

## Original Article

# Identification of risk factors for the development and prognosis of bone metastases in renal cell carcinoma: development and validation of a predictive model

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**Abstract:** To accurately identify the onset and prognostic risk factors of renal cell carcinoma bone metastases, and to construct and validate corresponding predictive models, thereby providing a basis for early diagnosis, treatment planning, and patient prognosis assessment. A retrospective analysis of the clinical data of 354 patients diagnosed with renal cell carcinoma at Shanghai East Hospital, School of Medicine Tongji University between April 2020 and April 2024. Patients were categorised into a bone metastasis group ( $n = 82$ ) and a non-bone metastasis group ( $n = 272$ ) based on the occurrence of bone metastases. Univariate and multivariate Cox regression analyses were employed to identify risk factors for bone metastasis, with a predictive nomogram model constructed. For patients with bone metastasis, Cox proportional hazard regression analysis was used to identify prognostic risk factors, and a prognostic prediction score card model was constructed. The internal validation was performed by Bootstrap method, and the discrimination ability, calibration degree and clinical practicability of the model were evaluated by receiver operating characteristic (ROC) curve, calibration curve and decision curve analysis (DCA). Multivariate Cox regression analysis revealed that age, WHO/ISUP grading, T stage, and N stage constituted independent risk factors for renal cell carcinoma bone metastasis ( $P < 0.05$ ). The AUC value of the nomogram prediction model was 0.862 in the training cohort and 0.882 in the validation cohort. Multivariate Cox regression analysis revealed that the timing of bone metastasis onset and the site of bone metastasis were independent risk factors affecting the prognosis of renal cell carcinoma patients with bone metastasis ( $P < 0.05$ ). The AUC value of the nomogram prediction model was 0.813 in the training set and 0.820 in the validation set, demonstrating good predictive accuracy. In summary, age, WHO/ISUP grading, T staging, and N staging constitute risk factors for the development of renal cell carcinoma bone metastases. The timing of bone metastasis occurrence and the metastatic site represent risk factors influencing patient prognosis. The nomogram prediction model constructed based on these risk factors demonstrates favourable predictive efficacy and clinical utility.

**Keywords:** Renal cell carcinoma, bone metastases, risk factors, predictive model, internal validation

## Introduction

Renal cell carcinoma is one of the most common malignant tumors in the urinary system, accounting for 90% to 95% of adult renal malignancies, and the incidence is increasing year by year [1]. Bone is one of the most common distant metastasis sites of renal cell carcinoma, with an incidence of 20% to 35% [2]. The process of bone metastasis involves renal cell carcinoma cells promoting angiogenesis through the overexpression of factors such as vascular endothelial growth factor, thereby creating con-

ditions conducive to haematogenous dissemination. Concurrently, they disrupt the homeostasis of the bone microenvironment by secreting factors including nuclear factor  $\kappa$ B receptor activator ligand, ultimately enabling their colonisation and proliferation within bone tissue. Bone metastasis of renal cell carcinoma not only causes severe bone pain, pathological fractures, hypercalcemia and other bone-related complications, but also significantly reduces the quality of life of patients [3]. Therefore, early identification of patients at high risk of bone metastasis and accurate prognostic stratifica-

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tion of patients with bone metastasis are crucial for the development of treatment strategies, improvement of treatment outcomes, and improvement of patients' quality of life.

Foreign studies have found that tumor stage, grade and histological type are closely related to bone metastasis [4]. In terms of prognostic factors, studies have shown that the patient's physical condition, the number and location of bone metastases, and whether there is visceral metastasis significantly affect the survival outcome [5]. Domestic scholars have analyzed the clinical characteristics and prognostic factors of patients with bone metastasis of renal cell carcinoma, and found that factors such as primary tumor size, surgical method and serum alkaline phosphatase level during bone metastasis are related to the prognosis of patients [6]. However, current research has yet to reach consensus on certain potential risk factors, with discrepancies observed between different studies. For instance, some investigations suggest that significantly elevated serum alkaline phosphatase levels in patients with bone metastases may serve as a potential marker for disease onset and prognosis [7], whereas another study failed to identify any association between this marker and the risk of bone metastasis [8]. Circulating tumour cells theoretically offer early indication of metastatic risk, yet their predictive efficacy in renal cell carcinoma bone metastases remains unresolved due to insufficient standardisation of detection techniques [9]. Moreover, most reported predictive models exhibit considerable variability in clinical performance, with AUC values typically ranging between 0.70 and 0.80. There remains a lack of integrated models with high discriminatory power, calibration, and clinical utility that have undergone thorough internal validation. Moreover, studies predicting prognosis in renal cell carcinoma patients with bone metastases remain relatively scarce, and the predictive accuracy and clinical applicability of existing prognostic models require further refinement.

Based on this, the present study aims to systematically screen for independent risk factors associated with the onset and prognosis of renal cell carcinoma bone metastases. Separate nomogram prediction models will be constructed and subjected to internal valida-

tion, with the objective of providing predictive performance superior to existing models. This endeavour seeks to furnish scientific evidence for clinical early diagnosis, the formulation of personalised treatment plans, and the assessment of patient prognosis.

### Materials and methods

#### *Study population*

A retrospective analysis was conducted on the clinical data of 354 patients diagnosed with renal cell carcinoma at Shanghai East Hospital, School of Medicine Tongji University between April 2020 and April 2024. Inclusion criteria: (1) Age  $\geq 18$  years; (2) Diagnosis of renal cell carcinoma confirmed by histopathological examination (surgical resection specimen or needle biopsy specimen); (3) Complete clinical records; (4) Underwent regular follow-up for  $\geq 3$  months post-diagnosis. Exclusion criteria: (1) Concurrent malignant tumours in other tissues or organs; (2) History of renal malignancy or ipsilateral/contralateral renal surgery; (3) Bone injury due to non-neoplastic factors (e.g., trauma, osteoporosis); (4) Severe cardiac, hepatic, or renal failure, or irreversible neurological disorders; (5) Pregnant or lactating women; (6) Significant gaps in clinical documentation; (7) Loss to follow-up after diagnosis.

To ensure sufficient statistical power, a prior sample size calculation was performed during the study design phase. Using G\*Power 3.1 software (Heinrich Heine University Düsseldorf, Düsseldorf, North Rhine-Westphalia, Germany), statistical power ( $1-\beta$ ) was set at 0.90 with  $\alpha = 0.05$  (two-tailed). Based on an approximate effect size  $OR \approx 2.50$  reported in prior literature [8], and anticipating four predictor variables with a 25% bone metastasis incidence rate, the minimum total sample size required was calculated as 320 cases. The retrospective collection of data from 354 patients in this study met this estimation requirement. This study was approved by the Ethics Committee of Shanghai East Hospital, School of Medicine Tongji University.

#### *Grouping criteria*

The primary basis for grouping was the radiological diagnosis of renal cell carcinoma bone metastases. The diagnostic criteria for bone

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metastasis are as follows: All patients underwent computed tomography (CT) and magnetic resonance imaging (MRI) for bone metastasis screening after the diagnosis of renal cell carcinoma. The imaging reports were independently reviewed by at least two radiologists using a double-blind method. Key observations focused on identifying typical features of malignant bone metastases, including osteolytic bone destruction, osteoblastic bone destruction, or mixed bone destruction. This was combined with an assessment of lesion distribution, morphology, and relationship to surrounding tissues to exclude benign bone conditions such as osteoporosis, osteoarthritis, or post-traumatic bone changes [10]. If the two radiologists come to the same conclusion, and the lesions are consistent with the clinical course characteristics of renal cell carcinoma, excluding the new bone lesions after the diagnosis of renal cell carcinoma or the bone lesions found at the same time with renal cell carcinoma, the bone metastasis of renal cell carcinoma can be diagnosed. If there are differences, the imaging results should be submitted to the expert imaging consultation group for further discussion and adjudication to ensure the accuracy of diagnosis.

According to the above diagnostic criteria, 354 patients were divided into bone metastasis group ( $n = 82$ ) and non-bone metastasis group ( $n = 272$ ). The patients in the non-bone metastasis group were followed up to the deadline of the study (August 31, 2025). No bone metastasis-related lesions were found in multiple imaging examinations during the period, and no clinical symptoms related to bone metastasis were observed.

### *Data collection*

Clinical data were collected via the hospital's electronic medical record system, pathology department archive database, radiology reporting system, and follow-up management platform, as detailed below:

**Baseline characteristics:** Data collected at the time of renal cell carcinoma diagnosis included gender, age, body mass index (BMI), and the presence of comorbidities such as hypertension and diabetes mellitus.

**Tumour pathological characteristics data:** Collect the pathological subtype, World Health

Organisation/International Society of Urological Pathology (WHO/ISUP) grade, primary tumour size, and tumour-node-metastasis (TNM) staging at the time of renal cell carcinoma diagnosis; For patients with bone metastases, the following were extracted from imaging reports: time of bone metastasis onset, metastatic sites, number of metastatic lesions, and presence of concomitant metastases to other organs.

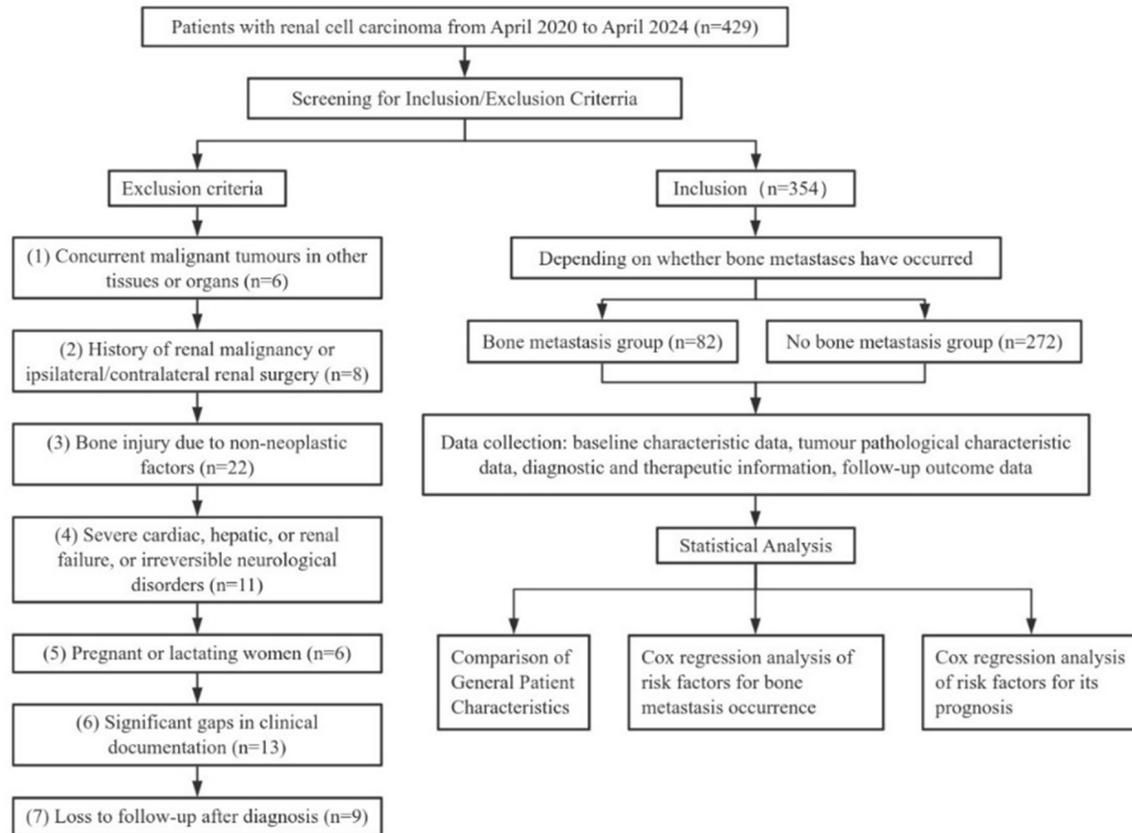
**Clinical information:** Document the primary tumour treatment modality and systemic therapy regimen for each patient. For patients with bone metastases, additionally record local treatment measures administered to the bone metastases.

**Follow-up outcome data:** Follow-up commenced on the date of renal cell carcinoma diagnosis and concluded on 31 August 2025, employing a combined approach of telephone follow-up, outpatient review, and hospital records. Telephone follow-ups utilised a structured questionnaire focusing on patients' survival status, occurrence of new clinical symptoms such as bone pain, subsequent diagnostic and therapeutic processes, and referral circumstances. Outpatient electronic medical records were reviewed to document findings from each return visit, including physical examination results, laboratory test outcomes, and imaging reports. For hospitalised patients during the follow-up period, inpatient records were thoroughly examined to obtain comprehensive information on disease progression and treatment. Comprehensive follow-up assessments were conducted every 3-6 months during the first two years post-diagnosis. Thereafter, at least one follow-up assessment per year was performed. For patients with bone metastases, follow-up frequency is increased as clinically indicated. Overall survival (OS) is recorded, defined as the time from renal cell carcinoma diagnosis to death from any cause or confirmation of survival at the last follow-up visit [11]. Follow-up is conducted by a standardised team comprising two dedicated follow-up nurses, one clinician, and one data administrator.

### *Statistical analysis*

All data analyses were conducted using Statistical Product and Service Solutions 27.0 (IBM, Armonk, NY, USA). The normality of continuous variables was assessed using the

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**Figure 1.** Research flowchart.

Kolmogorov-Smirnov test. Where variables were normally distributed, they were expressed as mean  $\pm$  standard deviation (SD); where not normally distributed, they were expressed as median (interquartile range). Intergroup comparisons were performed using the independent samples t-test or Mann-Whitney U test. Count data were expressed as frequency and percentage [n (%)]. Intergroup comparisons were performed using the chi-square test or Fisher's exact probability test. Ordinal data were compared using the rank-sum test. Univariate and multivariate Cox regression analyses were employed to identify risk factors for renal cell carcinoma bone metastasis. For patients with bone metastasis, OS was used as the endpoint, and univariate and multivariate Cox regression analyses were conducted to identify risk factors influencing bone metastasis prognosis. A nomogram prediction model was constructed based on risk factors. Internal validation was performed using the Bootstrap method (B = 1000). Model discrimination was assessed via the receiver operating char-

acteristic (ROC).  $P < 0.05$  was considered statistically significant. The flowchart is shown in **Figure 1**.

### Results

#### *Comparison of general patient characteristics between the two groups*

This study included 354 patients with renal cell carcinoma. The median time from renal cell carcinoma diagnosis to the occurrence of bone metastases in the bone metastasis group was (11.50 $\pm$ 5.04) months. The median time from renal cell carcinoma diagnosis to the end of follow-up in the group without bone metastases was (49.50 $\pm$ 9.98) months. There was no significant difference in gender, BMI, comorbidities, pathological subtypes, primary tumor treatment and systemic treatment between the bone metastasis group and the non-bone metastasis group ( $P > 0.05$ ). Compared with patients without bone metastasis, there were significant differences in age, WHO/ISUP grade,

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T stage, N stage and primary tumor size in patients with bone metastasis ( $P < 0.05$ ) (**Table 1**).

### *Cox regression analysis of risk factors for bone metastasis in renal cell carcinoma*

Using patient grouping as the dependent variable and the factors from **Table 1** as independent variables, these were incorporated into a Cox regression analysis. The results of the multivariate Cox regression analysis indicated that age ( $HR = 1.023$ ,  $\beta = 0.023$ ), WHO/ISUP grading ( $HR = 6.734$ ,  $\beta = 1.907$ ), T stage ( $HR = 1.794$ ,  $\beta = 0.584$ ), and N stage ( $HR = 2.243$ ,  $\beta = 0.808$ ) were identified as risk factors for renal cell carcinoma bone metastasis ( $P < 0.05$ ) (**Table 2**). The survival curve is shown in **Figure 2**.

### *Predictive model and performance for bone metastasis in renal cell carcinoma*

A nomogram prediction model was constructed based on the results of Cox regression analysis (**Figure 3**) to quantify risk factors for renal cell carcinoma bone metastasis. The predictive capability of this model was assessed via a ROC curve. Internal validation of the predictive model was performed using the Bootstrap method ( $B = 1000$ ). The model yielded an AUC value of 0.862 (95% CI: 0.806-0.918) in the training set and an AUC value of 0.882 (95% CI: 0.809-0.955) in the validation set (**Figure 4**).

### *Cox regression analysis of risk factors for prognosis in renal cell carcinoma with bone metastases*

As of 30 August 2025, the median OS was 28.1 months in the bone metastasis group and 37.5 months in the non-bone metastasis group (**Figure 5**). All clinical and pathological variables potentially associated with prognosis were included in univariate Cox regression analysis. A threshold of  $P < 0.05$  was set for variables to enter multivariate analysis. Variables with  $P < 0.05$  in the multivariate Cox regression analysis were ultimately retained as independent prognostic factors. Multivariate Cox regression analysis revealed that time to bone metastasis occurrence ( $HR = 0.244$ , 95% CI: 0.089-0.665) and site of bone metastasis ( $HR = 9.594$ , 95% CI: 1.246-73.885) constituted independent prognostic risk factors for renal

cell carcinoma patients with bone metastasis ( $P < 0.05$ ) (**Table 3**).

### *Prediction model and performance for prognosis of renal cell carcinoma bone metastases*

A nomogram model for predicting prognosis in renal cell carcinoma patients with bone metastases was constructed based on prognostic risk factors (time to bone metastasis occurrence and site of bone metastasis) identified through multivariate Cox regression analysis (**Figure 6**). The selection of 24 months as the survival assessment milestone is based on the following rationale: within the bone metastasis cohort, the median overall survival stands at 28.1 months. The 24-month mark approximates this median survival duration, enabling effective differentiation between patients with differing prognostic risks. Furthermore, this timeframe aligns with commonly employed clinical benchmarks for evaluating tumour treatment efficacy and prognosis. A ROC curve was plotted with 24 months as the survival endpoint. Its AUC value in the training set was 0.813 (95% CI: 0.674-0.952), while in the validation set it was 0.820 (95% CI: 0.621-1.020), indicating the model possesses favourable predictive accuracy and effectively distinguishes patients with differing prognostic risks. This may serve as a reference for clinical assessment of patient survival prognosis (**Figure 7**).

## Discussion

Renal cell carcinoma is one of the most aggressive malignant tumors of the urinary system. Its bone metastasis not only indicates that the disease has progressed to the advanced stage, but also is accompanied by a series of bone-related events, which significantly damages the quality of life of patients [12]. Through retrospective analysis of renal cell carcinoma patients, this study identified risk factors for the occurrence and prognosis of bone metastases and constructed a highly effective nomogram prediction model, providing valuable reference for clinical practice.

Multivariate Cox regression analysis showed that age, WHO/ISUP stage, T stage and N stage were risk factors for bone metastasis of renal cell carcinoma. First of all, WHO/ISUP classification has become the strongest predictor of bone metastasis in this study, which is consis-

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**Table 1.** Comparison of general characteristics between the two groups of patients

Variables	Bone metastasis group (n = 82)	No bone metastasis group (n = 272)	<i>t</i> / $\chi^2$ / <i>Z</i>	<i>P</i>
Sex, <i>n</i> (%)			2.354	0.125
Male	51 (62.20)	143 (52.57)		
Female	31 (37.80)	129 (42.43)		
Age, year, mean $\pm$ SD	70.17 $\pm$ 10.02	62.11 $\pm$ 14.62	4.670	<0.001
BMI, kg/m <sup>2</sup> , mean $\pm$ SD	20.63 $\pm$ 3.05	21.22 $\pm$ 3.41	1.406	0.161
Hypertension, <i>n</i> (%)			2.259	0.133
Yes	39 (47.56)	155 (56.99)		
No	43 (52.44)	117 (43.01)		
Diabetes, <i>n</i> (%)			0.337	0.562
Yes	35 (42.68)	126 (46.32)		
No	47 (57.32)	146 (53.68)		
Pathological subtyping, <i>n</i> (%)			1.525	0.453
ccRCC	46 (56.10)	159 (58.46)		
pRCC	21 (25.61)	78 (28.67)		
chRCC	15 (18.29)	35 (12.87)		
WHO/ISUP, <i>n</i> (%)			9.437	<0.001
Level 1-2	19 (23.17)	216 (79.41)		
Level 3-4	63 (76.83)	56 (20.59)		
T stage, <i>n</i> (%)			9.209	0.002
T1-T2	32 (39.02)	158 (58.09)		
T3-T4	50 (60.98)	114 (41.91)		
N stage, <i>n</i> (%)			5.810	0.016
N0	34 (41.46)	154 (56.62)		
N1-N2	48 (58.54)	118 (43.38)		
Tumour Size, <i>n</i> (%)			5.119	0.024
<5 cm	36 (43.90)	158 (58.09)		
$\geq$ 5 cm	46 (56.10)	114 (41.91)		
Lesion treatment, <i>n</i> (%)			4.100	0.251
Radical nephrectomy	45 (54.88)	144 (52.94)		
Partial nephrectomy	18 (21.95)	77 (28.31)		
Debulking nephrectomy	12 (14.63)	41 (15.07)		
Local ablation therapy	7 (8.54)	10 (3.68)		
Systemic treatment, <i>n</i> (%)			2.177	0.337
Targeted therapy	32 (39.02)	126 (46.32)		
Immunotherapy	36 (43.90)	114 (41.91)		
Combination therapy	14 (17.08)	32 (11.77)		
Bone metastasis time, <i>n</i> (%)				
$\leq$ 1 year after diagnosis	53 (64.63)			
>1 year after diagnosis	29 (35.37)			
Site of bone metastasis, <i>n</i> (%)				
Spine	38 (46.34)			
Rib	20 (24.39)			
Pelvis	15 (18.29)			
Multiple sites	9 (10.98)			
Metastases number, <i>n</i> (%)				
Isolated metastasis (1)	17 (20.73)			
Oligotransfers (2-3)	25 (30.49)			
Widespread metastasis (>3)	40 (48.78)			

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Visceral metastases, <i>n</i> (%)	
Yes	49 (59.76)
No	33 (40.24)
Therapeutic measures, <i>n</i> (%)	
Radiotherapy	35 (42.68)
Surgery	28 (34.15)
Osteoplasty	12 (14.63)
No treatment	7 (8.54)

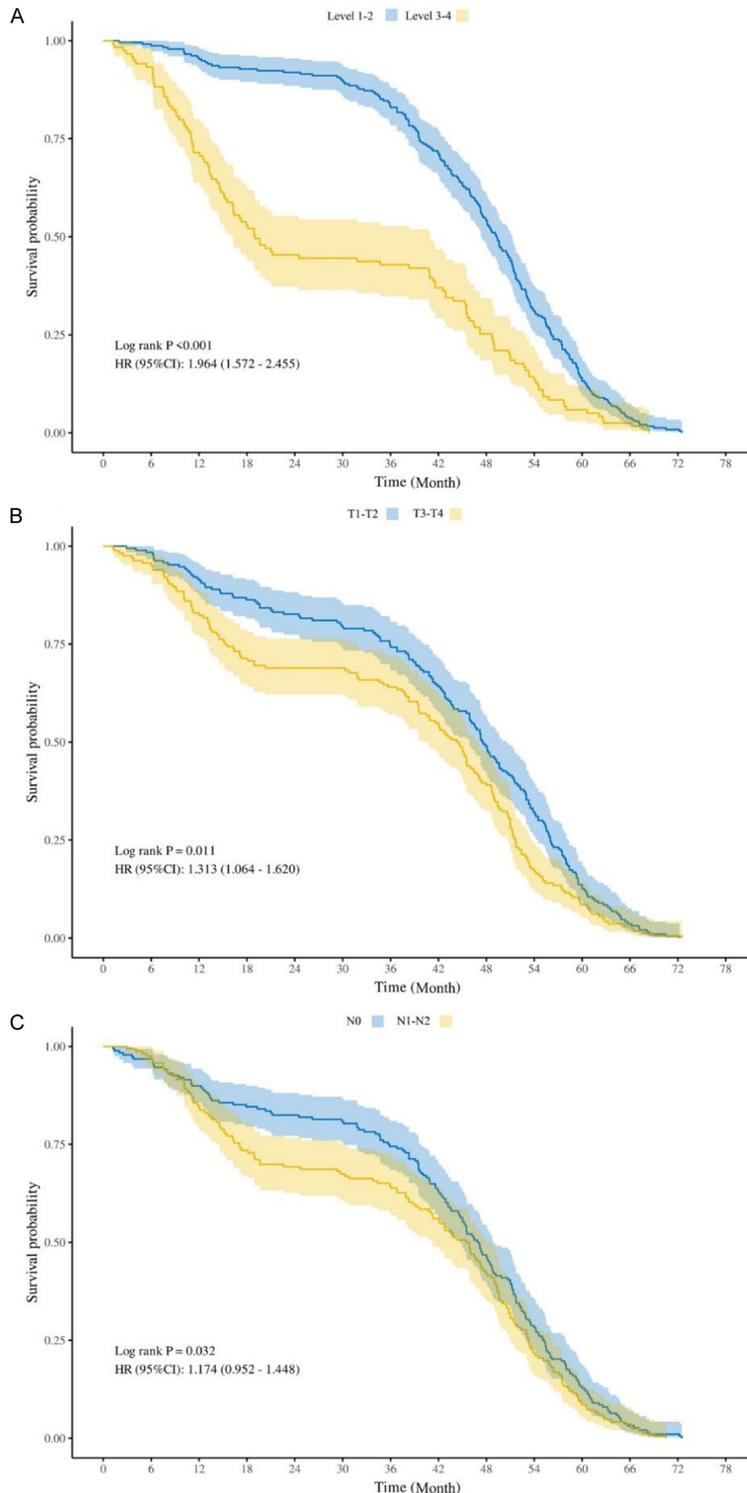
Note: ccRCC, clear cell renal cell carcinoma; pRCC, papillary renal cell carcinoma; chRCC, chromophobe renal cell carcinoma.

**Table 2.** Cox regression analysis of risk factors for bone metastasis in renal cell carcinoma

Variables	Univariate analysis				Multivariate analysis			
	$\beta$	SE	P	HR (95% CI)	$\beta$	SE	P	HR (95% CI)
Sex								
Female				1.000 (Reference)				
Male	0.394	0.282	0.162	1.483 (0.854-2.577)				
Age	0.031	0.010	0.003	1.031 (1.011-1.052)	0.023	0.012	0.049	1.023 (1.001-1.047)
BMI	0.050	0.041	0.222	1.051 (0.877-1.088)				
Hypertension								
No				1.000 (Reference)				
Yes	0.341	0.273	0.212	1.711 (1.217-3.214)				
Diabete								
No				1.000 (Reference)				
Yes	0.209	0.275	0.448	1.812 (1.473-3.392)				
Pathological subtyping								
ccRCC				1.000 (Reference)				
pRCC	0.075	0.311	0.809	1.078 (0.586-1.985)				
chRCC	0.137	0.382	0.720	1.147 (0.543-2.423)				
WHO/ISUP								
Level 1-2				1.000 (Reference)				1.000 (Reference)
Level 3-4	2.147	0.319	<0.001	2.451 (1.416-3.954)	1.907	0.329	<0.001	1.964 (1.572-2.455)
T stage								
T1-T2				1.000 (Reference)				
T3-T4	0.712	0.275	0.010	2.037 (1.188-3.495)	0.584	0.287	0.042	1.794 (1.022-3.149)
N stage								
N0				1.000 (Reference)				1.000 (Reference)
N1-N2	0.669	0.282	0.018	1.951 (1.123-3.391)	0.808	0.299	0.007	2.243 (1.248-4.032)
Tumour Size								
<5 cm				1.000 (Reference)				
≥5 cm	0.700	0.282	0.013	2.013 (1.159-3.498)	0.419	0.292	0.152	1.520 (0.857-2.695)
Lesion treatment								
Radical nephrectomy				1.000 (Reference)				
Partial nephrectomy	0.355	0.368	0.335	1.701 (0.341-3.444)				
Debulk nephrectomy	0.039	0.383	0.920	1.039 (0.490-2.203)				
Local ablation therapy	0.883	0.423	0.057	2.418 (1.056-5.536)				
Systemic treatment								
Targeted therapy				1.000 (Reference)				
Immunotherapy	0.034	0.292	0.909	1.034 (0.584-1.832)				
Combination therapy	0.070	0.430	0.870	1.073 (0.462-2.490)				

Note: Variable assignment method: Gender (male = 1, female = 0), WHO/ISUP staging (stages 1-2 = 0, stages 3-4 = 1), T staging (T1-T2 = 0, T3-T4 = 1), N staging (N0 = 0, N1-N2 = 1).

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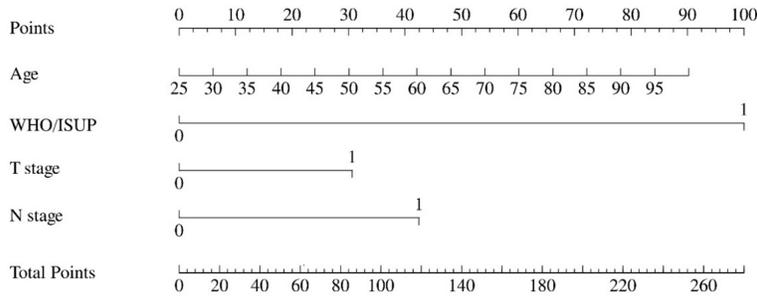
**Figure 2.** Survival curves with bone metastasis occurrence as the endpoint. Note: (A) WHO/ISUP; (B) T stage; (C) N stage.

tent with the results of most studies at home and abroad [6, 13-15]. As a core pathological indicator for assessing renal cell carcinoma

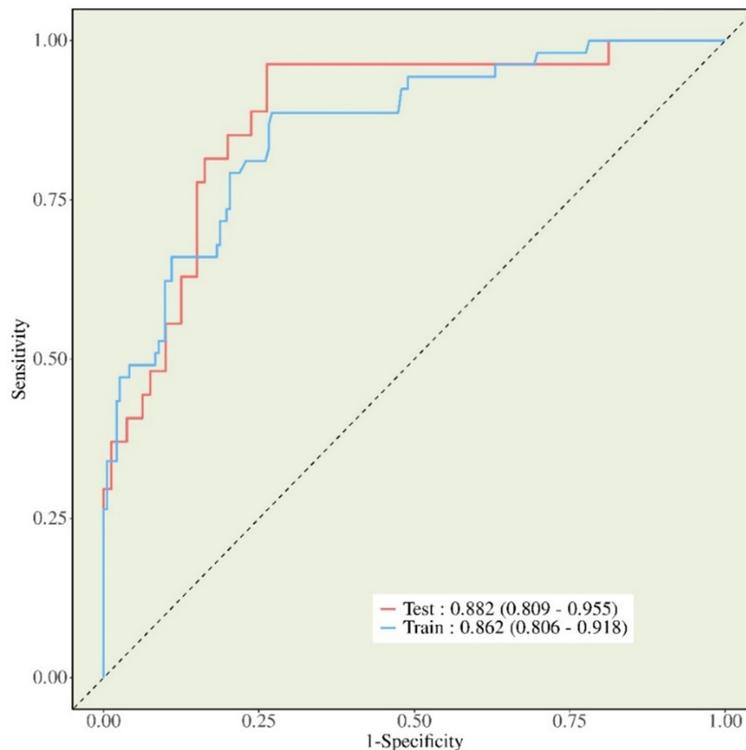
ma malignancy, an elevated WHO/ISUP grade signifies reduced tumour cell differentiation, increased proliferative activity, and greater propensity to breach the basement membrane and invade surrounding tissues [16]. High-grade tumor cells can destroy the bone matrix barrier by secreting matrix metalloproteinases, and express adhesion molecules such as integrins to enhance the binding ability to the bone microenvironment, and ultimately promote the formation and colonization of bone metastases [17]. Secondly, this study revealed that age is an independent risk factor for bone metastasis of renal cell carcinoma. With the increase of age, the body's immune function gradually declines, the number and activity of immune cells such as T lymphocytes and natural killer cells decrease, and the ability to monitor and remove tumor cells decreases, resulting in tumor cells more likely to escape immune surveillance and enter the blood circulation [18, 19]. Moreover, elderly patients frequently present with multiple comorbidities, leading to disrupted bone metabolism and reduced stability of the bone microenvironment. This renders them more susceptible to tumor cell invasion, thereby facilitating tumor progression and metastasis [20, 21]. Finally, both T stage and N stage elevations significantly increased the risk of bone metastasis, which was consistent with the pathological logic of tumor progression. The increased T

stage indicates that the primary tumor has broken through the renal capsule, invaded the perirenal fat, or infiltrated the renal vein/inferi-

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**Figure 3.** Nomogram prediction model for the development of bone metastases in renal cell carcinoma.



**Figure 4.** ROC curves of the training set and validation set models.

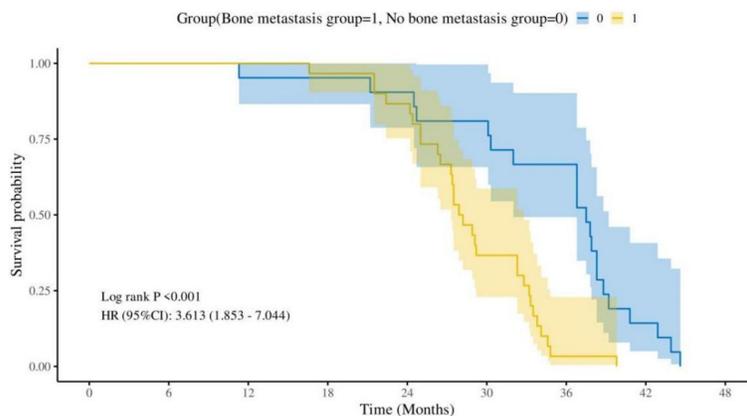
or vena cava, thereby promoting the direct entry of tumor cells into the blood-borne metastasis pathway. Such extensive local infiltration is frequently accompanied by increased tumour angiogenesis, thereby providing a conduit for tumour cells to enter the systemic circulation [22, 23]. Elevated N stage means lymph node metastasis, which indicates that the tumor has successfully broken through the limitations of the primary tumor and has the ability to spread through the lymphatic system. As the sentinel station of immune defense, once the lymph node is attacked by tumor cells,

not only its barrier function is lost, but also it may become a transit for tumor cells to further proliferate, adapt and attack distant organs, which accelerates the process of bone metastasis [24].

Multivariate Cox regression analysis showed that the time and site of bone metastasis were independent prognostic factors affecting the OS of patients. In terms of the time of bone metastasis, the risk of death in patients with bone metastasis one year after the diagnosis of renal cell carcinoma was lower than that in patients with metastasis within one year. This finding suggests that the delay in the occurrence of bone metastasis is associated with improved prognosis in patients. Patients with advanced bone metastases usually show slower tumor progression, lower tumor cell invasion and proliferation activity, and better response to treatment to control disease progression [25]. Conversely, early bone metastasis often signifies a primary tumour with highly invasive and rapidly disseminating biological characteristics. Such tumours frequently demonstrate reduced sensitivity to systemic therapies, exhibit accelerated disease

progression, and present greater therapeutic challenges [26, 27]. In clinical practice, the time of bone metastasis can be used as an indicator of prognosis evaluation. For patients with bone metastasis within 1 year after diagnosis, a more active comprehensive treatment plan can be adopted, and the changes of the condition can be closely monitored. For patients with onset time >1 year, local treatment can be selected according to symptoms on the basis of controlling the primary lesion, and the treatment intensity and quality of life of patients can be balanced. In terms of bone

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**Figure 5.** Patient survival curve.

metastasis sites, patients with multiple bone metastases have an increased risk of death. Multi-site bone metastasis usually indicates that the tumor has entered the systemic dissemination period, which not only increases the difficulty of treatment, but also easily leads to multiple skeletal-related events, such as pathological fractures and hypercalcemia, which seriously affects the nutritional status and quality of life of patients, thereby shortening the survival period [28, 29]. Patients with solitary metastasis can achieve good prognosis by local intervention such as surgery or radiotherapy to control the lesion and minimize complications, supplemented by systemic treatment to inhibit tumor progression [30, 31]. Clinically, for patients with multiple bone metastases, priority should be given to systemic treatment to control tumor load, while actively preventing bone-related events. For patients with single-site metastasis such as spine or ribs, local radiotherapy or surgery can be combined with systemic treatment to achieve precise tumor control and prolong survival [32, 33].

Although internal validation confirmed the model's favourable discrimination and calibration, its generalisability requires verification across a broader population. To this end, we selected urology, oncology, and radiology departments from five domestic Grade A tertiary hospitals as collaborative research centres, enrolling 216 patients for multicentre external validation. Validation results demonstrated that the AUC values for the bone metastasis incidence prediction model and the prognosis predic-

tion model were 0.822 and 0.718 respectively. Although slightly lower than the internal validation results, these values remain within the range of good predictive performance. This outcome confirms that the nomogram model constructed in this study possesses a degree of robustness and transferability across different healthcare settings, providing a basis for its future clinical translation. Subsequent efforts will focus on further optimising and updating the model by

incorporating data from additional centres and molecular biomarkers.

However, this study has certain limitations: it did not incorporate molecular biological indicators such as genetic testing and circulating tumor cells, potentially overlooking potential risk factors; the variable selection for the prognostic prediction model also has limitations. The model only included two variables - time to bone metastasis occurrence and bone metastasis site - and did not incorporate factors such as bone-related event incidence, systemic treatment efficacy, and serum alkaline phosphatase levels. This may result in the model having insufficient explanatory power and comprehensiveness regarding patient prognosis. The maximum follow-up period was five years, with incomplete long-term survival data for some patients; extended follow-up is required to assess the model's long-term predictive efficacy. Internal validation of the AUC was conducted without quantifying calibration or clinical utility. Although the nomogram demonstrated good discriminatory ability in both training and validation cohorts, the absence of calibration and clinical decision-making validation may limit its direct application in personalised medical decision-making. Future studies could enhance the model's clinical translational value by expanding sample sizes, conducting prospective data collection, and systematically reporting calibration curves alongside decision-support curve results. This study focused on constructing predictive models and validating their discriminatory power. It did not further compare baseline characteristics

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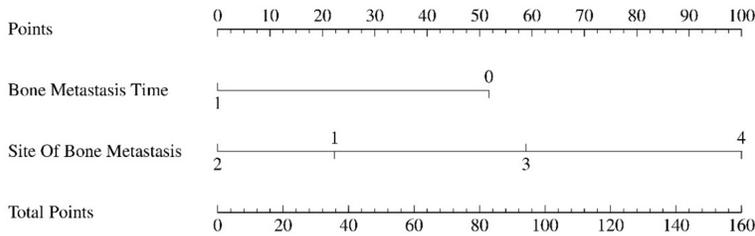
**Table 3.** Cox regression analysis of risk factors for prognosis in renal cell carcinoma with bone metastases

Variables	Univariate analysis				Multivariate analysis			
	$\beta$	SE	P	HR (95% CI)	$\beta$	SE	P	HR (95% CI)
Sex								
Female				1.000 (Reference)				
Male	0.080	0.450	0.859	1.083 (0.449-2.614)				
Age	0.034	0.017	0.051	1.034 (1.001-1.069)				
BMI	0.011	0.067	0.864	1.012 (0.887-1.154)				
Hypertension								
No				1.000 (Reference)				
Yes	0.188	0.447	0.674	1.028 (0.345-1.591)				
Diabete								
No				1.000 (Reference)				
Yes	0.545	0.469	0.245	1.080 (0.231-1.753)				
Pathological subtyping								
ccRCC				1.000 (Reference)				
pRCC	0.530	0.486	0.275	1.699 (0.656-4.404)				
chRCC	0.175	0.667	0.793	1.191 (0.323-4.401)				
WHO/ISUP								
Level 1-2				1.000 (Reference)				
Level 3-4	2.731	0.628	<0.001	15.352 (4.486-52.537)	0.459	0.658	0.485	1.583 (0.436-5.750)
T stage								
T1-T2				1.000 (Reference)				
T3-T4	0.583	0.450	0.195	1.792 (0.742-4.325)				
N stage								
N0				1.000 (Reference)				
N1-N2	1.063	0.488	0.029	2.896 (1.113-7.539)	0.280	0.703	0.691	1.323 (0.334-5.244)
Tumour Size								
<5 cm				1.000 (Reference)				
≥5 cm	1.066	0.488	0.029	2.905 (1.116-7.562)	0.627	0.711	0.378	1.873 (0.465-7.547)
Lesion treatment								
Radical nephrectomy				1.000 (Reference)				
Partial nephrectomy	-0.530	0.658	0.421	0.589 (0.162-2.140)				
Debulk nephrectomy	0.685	0.516	0.185	1.983 (0.721-5.457)				
Local ablation therapy	-0.031	1.049	0.976	0.970 (0.124-7.576)				
Systemic treatment								
Targeted therapy				1.000 (Reference)				
Immunotherapy	0.713	0.508	0.160	2.040 (0.755-5.517)				
Combination therapy	0.665	0.707	0.347	1.944 (0.486-7.773)				
Bone metastasis time								
≤1 year after diagnosis				1.000 (Reference)				
>1 year after diagnosis	-1.275	0.468	0.006	0.279 (0.112-0.698)	-1.411	0.512	0.006	0.244 (0.089-0.665)
Site of bone metastasis								
Spine				1.000 (Reference)				
Rib	-0.078	0.622	0.900	0.925 (0.273-3.126)				
Pelvis	1.107	0.600	0.065	3.026 (0.934-9.807)				
Multiple sites	2.450	0.919	0.008	11.593 (1.912-70.284)	2.261	1.042	0.030	9.594 (1.246-13.885)
Metastases number								
1				1.000 (Reference)				
2-3	0.038	0.490	0.939	1.038 (0.398-2.711)				
>3	0.194	0.459	0.672	1.023 (0.335-2.023)				

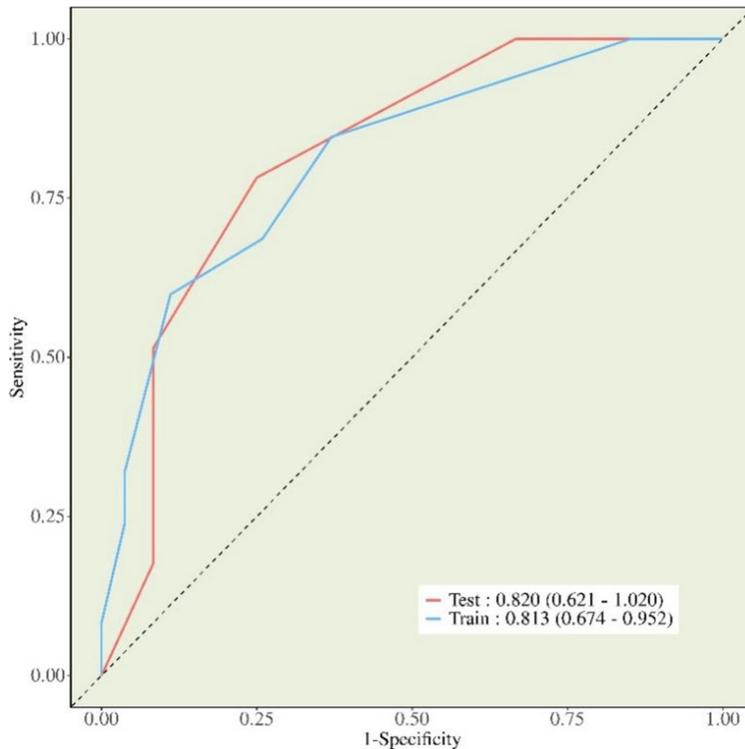
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Visceral metastases				
No				1.000 (Reference)
Yes	0.460	0.372	0.217	1.631 (0.304-2.309)
Therapeutic measures				
Radiotherapy				1.000 (Reference)
Surgery	0.423	0.434	0.330	1.655 (0.280-2.534)
Osteoplasty	0.648	0.630	0.304	1.523 (0.152-2.798)
No treatment	0.566	0.752	0.452	1.568 (0.130-2.479)

Note: Variable assignment method: Gender (male = 1, female = 0), WHO/ISUP staging (stages 1-2 = 0, stages 3-4 = 1), T staging (T1-T2 = 0, T3-T4 = 1), N staging (NO = 0, N1-N2 = 1).



**Figure 6.** Nomogram-based prognostic model for renal cell carcinoma bone metastases. Note: Assignment method: Bone metastasis time ( $\leq 1$  year after diagnosis = 1,  $>1$  year after diagnosis = 0); Site of bone metastasis (Spine = 1, Rib = 2, Pelvis = 3, Multiple sites = 4).



**Figure 7.** ROC curve at 24 months.

making it impossible to completely rule out the potential influence of residual confounding bias on the independence of metastasis time as a prognostic factor. Subsequent research should supplement subgroup baseline comparisons and incorporate methods such as propensity score matching and covariate adjustment to further enhance the robustness and reliability of the models. Furthermore, this study did not systematically collect data on distant metastases to other sites such as the lungs or liver during follow-up for patients in the non-bone metastasis group. Consequently, it was not possible to conduct further stratified analyses examining the confounding effects of metastases to other sites on the risk of bone metastasis in renal cell carcinoma. This limitation somewhat reduces the rigour of the findings regarding bone metastasis risk factors. Future research should refine the clinical data collection framework to incorporate dynamic monitoring information on multi-site metastases, thereby enhancing the model's causal inference capabilities through correction for confounding factors.

between early-stage and late-stage metastasis subgroups within the bone metastasis cohort,

In summary, this study has identified risk factors for the occurrence and prognosis of renal

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cell carcinoma bone metastases through analysis of clinical data from patients with renal cell carcinoma. In clinical practice, high-risk patients for bone metastases may be identified through comprehensive assessment of factors including age, WHO/ISUP staging, T staging, and N staging, thereby enabling enhanced regular screening for bone metastases. For patients with established bone metastases, prognosis risk should be evaluated based on the timing and location of metastasis. High-risk patients with early-stage or multi-site metastases should be prioritised for aggressive treatment strategies to reduce the incidence of skeletal-related events, prolong patient survival, and improve quality of life. The constructed model maintains high predictive efficacy while balancing clinical utility and scientific validity. It addresses the shortcomings of existing models - namely imprecise predictions, complex operation, and incomplete coverage - making it more suitable for implementation in routine clinical practice. This provides a more reliable tool for the precise prevention and control of renal cell carcinoma bone metastases.

### Conclusion

Age, WHO/ISUP classification, T stage and N stage are risk factors for bone metastasis of renal cell carcinoma. The time point and location of bone metastasis are risk factors affecting the prognosis of patients. The prediction model based on these risk factors has good predictive efficacy and clinical practicability, and can be used for early assessment of bone metastasis risk in patients with renal cell carcinoma and prognostic stratification of patients with bone metastasis.

### Disclosure of conflict of interest

None.

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