1% *vs.* 85.5%, P=0.007) in patients.

Kaplan-Meier survival curves of each prognostic factor

We plotted Kaplan-Meier survival curves for demographic factors (*Figure 2*), pathological factors (*Figure 3*), and the

Table 3 Univariate survival analyses of KCBM patients according to various clinicopathological variables

Characteristics	All cause						Kidney cancer-special					
	Total	Dead		Alive		P	Total	Dead		Alive		P
		No.	%	No.	%			No.	%	No.	%	
Total	4,234	3,670	86.7	564	13.3		3,465	2,901	83.7	564	16.3	
Age at diagnosis						<0.001						<0.001
<50	380	323	85.0	57	15.0		356	299	84.0	57	16.0	
50–70	2,384	1,999	83.9	385	16.1		2,033	1,648	81.1	385	18.9	
>70	1,470	1,348	91.7	122	8.3		1,076	954	88.7	122	11.3	
Gender						0.468						0.508
Female	1,317	1,149	87.2	168	12.8		1,073	905	84.3	168	15.7	
Male	2,917	2,521	86.4	396	13.6		2,392	1,996	83.4	396	16.6	
Race						0.317						0.243
White	3,519	3,039	86.4	480	13.6		2,869	2,389	83.3	480	16.7	
Black	434	386	88.9	48	11.1		358	310	86.6	48	13.4	
Other	281	245	87.2	36	12.8		238	202	84.9	36	15.1	
Marital status						<0.001						<0.001
Married	2,450	2,081	84.9	369	15.1		1,996	1,627	81.5	369	18.5	
Unmarried	1,784	1,589	89.1	195	10.9		1,469	1,274	86.7	195	13.3	
Insurance status						0.055						0.015
Insured	3,386	2,918	86.2	468	13.8		2,744	2,276	82.9	468	17.1	
Uninsured	848	752	88.7	96	11.3		721	625	86.7	96	13.3	
Histological type						<0.001						<0.001
Clear cell carcinoma	3,324	2,837	85.3	487	14.7		2,724	2,237	82.1	487	17.9	
Other	910	833	91.5	77	8.5		741	664	89.6	77	10.4	
Grade						<0.001						<0.001
I	61	47	77.0	14	23.0		47	33	70.2	14	29.8	
II	286	195	68.2	91	31.8		239	148	61.9	91	38.1	
III	663	524	79.0	139	21.0		582	443	76.1	139	23.9	
IV	400	327	81.8	73	18.3		347	274	79.0	73	21.0	
Unknown	2,824	2,577	91.3	247	8.7		2,250	2,003	89.0	247	11.0	
Stage_T						<0.001						<0.001
T0	57	49	86.0	8	14.0		44	36	81.8	8	18.2	
T1	1,013	845	83.4	168	16.6		784	616	78.6	168	21.4	
T2	668	571	85.5	97	14.5		572	475	83.0	97	17.0	
T3	1,088	896	82.4	192	17.6		941	749	79.6	192	20.4	
T4	424	392	92.5	32	7.5		357	325	91.0	32	9.0	

Table 3 (*continued*)

Table 3 (*continued*)

Characteristics	All cause						Kidney cancer-special					
	Total	Dead		Alive		P	Total	Dead		Alive		P
		No.	%	No.	%			No.	%	No.	%	
TX	984	917	93.2	67	6.8		767	700	91.3	67	8.7	
Stage_N						<0.001						<0.001
N0	2,320	1,891	81.5	429	18.5		1,918	1,489	77.6	429	22.4	
N1	1,266	1,179	93.1	87	6.9		1,037	950	91.6	87	8.4	
NX	648	600	92.6	48	7.4		510	462	90.6	48	9.4	
Other metastases*						<0.001						<0.001
0	1,822	1,460	80.1	362	19.9		1,466	1,104	75.3	362	24.7	
1	1,595	1,429	89.6	166	10.4		1,315	1,149	87.4	166	12.6	
2	725	693	95.6	32	4.4		603	571	94.7	32	5.3	
3	92	88	95.7	4	4.3		81	77	95.1	4	4.9	
Surgery						<0.001						<0.001
Yes	1,144	806	70.5	338	29.5		1,004	666	66.3	338	33.7	
No	3,090	2,864	92.7	226	7.3		2,461	2,235	90.8	226	9.2	
RT						0.127						0.517
Yes	2,133	1,832	85.9	301	14.1		1,806	1,505	83.3	301	16.7	
No	2,101	1,838	87.5	263	12.5		1,659	1,396	84.1	263	15.9	
CT						<0.001						0.007
Yes	2,119	1,796	84.8	323	15.2		1,806	1,483	82.1	323	17.9	
No	2,115	1,874	88.6	241	11.4		1,659	1,418	85.5	241	14.5	

*, number of extra-bone (brain, liver and lung) metastatic organs. KCBM, kidney cancer bone metastasis; CT, chemotherapy; RT, radiotherapy.

number of other metastatic organs and treatment (*Figure 4*). In addition, the log-rank test for all variables was shown in *Table 4*.

It was observed that the increased in age was significantly related to the worsening prognosis (*Figure 2A*,*B*). There was no significant correlation between gender difference and prognosis survival (*Figure 2C*,*D*). Compared with other people, white and black were significantly associated with poor prognosis (*Figure 2E*,*F*). Unmarried patients were significantly associated with poor prognosis (*Figure 2G*,*H*). Uninsured patients were significantly associated with poor prognosis (*Figure 2I*,*J*).

Observing the survival curves of pathological factors, the histological type was clear cell carcinoma was clearly associated with a good prognosis (*Figure 3A*,*B*). Grade II tumors were significantly associated with a good prognosis (*Figure 3C*,*D*). T4 and TX tumors were significantly associated with poor prognosis (*Figure 3E*,*F*). Compared with N1 and NX tumors, N0 tumors clearly had a better prognosis (*Figure 3G*,*H*).

Observing the survival curves of the number of other metastatic organs and treatment. In addition to bone, the number of other metastatic organs was 0 significantly correlated with a good prognosis (*Figure 4A*,*B*). Surgical treatment could significantly improve the prognosis of patients (*Figure 4C*,*D*). Receiving RT or CT could improve the prognosis of patients to some extent (radiotherapy: *Figure 4E*,*F*; chemotherapy: *Figure 4G*,*H*).

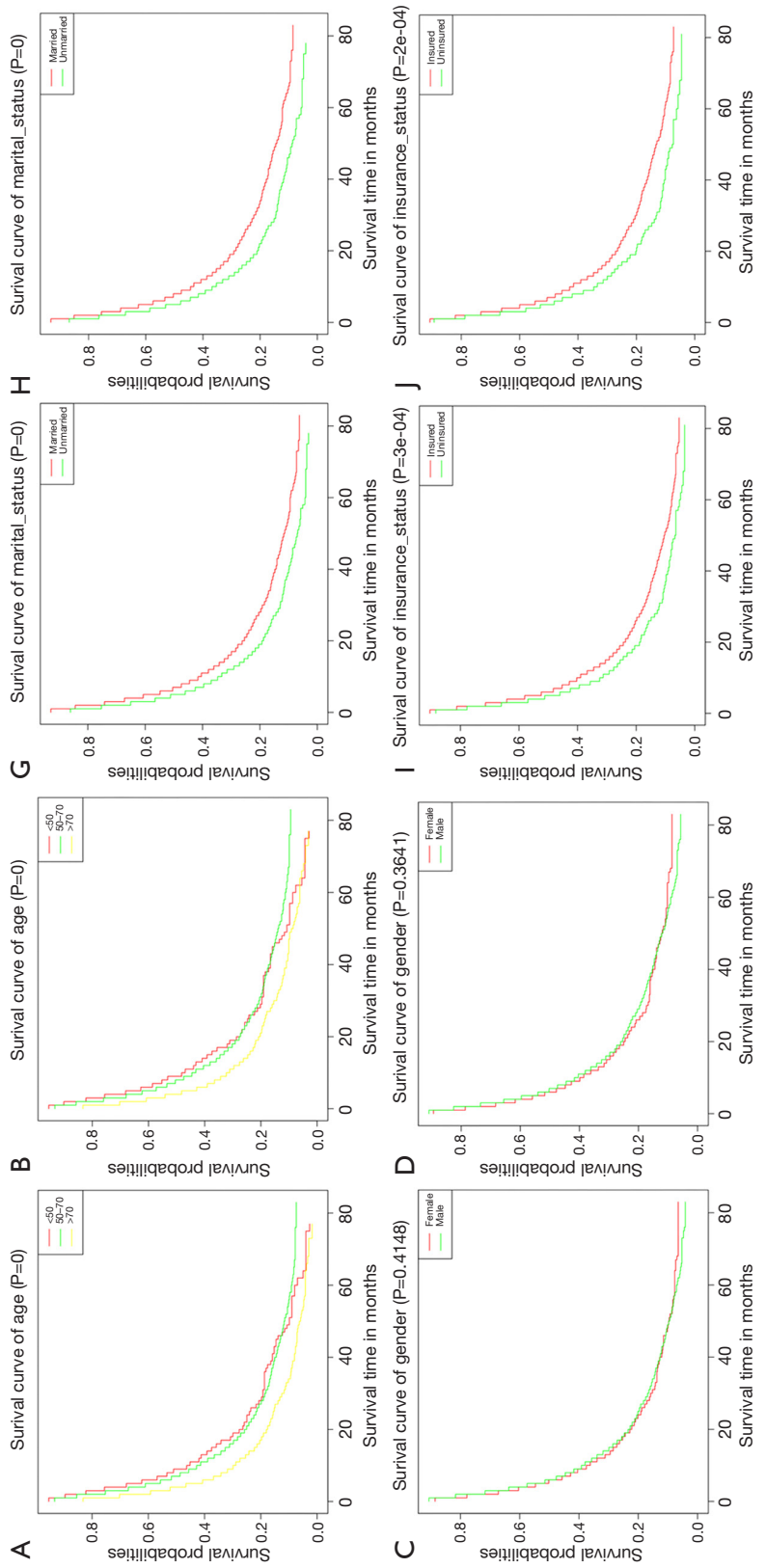

Figure 2 Survival curves in KCBM patients according to demographic factors. (A,B) Kaplan-Meier curves among patients stratified by age at diagnosis for OS (A) and KCSS (B); (C,D) Kaplan-Meier curves among patients stratified by gender for OS (C) and KCSS (D); (E,F) Kaplan-Meier curves among patients stratified by race for OS (E) and KCSS (F); (G,H) Kaplan-Meier curves among patients stratified by marital status for OS (G) and KCSS (H); (I,J) Kaplan-Meier curves among patients stratified by insurance status for OS (I) and KCSS (J). KCBM, kidney cancer bone metastasis; OS, overall survival; KCSS, kidney cancer-special survival.

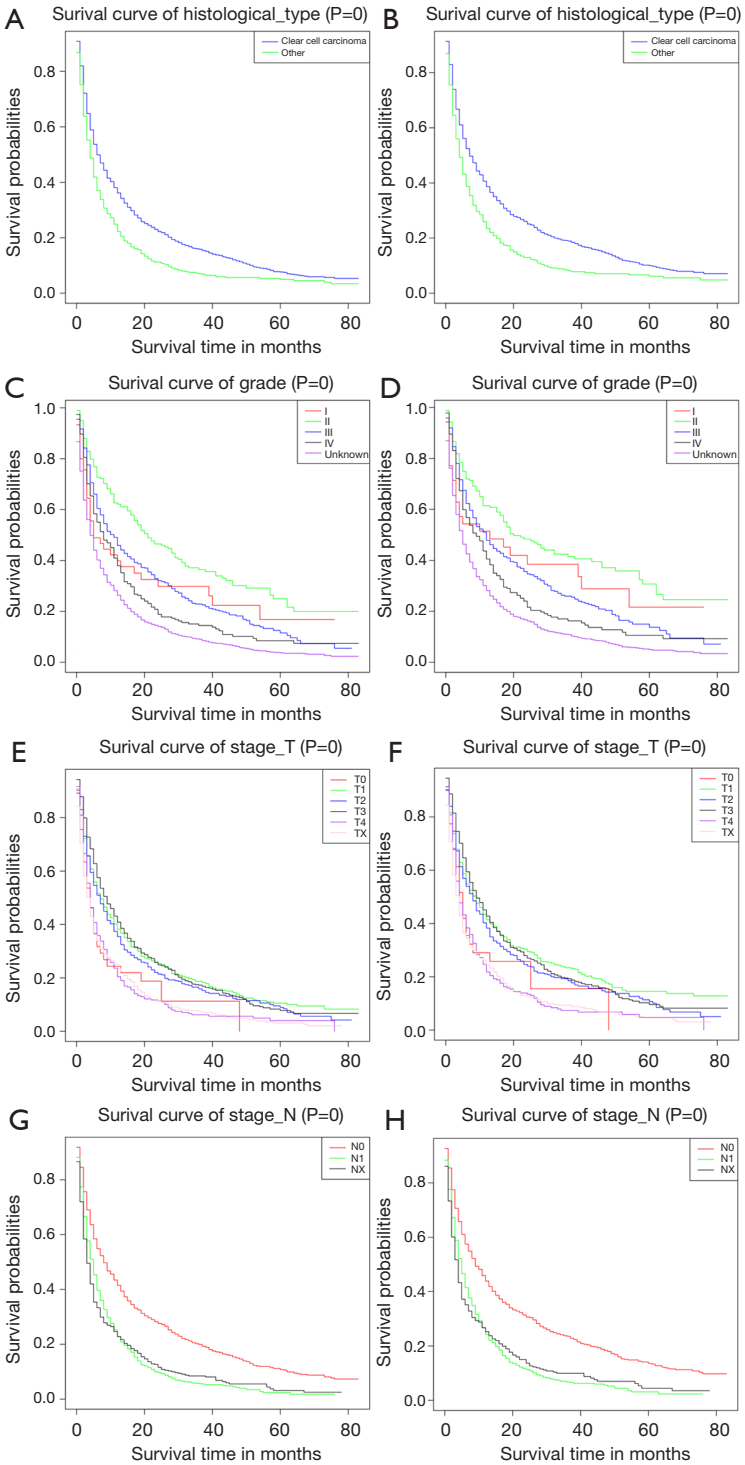

Figure 3 Survival curves in KCBM patients according to pathological factors. (A,B) Kaplan-Meier curves among patients stratified by histological type for OS (A) and KCSS (B). (C,D) Kaplan-Meier curves among patients stratified by grade for OS (C) and KCSS (D). (E,F) Kaplan-Meier curves among patients stratified by T stage for OS (E) and KCSS (F). (G,H) Kaplan-Meier curves among patients stratified by N stage for OS (G) and KCSS (H). KCBM, kidney cancer bone metastasis; OS, overall survival; KCSS, kidney cancer-special survival.

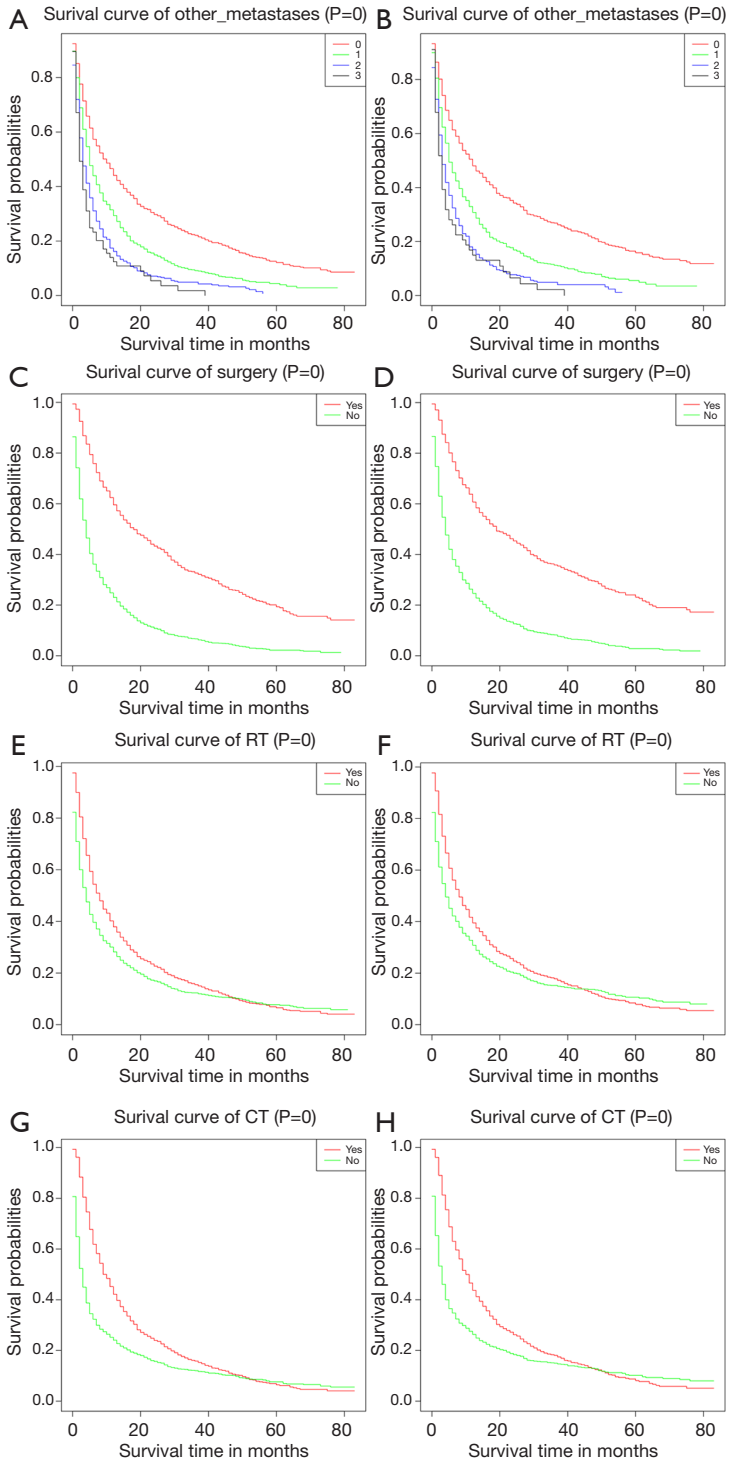

Figure 4 Survival curves in KCBM patients according to number of other metastatic organs and treatment. (A,B) Kaplan-Meier curves among patients stratified by other metastases for OS (A) and KCSS (B); (C,D) Kaplan-Meier curves among patients stratified by surgery/no surgery for OS (C) and KCSS (D); (E,F) Kaplan-Meier curves among patients stratified by RT/no RT for OS (E) and KCSS (F); (G,H) Kaplan-Meier curves among patients stratified by CT/no CT for OS (G) and KCSS (H); KCBM, kidney cancer bone metastasis; OS, overall survival; KCSS, kidney cancer-special survival; CT, chemotherapy; RT, radiotherapy.

Table 4 Multivariate Cox regression analysis for ACM and KCSM in KCBM patients

Characteristics	ACM				KCSM			
	HR	95% CI	P value	Log-rank (P value)	HR	95% CI	P value	Log-rank (P value)
Age at diagnosis				<0.001				<0.001
<50	1.000 (reference)				1.000 (reference)			
50–70	1.067	0.924–1.233	0.378		1.058	0.909–1.231	0.466	
>70	1.321	1.130–1.544	<0.001		1.307	1.107–1.544	0.002	
Gender								
Female	1.000 (reference)			0.415	1.000 (reference)			0.364
Male	0.994	0.912–1.084	0.892		1.0318	0.936–1.137	0.528	
Race				0.017				0.024
White	1.000 (reference)				1.000 (reference)			
Black	1.021	0.897–1.163	0.750		1.009	0.873–1.167	0.903	
Other	0.937	0.804–1.090	0.398		0.945	0.799–1.119	0.513	
Marital status				<0.001				<0.001
Married	1.000 (reference)				1.000 (reference)			
Unmarried	1.084	0.999–1.176	0.053		1.082	0.987–1.186	0.094	
Insurance status				<0.001				<0.001
Insured	1.000 (reference)				1.000 (reference)			
Uninsured	1.078	0.973–1.194	0.150		1.057	0.945–1.184	0.333	
Histological type				<0.001				<0.001
Clear cell carcinoma	1.000 (reference)				1.000 (reference)			
Other	1.530	1.371–1.708	<0.001		1.616	1.430–1.827	<0.001	
Grade				<0.001				<0.001
I	1.000 (reference)				1.000 (reference)			
II	0.848	0.580–1.241	0.396		0.877	0.561–1.373	0.567	
III	1.290	0.902–1.844	0.163		1.318	0.863–2.012	0.201	
IV	1.718	1.184–2.494	0.004		1.677	1.081–2.602	0.021	
Unknown	1.174	0.833–1.653	0.360		1.167	0.776–1.757	0.459	
Stage_T				<0.001				<0.001
T0	1.000 (reference)				1.000 (reference)			
T1	0.870	0.619–1.222	0.421		0.953	0.638–1.423	0.813	
T2	0.823	0.582–1.164	0.271		0.895	0.596–1.346	0.595	
T3	0.935	0.661–1.322	0.703		1.026	0.683–1.541	0.903	
T4	1.020	0.716–1.453	0.914		1.124	0.742–1.701	0.582	
TX	0.872	0.621–1.225	0.430		0.960	0.644–1.433	0.843	

Table 4 (*continued*)

Table 4 (*continued*)

Characteristics	ACM				KCSM			
	HR	95% CI	P value	Log-rank (P value)	HR	95% CI	P value	Log-rank (P value)
Stage_N				<0.001				<0.001
N0	1.000 (reference)				1.000 (reference)			
N1	1.448	1.320–1.589	<0.001		1.457	1.314–1.616	<0.001	
NX	1.150	1.016–1.302	0.027		1.120	0.972–1.289	0.116	
Other metastases*				<0.001				<0.001
0	1.000 (reference)				1.000 (reference)			
1	1.474	1.344–1.616	<0.001		1.529	1.377–1.698	<0.001	
2	1.999	1.778–2.247	<0.001		2.124	1.861–2.423	<0.001	
3	2.532	1.959–3.274	<0.001		2.623	1.976–3.481	<0.001	
Surgery				<0.001				<0.001
Yes	1.000 (reference)				1.000 (reference)			
No	2.577	2.264–2.934	<0.001		2.608	2.262–3.008	<0.001	
RT				<0.001				<0.001
Yes	1.000 (reference)				1.000 (reference)			
No	1.057	0.974–1.146	0.184		1.004	0.916–1.100	0.938	
CT				<0.001				<0.001
Yes	1.000 (reference)				1.000 (reference)			
No	1.847	1.698–2.009	<0.001		1.840	1.674–2.021	<0.001	

*, number of extra-bone (brain, liver and lung) metastatic organs. reference: data as a standard reference. ACM, all-cause mortality; KCSM, kidney cancer-special mortality; KCBM, kidney cancer bone metastasis; CT, chemotherapy; RT, radiotherapy.

Multivariate cox regression of prognostic factors in KCBM patients and the construction of nomograms

Multivariate cox regression analysis of all variables, and HR and 95% CIs were shown in *Table 4*. We have established their own nomogram for OS (*Figure 5*) and KCSS (*Figure 6*) respectively. These two nomograms included factors such as age, marital status, insurance status, histological type, grade, T stage, N stage, number of extra-bone metastatic organs, surgery, RT, and CT.

Interior and external verification of nomogram

The C-index of the nomogram of OS and KCSS was 0.733 and 0.752, respectively. The ROC curve results of the model establishment group and the validation group were shown in *Figure 7* (ROC curve of OS) and *Figure 8* (ROC curve of KCSS), respectively. In all ROC curves, all AUC values were greater than 0.7. The calibration plots of the model establishment group and the validation group showed good consistency between the predicted nomograms of OS (*Figure 9*) and KCSS (*Figure 10*).

Discussion

In the first visit to kidney cancer, 20–50% of patients have a local invasion or distant metastasis (18). Distant metastasis seriously affects the quality of life of patients and increases the difficulty of treatment (19). Especially bone metastasis is recognized as an important prognostic factor for patients with renal cancer. Bone metastasis, suggesting that the tumor enters the late stage, is

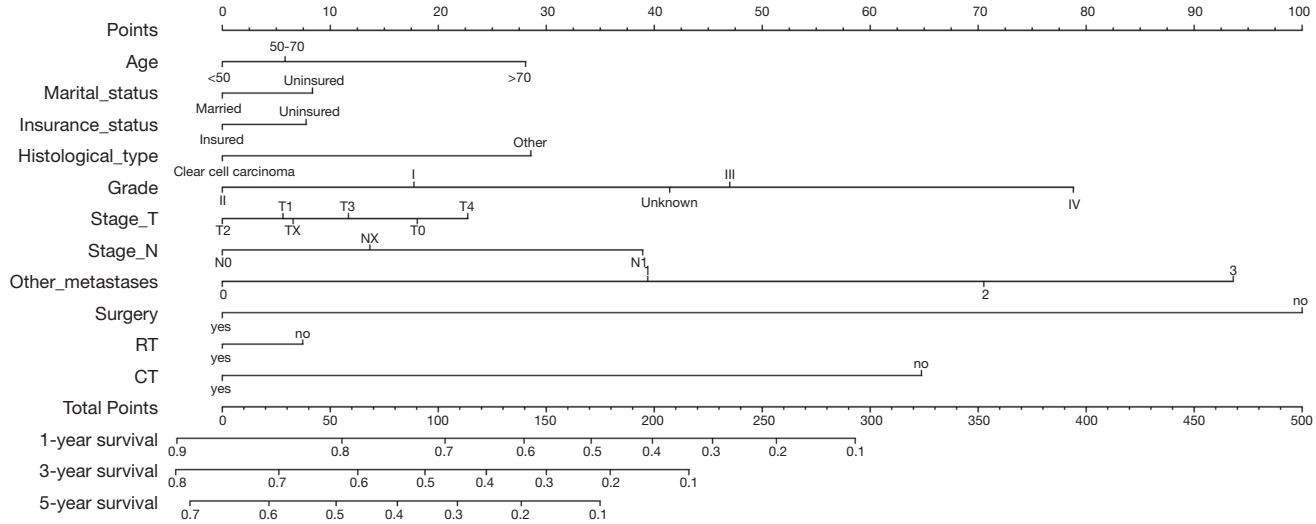

Figure 5 Nomogram of overall survival at 1, 3, and 5 years in patients with kidney cancer bone metastasis prediction.

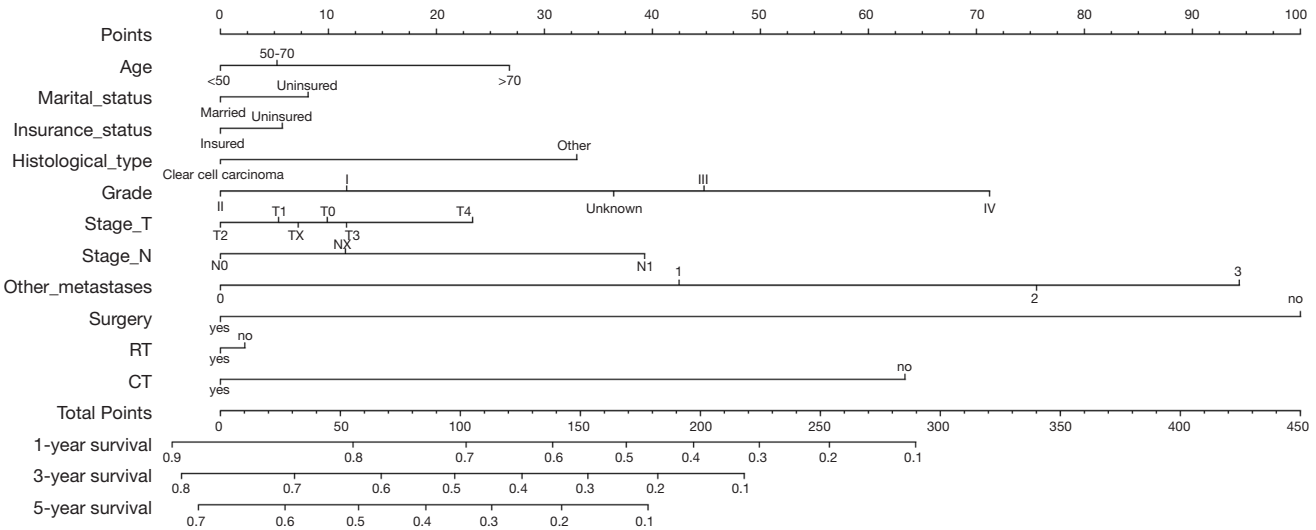

Figure 6 Nomogram of kidney cancer-special survival at 1, 3, and 5 years in patients with kidney cancer bone metastasis prediction.

generally considered to have a shorter survival period (18-20). Seaman *et al.* (20) found that the average survival time for patients with renal cell carcinoma and bone metastases was 13.8 months, compared with 25.3 months for patients without bone metastases. It was also believed that the prognosis of patients with cancer was related to the presence of bone metastases in the diagnosis of kidney cancer, and also to the patient's own physical condition and treatment (21). Therefore, summarizing the clinical features and treatment methods of KCBM was conducive to improving the treatment level of such diseases. In addition, the prognostic prediction model established by using the currently collected data makes doctors had a more objective judgment on the prognosis of KCBM patients, and it was also convenient to promote and apply.

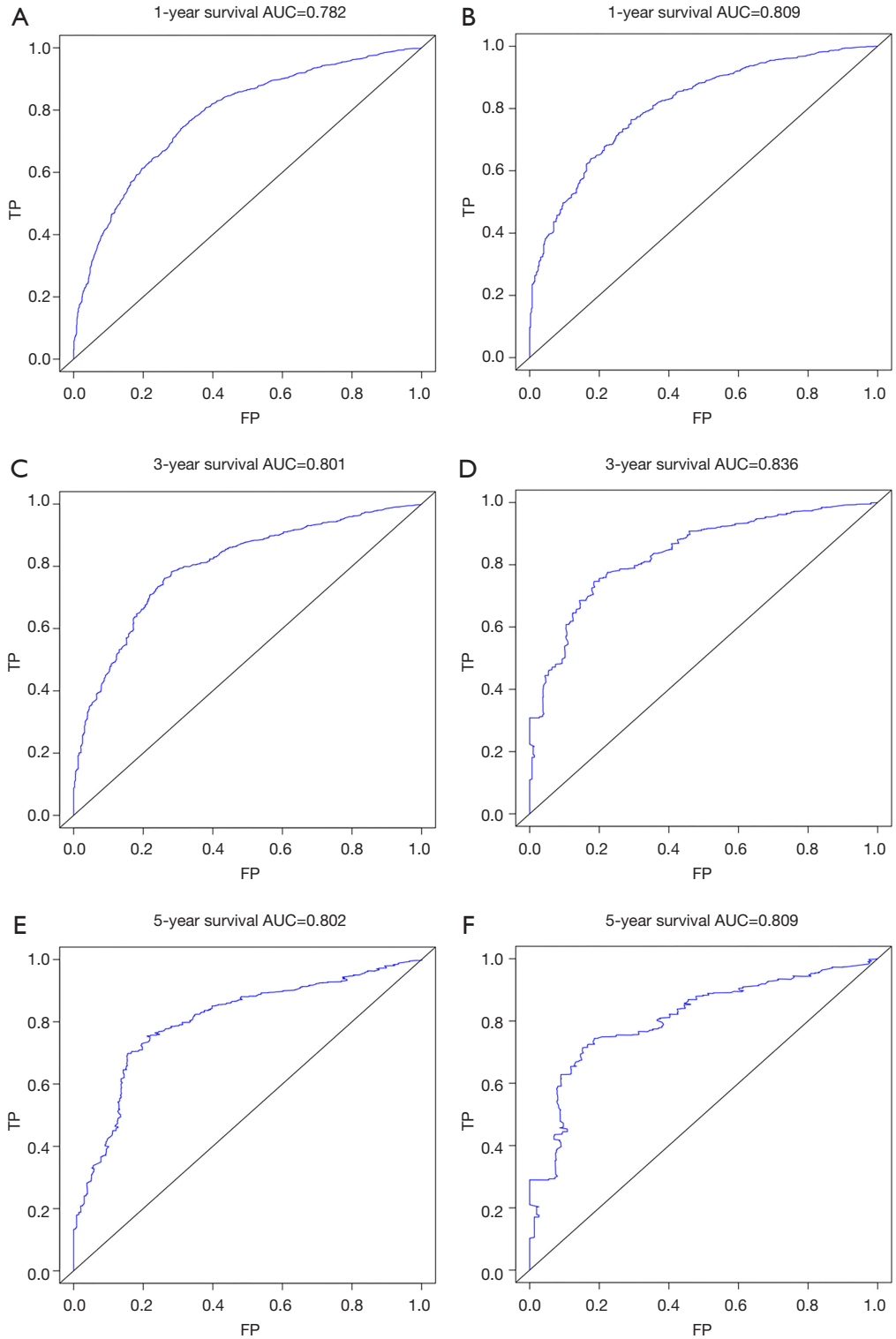

Figure 7 ROC curve of overall survival (OS). (A,C,E) ROC curves for 1 year (A), 3 years (C), and 5 years (E), respectively, validated by the model establishment group; (B,D,F) ROC curves for 1 year (B), 3 years (D), and 5 years (F), respectively, validated by the validation group; AUC, area under the ROC curve.

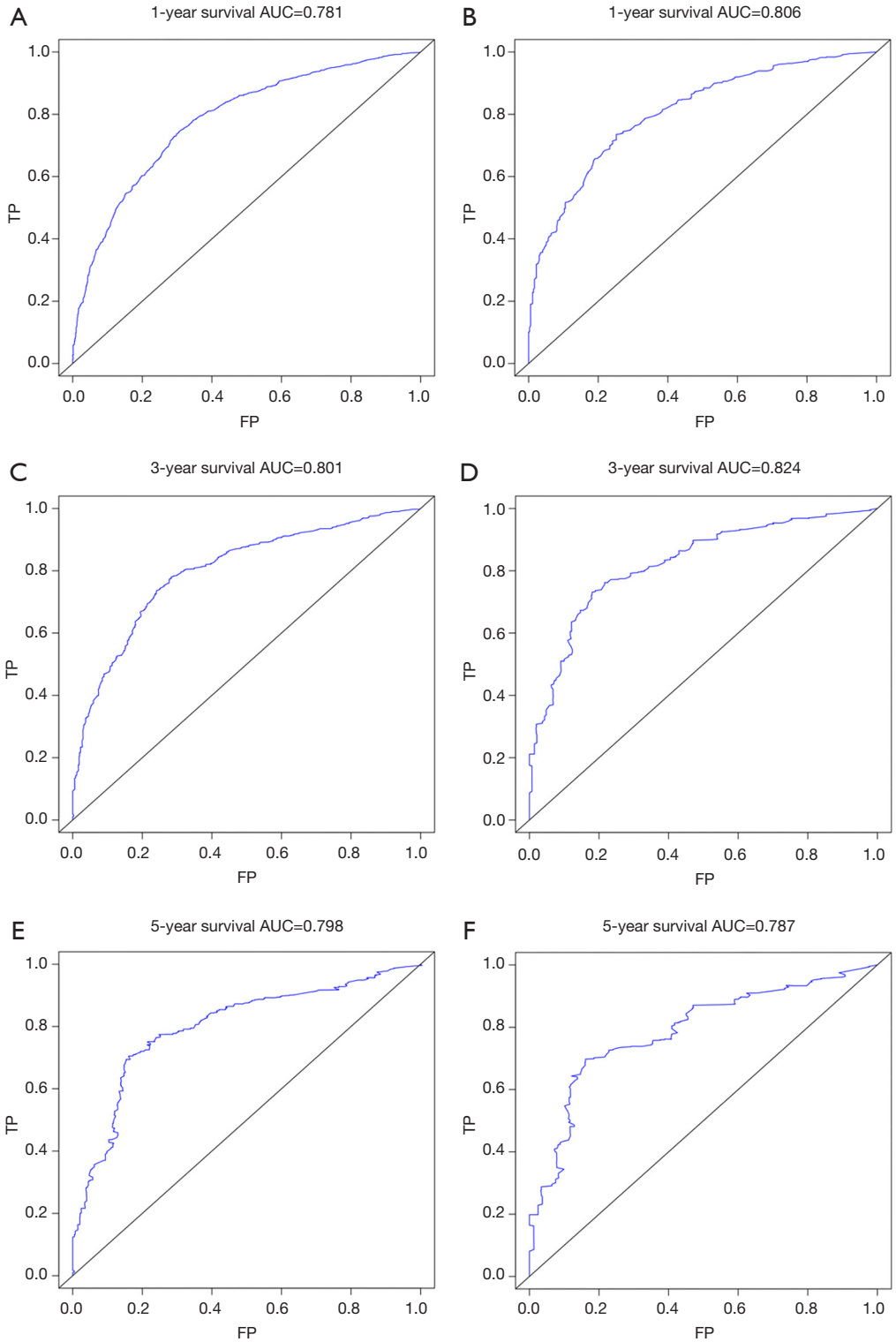

Figure 8 ROC curve of kidney cancer-special survival (KCSS). (A,C,E) ROC curves for 1 year (A), 3 years (C), and 5 years (E), respectively, validated by the model establishment group; (B,D,F) ROC curves for 1 year (B), 3 years (D), and 5 years (F), respectively, validated by the validation group. AUC, area under the ROC curve.

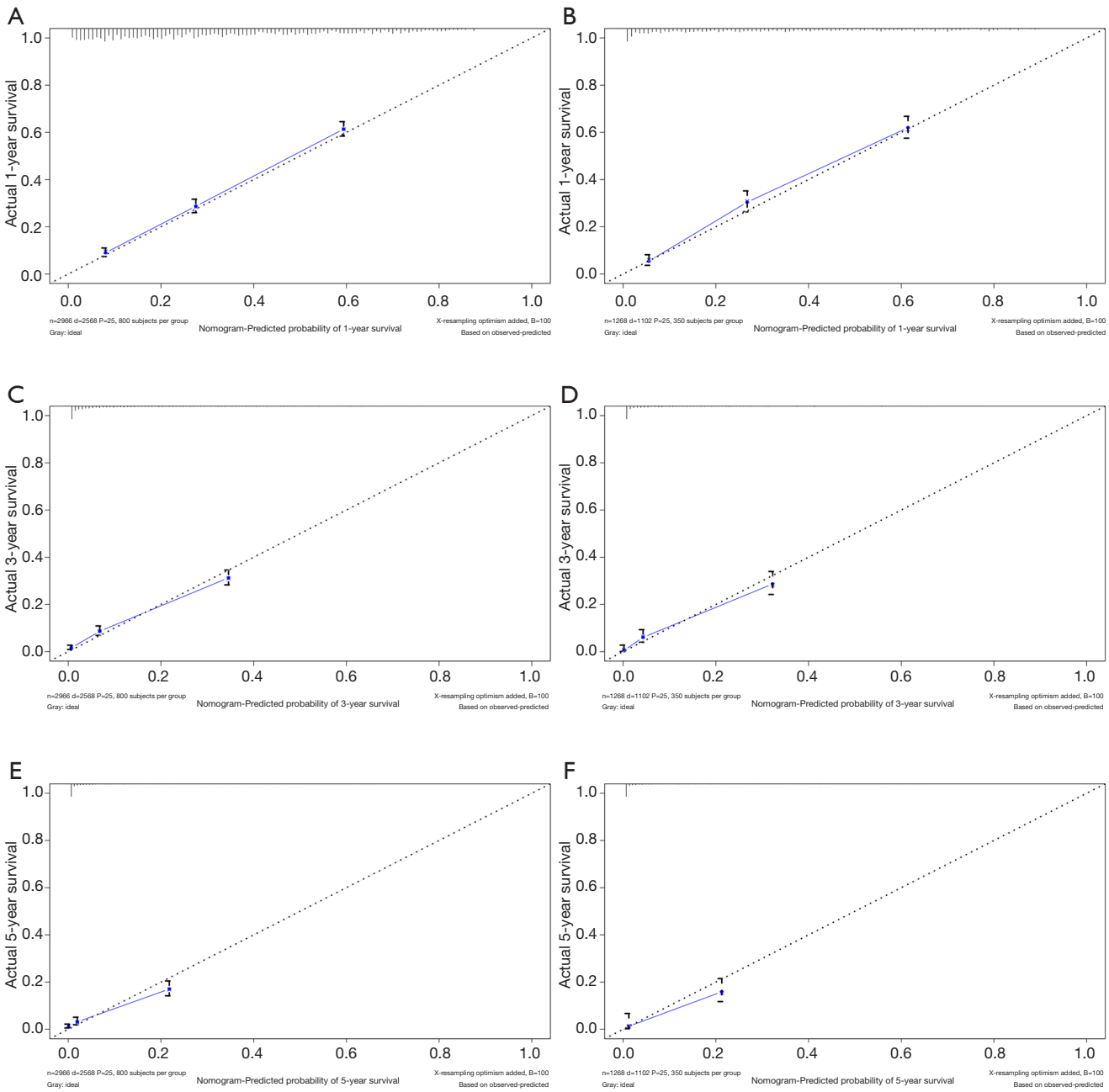

Figure 9 Calibration plots of overall survival (OS). (A,C,E) Calibration plots for 1 year (A), 3 years (C), and 5 years (E), respectively, validated by the model establishment group; (B,D,F) calibration plots for 1 year (B), 3 years (D), and 5 years (F), respectively, validated by the validation group.

Demographic features of KCBM patients

The incidence rates varied from country to country or from region to region. Generally speaking, the incidence rate in developed countries was higher than that in developing countries. Urban areas were higher than in rural areas. There were approximately twice as many male patients as female patients. The age of high incidence was 50 to 70 years old (22). In our study, patients enrolled in the study were aged 50–70 years (56.3%), and the number of male patients was

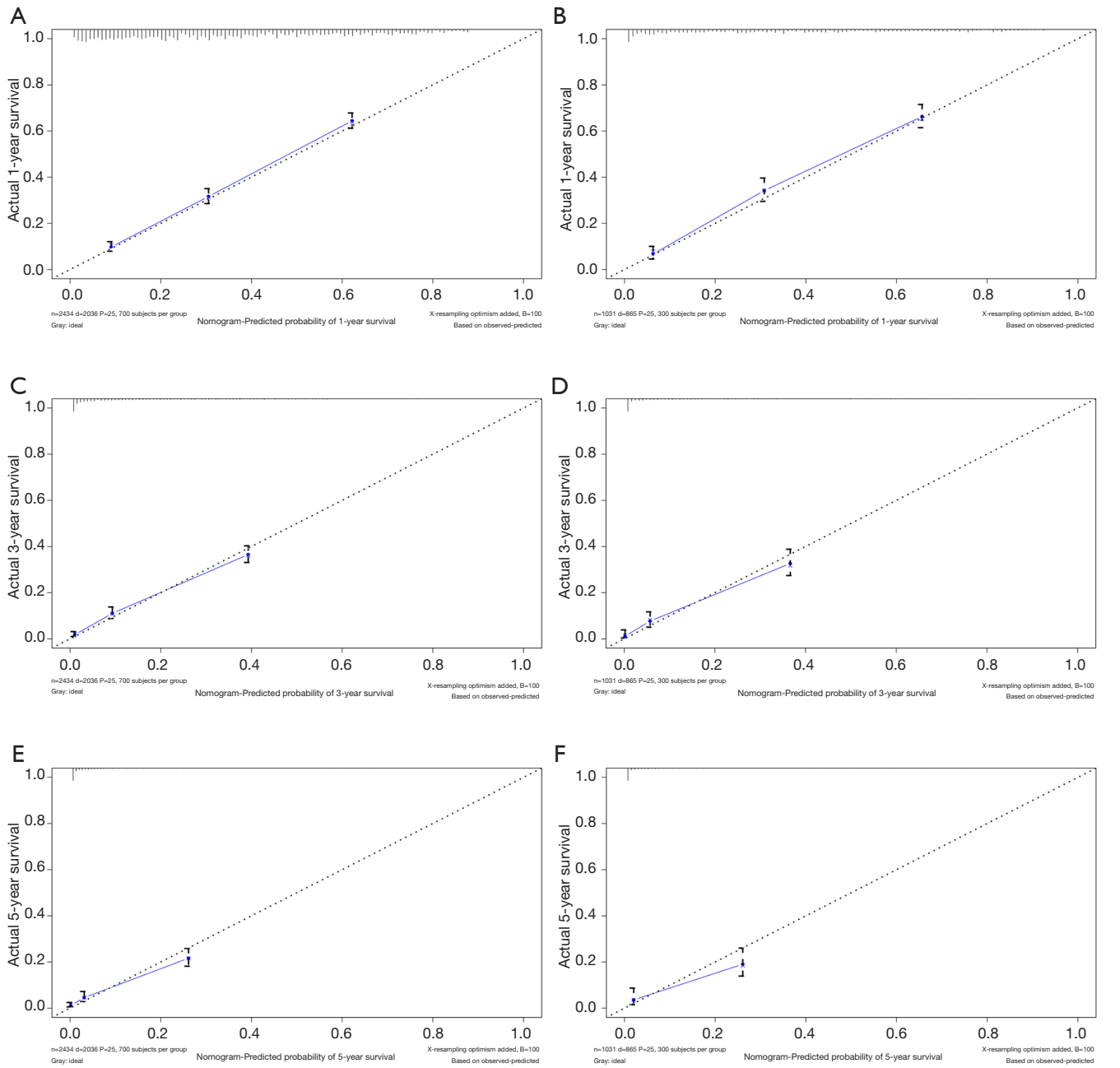

Figure 10 Calibration plots of kidney cancer-special survival (KCSS). (A,C,E) Calibration plots for 1 year (A), 3 year (C), and 5 years (E), respectively, validated by the model establishment group; (B,D,F) calibration plots for 1 year (B), 3 years (D), and 5 years (F), respectively, validated by the validation group.

more than twice that of female patients (68.9% *vs.* 31.1%), which was similar to previous reports. The race was related to the prognosis of kidney cancer. Stafford *et al.* (23) analyzed the demographic factors and causes of death of 39,434 kidney cancer patients from the California Cancer Registry from 1988 to 2004 and found that black had higher mortality than whites and other races. This conclusion was also confirmed in our study. The ACM and KCSM were the

highest in black patients with KCBM. In this study, it was found that people who were unmarried (separated, divorced, or single) had higher ACM and KCSM. Epidemiological investigations of not only kidney cancer but also a variety of cancers had all found an increase in mortality from unmarried status. A study found that patients who were unmarried were more likely not to undergo surgery. In the clear cell cancer patient population, the T stage of patents who had never been married was higher than those who were married, separated or divorced. Unmarried kidney cancer patients had higher ACM and cancer-specific mortality than those who were married (24). The status of insurance was also analyzed, and it was found that the ACM and KCSM of patients insured were significantly lower than those of patients not insured. This might be related to the patient's ability to pay for the cost of treatment. The patient might be more actively faced with future treatments without worrying about the high cost of treatment, and clinicians will have fewer concerns when choosing treatment. A sound and comprehensive insurance system had a positive effect on the prognosis of KCBM patients.

Tumor pathological features of KCBM patients

The pathology of the tumor was also an important factor affecting the prognosis. Reports in the literature suggested that patients with a histological type of clear cell carcinoma had a better prognosis than patients with other tissue types (25-27). In our study, the probability of survival in patients with a histological type of clear cell carcinoma was significantly higher than in other types of patients, supporting the previous literature. Tumor grading and staging were closely related to prognosis. Nese *et al.* (28) found that according to different grades, the 5-year survival rate showed significant stratification in all types of renal cell carcinoma, with grade I being 77.8%, grade II being 69.6%, grade III being 48.8%, and grade IV being 35.5%. In our research, we also observed a very obvious stratification phenomenon. As the grading increases, the patient's expected survival time decreases significantly. The same situation also occurred in the TNM stage of the tumor, the T or N stage increased, and the patient's expected survival time also decreased significantly.

The number of other metastatic organs, and treatment features of KCBM patients

In addition to bone tissue, the lungs, brain, and liver were also organs that were prone to metastasis (29,30). Our study found that an increase in the number of metastatic organs indicates a poor prognosis. Therefore, it was recommended to conduct a comprehensive examination of patients with kidney cancer to determine the specific number of metastatic organs. The treatment of kidney cancer also affected the prognosis of patients with KCBM. There were reports that when kidney cancer was combined with multiple organs (especially the liver, brain, etc.), nephrectomy did not effectively increase the survival rate, which in turn led to an increase in death rate within 6 months after surgery (31). In addition, in a new CARMENA (Cancer du Rein Metastatique Nephrectomie et Anti angiogéniques) trial, the MSKCC (Memorial Sloan Kettering Cancer Center) prediction model was classified as an intermediate-risk or poor-risk patient with metastatic kidney cancer, the efficacy of the targeted drug sunitinib alone is not inferior to nephrectomy followed by sunitinib (32). This study changed our preference for surgery, especially in patients with intermediate-risk or poor-risk of metastatic kidney cancer. However, in this study, patients who underwent surgery had significantly lower ACM (70.5% *vs.* 92.7%, P<0.001) and KCSM (66.3% *vs.* 90.8%, P<0.001) than those who did not. It was reasonable to believe that the surgical treatment of kidney cancer was an effective method to improve prognosis. Although kidney cancer itself was not sensitive to radiotherapy, radiotherapy for bone metastases could alleviate bone pain, reduce the risk of pathological fractures, and relieve spinal cord compression (33,34). Our study also found that radiotherapy did not reduce ACM (85.9% *vs.* 87.5%, P=0.127) and KCSM (83.3% *vs.* 84.1%, P=0.517). Chemotherapy as important treatment, whether it was neoadjuvant chemotherapy or postoperative supplemental chemotherapy, was of great significance. In the present study, the risk of ACM and the risk of KCSM in patients who did not receive chemotherapy were 1.847 and 1.840 times higher than those who received chemotherapy, respectively. We insisted that active chemotherapy remained an effective way to improve prognosis.

Establishment and verification of nomograms

To make the results of multivariate Cox regression more visual and easy to use. We established nomograms for OS and KCSS, respectively, and verified the accuracy of the two prediction models. The C-index of both nomograms was greater than 0.7, achieving moderate accuracy. Secondly, the AUC values calculated by the ROC curve were also between 0.71 and 0.9, achieving moderate accuracy. Finally, we had

separately drawn the calibration plots. In all the calibration plots, we could observe the better fitting degree between the predicted value and the actual value. Therefore, we believed that the predictive model as a whole has achieved moderate accuracy and could be used in actual clinical work.

Limitations

This study is based on the registration information of KCBM patients in the SEER database. Although the database summarizes the information of KCBM patients as detailed as possible, it still has its limitations. Firstly, we cannot obtain the performance status, comorbidities, time to metastasis, type of surgery/radiotherapy/systemic therapy performed and when during the natural history of the disease. Secondly, we cannot obtain the specific symptoms of bone metastases from individual patients and the bisphosphonate treatment of these patients from the database. The lack of these data makes the prediction accuracy of the model lower. Finally, the SEER database only describes whether patients receive chemotherapy, and does not show the toxic effects of chemotherapy, which also affects our judgment of the relationship between chemotherapy and prognosis. In addition to the limitations of the database itself, we also believe that the verification of the clinical prediction model requires more external data and requires multi-center, large sample data for repeated verification, which is a long-term and complicated work.

Conclusions

In this study, nomograms of OS and KCSS were established based on the published data of KCBM patients in the SEER database, and the model was validated internally and externally. These verifications confirmed the validity and accuracy of the model. At present, this model has the ability to predict the prognosis of KCBM patients and can be used in clinical work. However, in the future, more sophisticated external data is needed to repeatedly verify the model in order to achieve better clinical application capabilities.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tau.2020.01.24). 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.

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