



# Prognostic indicators for survival in renal cell carcinoma with venous thrombus and development of predictive nomograms

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**Background:** Previous predictive models of prognosis of patients with renal cell carcinoma (RCC) and venous tumour thrombus (VTT) didn't included patients have not undergoing radical nephrectomy (RN). We analysed both patients receive RN or not to investigate the prognostic factors of survival for patients with RCC and VTT comprehensively.

**Methods:** The clinical data of patients with RCC and VTT diagnosed from 2000–2018 in the Surveillance Epidemiology and End Results (SEER) database were downloaded and compared with the clinical data of patients with VTT admitted to the Department of Urology of the Tongji Hospital (TJH) from 2004–2020. The matched cases were divided into a training set and a validation set. The training set was used to establish nomograms based on key prognostic factors. The reliability of the nomograms for predicting the survival of patients in the training set, those in the validation set and TJH patients and was evaluated by C-indexes, ROC curves and calibration curves.

**Results:** Multivariate Cox regression analysis identified nine prognostic factors for overall survival (OS): age, tumour size, histologic classification, nuclear grade, location of VTT, N stage, M stage, surgery, and systemic treatments ( $P < 0.001$ ). Nomograms for OS and cancer specific survival (CSS) were established based on key prognostic factors obtained from the multivariate analysis. The C-indexes of the nomogram for predicting OS in the training set, validation set, TJH cohort were 0.762 (95% CI: 0.746–0.778), 0.718 (95% CI: 0.687–0.749), and 0.819 (95% CI: 0.745–0.893), respectively. The calibration curves are all close to a straight line with a slope of 1. Based on the ROC curves, the nomograms had greater areas under the curve (AUCs) than the tumor, node and metastasis (TNM) staging system in predicting the 3-year OS and CSS. All three validations showed that the nomograms established based on key prognostic factors have reliable accuracy in predicting the survival of both TJH and SEER patients who developed RCCs with VTT.

**Conclusions:** Beside the location of VTT, the tumour size can also predict the survival of patients with RCC and VTT. Nomograms based on key prognostic factors can predict the survival of patients from both America and central China with reliable accuracy.

**Keywords:** Renal cell carcinoma (RCC); venous tumour thrombus (VTT); prognosis; nomogram; SEER database

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## Introduction

Renal cell carcinoma (RCC) accounts for 2–3% of all adult malignancies. In the past 10 years, the incidence rate of RCC has gradually increased. As many as half of the cases in developed countries are accidentally discovered, which is attributed to the popularization of and improvements in the means of detection. According to reports, the mortality rate of RCC in highly developed countries has declined since 1990 (1,2). Despite the rapid development of diagnosis and treatment methods for RCC, some patients are still diagnosed with advanced tumours with venous tumour thrombus (VTT), which poses a great challenge to urological surgeons. According to reports, approximately 4–10% of patients with RCCs develop VTT (3). Surgery is the main therapeutic means for these patients, and some patients achieve long-term survival after radical nephrectomy (RN) and thrombectomy (4). Limited by their sample sizes, previous studies showed great differences when describing the prognosis and prognostic factors of patients with RCCs and VTT, and the survival time of patients varied from several months to more than ten years (5–8). Prognostic models play an important role in assisting clinicians predicting prognosis based on personal experience. The prognostic models established by previous studies are based on patients who underwent nephrectomy and thrombectomy, but some patients didn't receive surgery and previous models may have limited value for them (9,10). This study aimed to identify the independent prognostic factors for patients with RCC and VTT using large-sample data and to predict the survival of patients by establishing nomograms. We present the following article in accordance with the TRIPOD reporting checklist (11–13) (available at <https://tau.amegroups.com/article/view/10.21037/tau-22-128/rc>).

## Methods

### Source of patients

The process of patient screening and data analysis was shown in *Figure 1*. The SEER database of the National Cancer Institute collects cancer diagnosis, treatment, and survival data for approximately 30% of the US patients and is an important population-based resource (14). The clinical data of patients with renal malignant tumours diagnosed from 2000–2018 were downloaded from SEERstat software. The relevant guidelines and regulations of the SEER database were referred to when performing all methods.

The inclusion criteria were as follows: primary renal tumours; known follow-up time; and pathological confirmation of malignancy. The exclusion criteria were as follows: non-RCC histologic classification; without VTT.

A total of 212,044 patients with renal malignant tumours were identified according to the criteria above, and further screening was conducted to exclude 16,424 cases of non-RCC, such as squamous cell carcinoma, urothelial carcinoma, and lymphoma 181,108 patients without VTT were also screened out. Finally, 14,512 cases of RCCs with VTT were obtained.

Furthermore, the clinical data of 209 patients with renal tumours and VTT admitted to Tongji Hospital (TJH) from January 2004 to December 2020 were collected. After screening, 153 cases pathologically confirmed RCC and VTT were obtained. Among them, 84 patients had complete clinical data and received full follow-up.

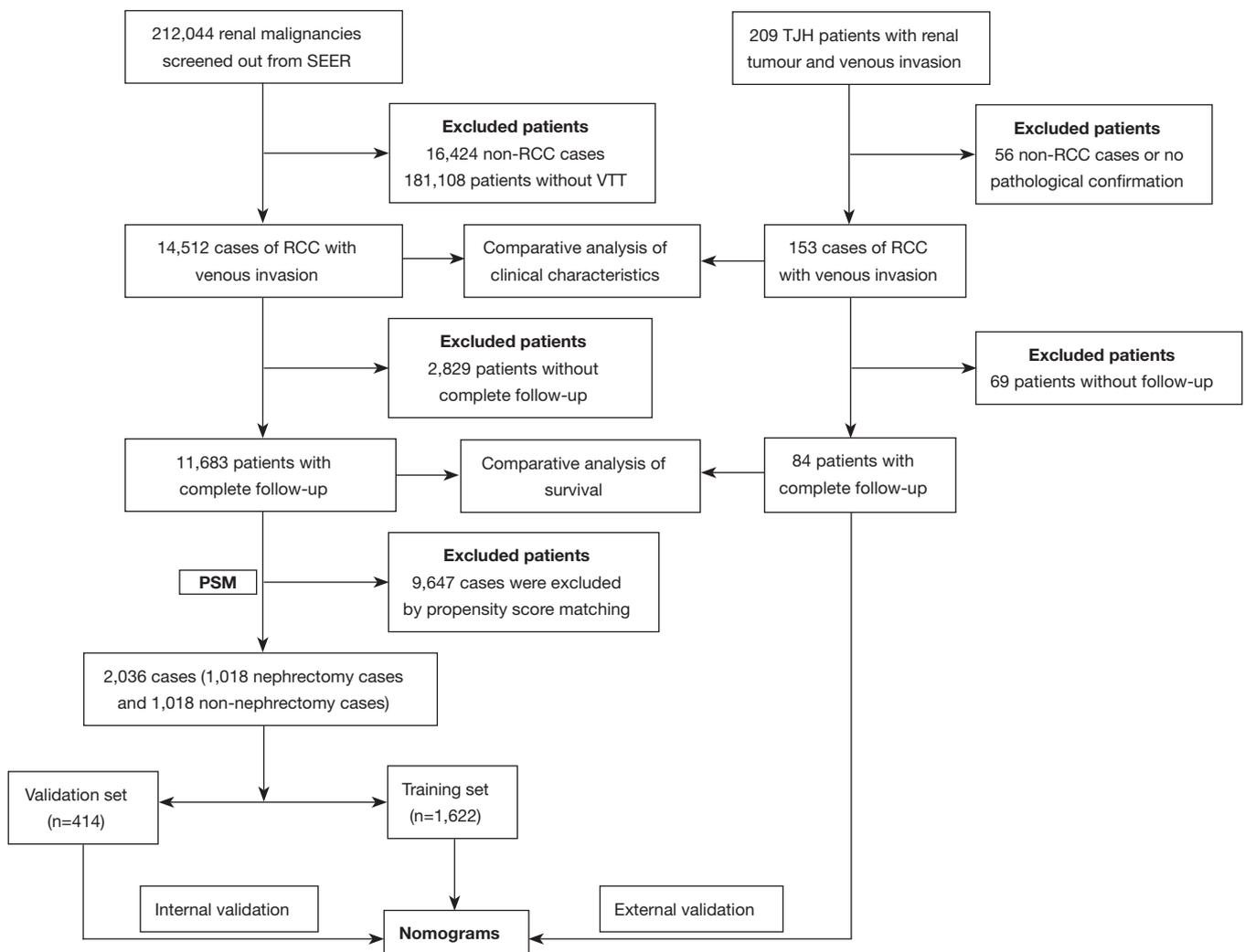
The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

### Statistical analysis

All tumor, node and metastasis (TNM) stages were reclassified to the eighth edition. Categorical variables were integrated, and the cases were divided into the nephrectomy + thrombectomy group and the non-nephrectomy management group according to the surgical approach. Patients who underwent local tumour resection only or biopsy only were combined into the non-nephrectomy management group (hereinafter referred to as the non-nephrectomy group). Patients who underwent cytoreductive nephrectomy + thrombectomy, nephroureterectomy + thrombectomy, radical nephrectomy + thrombectomy or radical nephrectomy + thrombectomy + other organ resection were combined into the nephrectomy + thrombectomy group (hereinafter referred to as the nephrectomy group).

Data analysis and plotting were conducted with R 3.5.3 ([www.r-project.org](http://www.r-project.org)), and a comparative analysis was conducted between 14,512 SEER cases and 153 TJH cases. Continuous variables that fit a non-normal distribution, such as age and tumour size, were analysed by Kruskal-Wallis test, and Fisher's exact test was used for categorical variables (*Table 1*). Kaplan-Meier survival analysis was conducted with the "survival" package of R.

Propensity score matching (PSM), as a statistical tool, aims to help strengthen the causality in observational data by reducing the inherent selection bias (15). The 'matchit'



**Figure 1** Flow diagram of the research process. VTT, venous tumor thrombus; RCC, renal cell carcinoma; PSM, propensity score matching; TJH, Tongji Hospital.

function of the ‘MatchIt’ package was used to match patients with complete survival information from the TJH and SEER database in a 1:2 ratio by the “nearest” method. Kaplan-Meier survival analysis was performed again on the two matched groups. All clinical and pathologic features were used as caliper.

The thrombectomy procedure is extremely complicated. Whether the surgeon recommends nephrectomy + thrombectomy is obviously affected by the clinical characteristics of patients. Therefore, propensity score matching was performed in the SEER cases. The “nearest” method was used to match 1,018 cases in the non-nephrectomy group and 1,018 cases in the nephrectomy group in a ratio of 1:1, all clinical features were used as

caliper. The difference in clinical characteristics between the two groups was eliminated after matching (Table 2).

The cases obtained by PSM were randomly divided into a training set and a validation at a ratio of 8:2, and there was no significant difference in characteristics between the training set and the validation set (Table S1).

Survival analysis of OS and CSS was performed on the training set. First, univariate Cox regression was conducted, and then variables with significant differences were selected for multivariate Cox regression. Both univariate and multivariate Cox regression were analysed by the “coxph” function of the “survival” package. The key prognostic factors identified by multivariate Cox regression were used to build the nomograms for OS and CSS. Then, the

**Table 1** Comparison of the characteristics of patients with RCC and VTT in the SEER database and Tongji Hospital

Characteristics	SEER (n=14,512)	TJH (n=153)	P
Age (years), median [IQR]	64.00 [56.00, 72.00]	58.00 [50.00, 63.00]	<0.001
Size (mm), median [IQR]	84.00 [60.00, 110.00]	89.00 [70.75, 110.50]	0.029
Race, n (%)			<0.001
Black	1,051 (7.2)	0 (0.0)	
Other	975 (6.7)	153 (100.0)	
Unknown	50 (0.3)	0 (0.0)	
White	12,433 (85.7)	0 (0.0)	
Sex, n (%)			0.067
Female	4,648 (32.0)	38 (24.8)	
Male	9,864 (68.0)	115 (75.2)	
Laterality, n (%)			<0.001
Bilateral	47 (0.3)	1 (0.7)	
Left	7,018 (48.4)	47 (33.3)	
Right	7,447 (51.3)	93 (66.0)	
T, n (%)			<0.001
T3a	9,786 (67.4)	33 (24.6)	
T3a or T3b	1,876 (12.9)	0 (0.0)	
T3b	1,204 (8.3)	66 (49.3)	
T3b or T3c	860 (5.9)	0 (0.0)	
T3c	652 (4.5)	14 (10.4)	
T4	134 (0.9)	21 (15.7)	
N, n (%)			<0.001
N0	11,351 (78.2)	73 (54.5)	
N1	2,389 (16.5)	51 (38.1)	
NX	772 (5.3)	10 (7.5)	
M, n (%)			0.003
M0	10,681 (73.6)	83 (61.9)	
M1	3,831 (26.4)	51 (38.1)	
Location of VTT, n (%)			<0.001
Above diaphragm or invading the IVC wall	676 (4.7)	17 (11.1)	
Below the diaphragm	1,204 (8.3)	98 (64.1)	
In the IVC	860 (5.9)	0 (0.0)	
In the RV	5,420 (37.3)	38 (24.8)	
In the RV or IVC below the diaphragm	6,352 (43.8)	0 (0.0)	

Table 1 (continued)

Table 1 (continued)

Characteristics	SEER (n=14,512)	TJH (n=153)	P
Histology, n (%)			<0.001
ccRCC	9,616 (66.3)	72 (47.1)	
ChRCC	223 (1.5)	1 (0.7)	
Other	4,103 (28.3)	65 (42.5)	
PRCC	570 (3.9)	15 (9.8)	
Grade, n (%)			<0.001
Grade I	400 (2.8)	9 (5.9)	
Grade II	3,602 (24.8)	38 (24.8)	
Grade III	5,134 (35.4)	35 (22.9)	
Grade IV	2,488 (17.1)	23 (15.0)	
Unknown	2,888 (19.9)	48 (31.4)	
Radiation, n (%)			<0.001
None/unknown	13,394 (92.3)	153 (100.0)	
Yes	1,118 (7.7)	0 (0.0)	
Systemic treatments, n (%)			0.677
No/unknown	11,817 (81.4)	127 (83.0)	
Yes	2,695 (18.6)	26 (17.0)	
Surgery, n (%)			<0.001
Nephrectomy	12,516 (86.2)	88 (57.5)	
Non-nephrectomy	1,996 (13.8)	65 (42.5)	

RCC, renal cell carcinoma; VTT, venous tumor thrombus; IQR, interquartile range; IVC, inferior vena cava; RV, renal vein; ccRCC, clear cell renal cell carcinoma; ChRCC, chromophobe renal cell carcinoma; PRCC, papillary renal cell carcinoma; TJH, Tongji Hospital.

nomograms were validated in the training set, validation set, and TJH cohort. First, the C-index was calculated and applied to evaluate the predictive accuracy. Then, bootstrap validation (1,000 resamples) was conducted, and calibration plots were created. Finally, time-dependent ROC curves were generated to compare the ability of the nomograms to predict survival with that of prognostic models trained in all SEER cases and based on TNM staging. The nomograms were constructed with the “rms” package (16), and the ROC curves were drawn with the “survivalROC” package.

## Results

### Comparison of SEER and Tongji cohort

The baseline characteristics of 14,512 SEER patients and 153 TJH patients were compared (Table 1). The two groups

were mainly male, with 9,864 (68.0%) and 115 (75.2%) male patients in the two groups, respectively. The median age of the SEER cohort was 64-year-old, and that of TJH patients was 58-year-old; the TJH patients were significantly younger than the SEER patients ( $P<0.001$ ). The SEER patients had more left renal tumours [7,018 (48.4%) vs. 47 (33.3%),  $P<0.001$ ]; clear cell RCC (ccRCC) was the main histological type in both groups, but the proportions of each subtype were different between the two groups ( $P<0.001$ ). The TJH cases were more advanced than the SEER cases according to TNM stage [the eighth edition of the (American Joint Committee on Cancer) TNM staging criteria were used here], and the TJH patients also had tumour thrombus with a higher location ( $P<0.001$ ); There was no significant difference in the proportion of patients who received systemic treatments (including chemotherapy,

**Table 2** Population characteristics of the patients with RCC and VTT in the SEER database before and after matching by propensity score

Characteristics	Before match			After match		
	Nephrectomy (n=6,101)	Non-nephrectomy (n=1,018)	P	Nephrectomy (n=1,018)	Non-nephrectomy (n=1,018)	P
Age (years), median [IQR]	63.00 [56.00, 71.00]	65.00 [57.00, 73.00]	0.001	65.00 [58.00, 72.00]	65.00 [57.00, 73.00]	0.547
Size (mm), median [IQR]	85.00 [62.00, 110.00]	82.00 [54.25, 110.75]	0.004	80.00 [60.00, 105.00]	82.00 [54.25, 110.75]	0.745
Race, n (%)			0.003			0.996
Black	412 (6.8)	102 (10.0)		101 (9.9)	102 (10.0)	
Other	432 (7.1)	77 (7.6)		79 (7.8)	77 (7.6)	
Unknown	36 (0.6)	4 (0.4)		3 (0.3)	4 (0.4)	
White	5,221 (85.6)	835 (82.0)		835 (82.0)	835 (82.0)	
Sex, n (%)			0.029			0.963
Female	1,886 (30.9)	350 (34.4)		348 (34.2)	350 (34.4)	
Male	4,215 (69.1)	668 (65.6)		670 (65.8)	668 (65.6)	
Laterality, n (%)			<0.001			0.062
Bilateral	8 (0.1)	17 (1.7)		6 (0.6)	17 (1.7)	
Left	2,871 (47.1)	471 (46.3)		466 (45.8)	471 (46.3)	
Right	3,222 (52.8)	530 (52.1)		546 (53.6)	530 (52.1)	
T, n (%)			<0.001			0.879
T3a	4,656 (76.3)	654 (64.2)		668 (65.6)	654 (64.2)	
T3b	929 (15.2)	236 (23.2)		225 (22.1)	236 (23.2)	
T3c	504 (8.3)	119 (11.7)		118 (11.6)	119 (11.7)	
T4	12 (0.2)	9 (0.9)		7 (0.7)	9 (0.9)	
N, n (%)			<0.001			0.539
N0	5,168 (84.7)	604 (59.3)		607 (59.6)	604 (59.3)	
N1	799 (13.1)	344 (33.8)		353 (34.7)	344 (33.8)	
NX	134 (2.2)	70 (6.9)		58 (5.7)	70 (6.9)	
M, n (%)			<0.001			0.715
M0	4,686 (76.8)	381 (37.4)		390 (38.3)	381 (37.4)	
M1	1,415 (23.2)	637 (62.6)		628 (61.7)	637 (62.6)	
Location of VTT, n (%)			<0.001			0.805
Above diaphragm or invading the IVC wall	516 (8.5)	128 (12.6)		125 (12.3)	128 (12.6)	
Below the diaphragm	929 (15.2)	236 (23.2)		225 (22.1)	236 (23.2)	
In the RV	4,656 (76.3)	654 (64.2)		668 (65.6)	654 (64.2)	

Table 2 (continued)

Table 2 (continued)

Characteristics	Before match			After match		
	Nephrectomy (n=6,101)	Non-nephrectomy (n=1,018)	P	Nephrectomy (n=1,018)	Non-nephrectomy (n=1,018)	P
Histology, n (%)			<0.001			<0.001
ccRCC	4,729 (77.5)	535 (52.6)		726 (71.3)	535 (52.6)	
ChRCC	101 (1.7)	16 (1.6)		14 (1.4)	16 (1.6)	
Other	1,014 (16.6)	417 (41.0)		227 (22.3)	417 (41.0)	
PRCC	257 (4.2)	50 (4.9)		51 (5.0)	50 (4.9)	
Grade, n (%)			<0.001			<0.001
Grade I	95 (1.6)	32 (3.1)		15 (1.5)	32 (3.1)	
Grade II	1,488 (24.4)	172 (16.9)		171 (16.8)	172 (16.9)	
Grade III	2,485 (40.7)	202 (19.8)		397 (39.0)	202 (19.8)	
Grade IV	1,330 (21.8)	55 (5.4)		300 (29.5)	55 (5.4)	
Unknown	703 (11.5)	557 (54.7)		135 (13.3)	557 (54.7)	
Radiation, n (%)			<0.001			0.03
None/unknown	5,743 (94.1)	836 (82.1)		873 (85.8)	836 (82.1)	
Yes	358 (5.9)	182 (17.9)		145 (14.2)	182 (17.9)	
Systemic treatments, n (%)			<0.001			0.015
No/unknown	4,956 (81.2)	580 (57.0)		635 (62.4)	580 (57.0)	
Yes	1,145 (18.8)	438 (43.0)		383 (37.6)	438 (43.0)	

RCC, renal cell carcinoma; VTT, venous tumor thrombus; IVC, inferior vena cava; IQR, interquartile range; RV, renal vein; ccRCC, clear cell renal cell carcinoma; ChRCC, chromophobe renal cell carcinoma; PRCC, papillary renal cell carcinoma.

immunotherapy and targeted therapy) between the two groups. The SEER patients were followed-up for 1–226 months, with a median follow-up of 41 months. At the last follow-up, there were 9,036 deaths, 6,934 (76.7%) patients died of RCC. Eighty-four TJH cases were followed-up for 2–120 months, with a median follow-up of 16 months. 26 patients died by the last follow-up, and all of them died of RCC. Survival analysis was performed on the two groups. The 1-, 3-, and 5-year OS and CSS rates of the SEER patients were 79.0%, 60.9%, and 50.2%, and 81.0%, 65.3%, and 57.1%, respectively. The median OS and CSS were 60 and 87 months, respectively. The 1-, 2- and 3-year OS rates of the TJH patients were the same as the CSS rates, which were 77.7%, 61.5%, and 39.5%, respectively. The median OS and CSS were both 32 months. The log-rank test showed that there was no significant difference in OS ( $P=0.72$ ) and CSS ( $P=0.66$ ) between SEER and TJH

cohorts. After balancing the characteristics of the patients (Table S2), there was still no significant difference in the OS ( $P=0.096$ ) and CSS ( $P=0.37$ ) between the two groups (Figure S1).

#### Subset of SEER cases

The differences in variables between the non-nephrectomy group and the nephrectomy group among the 2,036 SEER cases obtained after PSM were eliminated (Table 2). The Kaplan-Meier method was applied to analyse the influence of surgery on the OS and CSS of the SEER patients before and after matching. As a result, the difference in survival caused by surgery was reduced after matching (Figure S2).

A total of 2,036 SEER cases obtained after PSM were randomly divided into a training set (1,622 cases) and a validation set (414 cases) at an 8:2 ratio. There were no

significant differences in the variables between the two groups (Table S1).

### Cox regression analysis of OS/CSS

Univariate Cox regression analysis was performed for each variable in the training set. Univariate Cox regression analysis showed that the significant prognostic factors of OS were age, race, histologic classification, tumour size, nuclear grade, T stage, N stage, M stage, location of tumour thrombus, surgery, radiotherapy and systemic treatments; the significant prognostic factors of CSS were race, histological classification, tumour size, nuclear grade, T stage, N stage, M stage, location of tumour thrombus, surgery, radiotherapy and systemic treatments. Multivariate Cox regression analysis was performed on OS and CSS (the tumour thrombus of 11 T4 stage patients in the training cohort were all above the diaphragm, and the T stage coincided with the tumour thrombus classification, so the T stage was excluded from the multivariate analysis). Nine key prognostic factors of OS were found: age ( $P<0.001$ ), location of VTT ( $P=0.039$ ), tumour size ( $P=0.002$ ), histological classification ( $P<0.001$ ), nuclear grade ( $P<0.001$ ), N stage ( $P<0.001$ ), M stage ( $P<0.001$ ), surgery ( $P<0.001$ ), and systemic treatments ( $P<0.001$ ); 8 key risk factors related to CSS were identified: location of VTT ( $P=0.021$ ), tumour size ( $P=0.007$ ), histological classification ( $P<0.001$ ), nuclear grade ( $P<0.001$ ), N stage ( $P<0.001$ ), M stage ( $P<0.001$ ), surgery ( $P<0.001$ ) and systemic treatments ( $P<0.001$ ). In the analysis of OS and CSS, the papillary RCC showed worse prognosis than ccRCC. The location of tumour thrombus and tumour size were independent prognostic factor of RCC patients with VTT, whereas systemic treatments was a risk factor in univariate analysis but a protective factor in multivariate analysis; a high age was a risk factor for OS but not for CSS (Table 3 and Table S3).

### Establishment and validation of nomogram

The key prognostic factors screened by multivariate Cox regression analysis were applied to establish nomograms to predict the median OS and CSS and 1-, 3-, and 5-year OS and CSS rates (Figure 2 and Figure S3). Variables of every patient can found corresponding scores in the “point” line on the nomograms, and all scores of variables are added to obtain a total score of this patient. The median survival time or survival probability corresponding to the total score is the expected median survival time or survival probability

of that patient. A total of 1,622 cases from the training set, 414 cases from the validation set and 84 TJH cases were applied to validate the nomograms internally and externally. The C-indexes of the nomogram for predicting OS in the training set, validation set, TJH cohort were 0.762 (95% CI: 0.746–0.778), 0.718 (95% CI: 0.687–0.749), and 0.819 (95% CI: 0.745–0.893), respectively; and those of the nomogram for predicting CSS in the training set, validation set, and TJH cohort were 0.776 (95% CI: 0.760–0.792), 0.724 (95% CI: 0.693–0.755), and 0.818 (95% CI: 0.745–0.891), respectively. The calibration curves are all close to a straight line with a slope of 1 (Figure 3 and Figure S4). Another prognostic model was established based on TNM stage in the training set. Time-dependent ROC curves were applied to compare the accuracy of the nomograms and TNM model for predicting OS and CSS. The areas under the curve (AUCs) of the nomogram for predicting the 3-year OS of the training set, validation set, and TJH cohort were 0.843, 0.830, and 0.914, respectively, and those for predicting the 3-year CSS were 0.856, 0.833, and 0.902, respectively. The AUCs of the TNM model for predicting the 3-year OS rates were 0.831, 0.789, and 0.869, and those for predicting the 3-year CSS were 0.843, 0.805, and 0.884, respectively. The AUCs obtained from the nomogram were greater than those obtained from the TNM model (Figure 4). All the validations proved that the nomograms established based on key prognostic factors have reliable accuracy in predicting the survival of both Chinese and American patients who developed RCCs with VTT.

### Discussion

VTT is a characteristic of RCC progression. RCC with VTT was classified as T3 in the AJCC staging system. Approximately one-third of patients with tumour thrombus have distant metastasis (17,18). Patients with RCC and VTT have poor prognosis, the progression of surgical technique improved the 5-year OS of patients with non-metastatic RCC and VTT from 17% to 40%, but it is still not optimistic, especially in patients with metastases (19). Therefore, it is important to identify the prognostic factors of these patients and predict their survival. Then, we will discuss these controversial prognostic factors respectively.

A focus of discussion is always how the location of VTT affects patients' prognosis. Some researchers believe that the location of VTT does not affect survival significantly (6,8,19–25). Some other studies support that the location of VTT has a significant impact on survival; in other words,

**Table 3** Univariate and multivariate Cox proportional hazards regression for overall survival

Characteristics	Univariate			Multivariate		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Age (per year)	1.01	1–1.01	0.007	1.02	1.01–1.02	<0.001
Systemic treatments						
No	1 (reference)			1 (reference)		
Yes	1.92	1.7–2.16	<0.001	0.71	0.62–0.82	<0.001
Grade			<0.001			<0.001
Grade I	1 (reference)			1 (reference)		
Grade II	0.95	0.57–1.57	0.833	1.29	0.78–2.15	0.323
Grade III	1.35	0.83–2.20	0.231	1.50	0.91–2.46	0.109
Grade IV	2.11	1.29–3.47	0.003	1.71	1.03–2.84	0.040
Unknown	3.07	1.89–5.00	<0.001	1.98	1.21–3.24	0.007
Histology			<0.001			<0.001
ccRCC	1 (reference)			1 (reference)		
ChRCC	0.56	0.29–1.07	0.081	0.84	0.43–1.62	0.599
Other	2.35	2.08–2.67	<0.001	1.53	1.33–1.76	<0.001
PRCC	1.76	1.33–2.32	<0.001	1.44	1.08–1.92	0.013
M						
M0	1 (reference)			1 (reference)		
M1	4.42	3.82–5.11	<0.001	3.39	2.82–4.09	<0.001
N						
N0	1 (reference)			1 (reference)		
N1	3.39	2.98–3.86	<0.001	1.95	1.69–2.26	<0.001
NX	2.59	2.08–3.24	<0.001	1.62	1.28–2.04	<0.001
Race						
Black	1 (reference)			1 (reference)		
Other	0.76	0.57–1.01	0.058	0.97	0.72–1.31	0.862
Unknown	1.26	0.31–5.11	0.742	1.09	0.27–4.49	0.902
White	0.73	0.61–0.88	0.001	1.05	0.86–1.28	0.616
Radiation						
None/unknown	1 (reference)			1 (reference)		
Yes	1.92	1.66–2.23	<0.001	1.17	1.00–1.36	0.050

Table 3 (continued)

Table 3 (continued)

Characteristics	Univariate			Multivariate		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Size (per 1 mm)	1.01	1.01–1.01	<0.001	1.00	1.00–1.00	0.002
Surgery						
Nephrectomy	1 (reference)			1 (reference)		
Non-nephrectomy	1.37	1.21–1.54	<0.001	1.44	1.24–1.67	<0.001
Location of VTT						
Above diaphragm or invading the IVC wall	1 (reference)			1 (reference)		
Below the diaphragm	0.76	0.62–0.92	0.006	0.89	0.73–1.09	0.273
In the RV	0.46	0.38–0.54	<0.001	0.80	0.66–0.96	0.014

ccRCC, clear cell renal cell carcinoma; ChrRCC, chromophobe renal cell carcinoma; PRCC, papillary renal cell carcinoma; VTT, venous tumor thrombus; IVC, inferior vena cava; RV, renal vein.

these authors agree with the 2017 AJCC TNM staging system (7,26-30). There are also studies that support that invasion of the venous wall is an important risk factor (5,27,29). Some research indicates that the location of VTT is an independent prognostic factor in non-metastatic RCC patients but not in metastatic patients (3,29). The above studies were carried out in patients who underwent nephrectomy and thrombectomy, and there is a lack of data for patients who did not undergo nephrectomy and thrombectomy. In our study, before the establishment of the prognosis models, PSM was conducted between the nephrectomy group and the non-surgical group, and we found that the location of VTT indeed affect survival, but not significantly as tumour size, N stage and M stage.

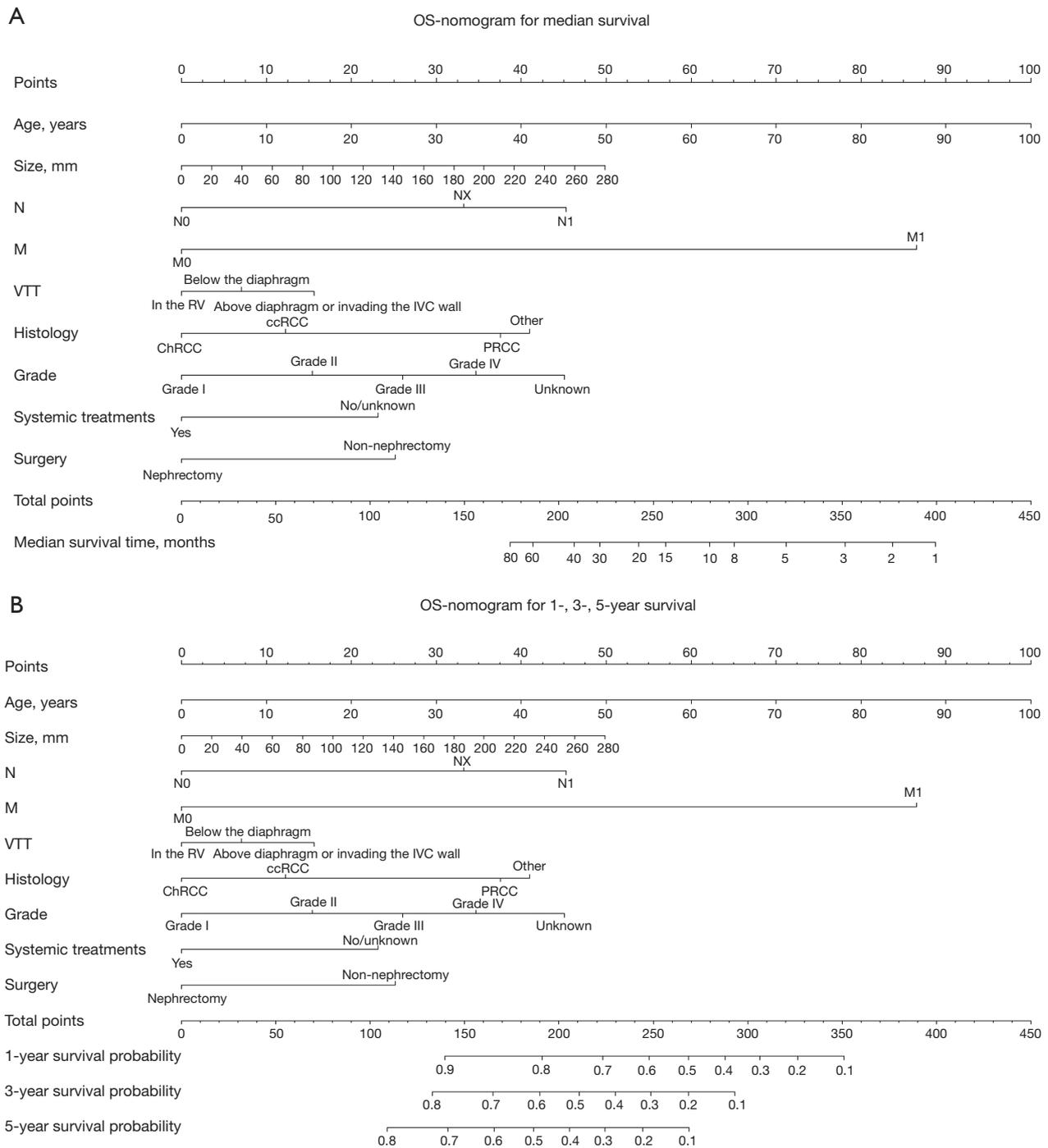
VTT is usually accompanied by metastasis. Regardless of whether there is VTT, distant metastasis is an important risk factor (31-34). The 2019 EAU guidelines recommend that RN and thrombectomy should be performed in patients without distant metastasis regardless of the location of VTT, but there is no clear recommendation for metastatic cases (4). It remains controversial whether cytoreductive nephrectomy (CN) should be performed for patients with metastatic RCC and VTT. Some studies with few cases believed that CN can improve quality of life or improve OS, so it should be performed (28,35-37), nevertheless the CARMENA study showed that CN does not improve the survival of mRCC patients (38). In our study, metastatic cases accounted for a large proportion of all cases obtained by PSM (61.4%), and the results

demonstrate that nephrectomy and thrombectomy predict favourable outcomes in patients with RCC and VTT.

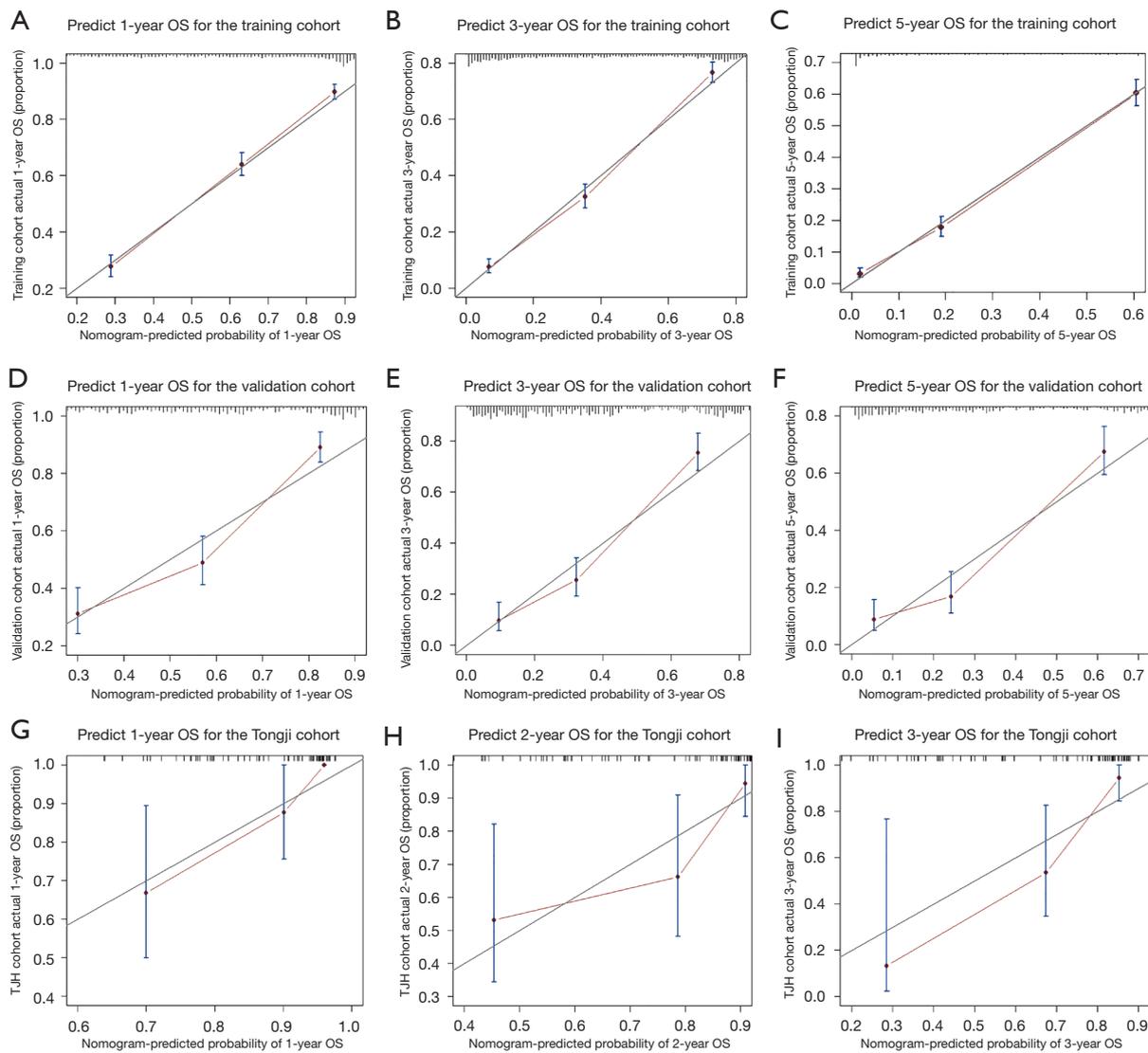
When studying the influence of pathological classification on the prognosis of patients with RCC and VTT, Kim *et al.* found histological classification to be an important prognostic factor, and patients with type II papillary RCC had a significantly worse prognosis than those with ccRCC (39). Ciancio *et al.* found that the prognosis of patients with ccRCC and VTT are better than that of patients with non-ccRCC (20). Kaushik *et al.* found that non-ccRCC is associated with some unfavourable pathological features, but after matching with ccRCC patients, there was no significant difference in survival and recurrence between the two groups (40). In our study, patients with papillary RCC and other non-ccRCC had worse outcomes than those with ccRCC. In the TJH cohort, 7 of the 15 PRCC were further classified and all of them were type II, which may indicate that the majority of PRCC patients with VTT are type II.

The maximum diameter of the renal tumour (tumour size) is the basis for T1-T2 staging, but this parameter is not applied in T3 staging. In the studies from Chen and Tang, tumour size had no significant effect on the survival of patients with RCC and VTT (5,7). However, tumour size was an independent prognostic factor in other studies (9,19,27,41,42). In our study, a greater tumour size indicated a worse prognosis.

Regarding the differences between our institution and SEER database cases, we believe that it may be mainly caused by differences in socioeconomic factors. For



**Figure 2** OS nomogram for predicting the median OS and the 1-, 3-, and 5-year OS probabilities. (A) OS nomogram for predicting the median OS; (B) OS nomogram for predicting the 1-, 3-, and 5-year OS probabilities. OS, overall survival; ccRCC, clear cell renal cell carcinoma; ChRCC, chromophobe renal cell carcinoma; PRCC, papillary renal cell carcinoma.

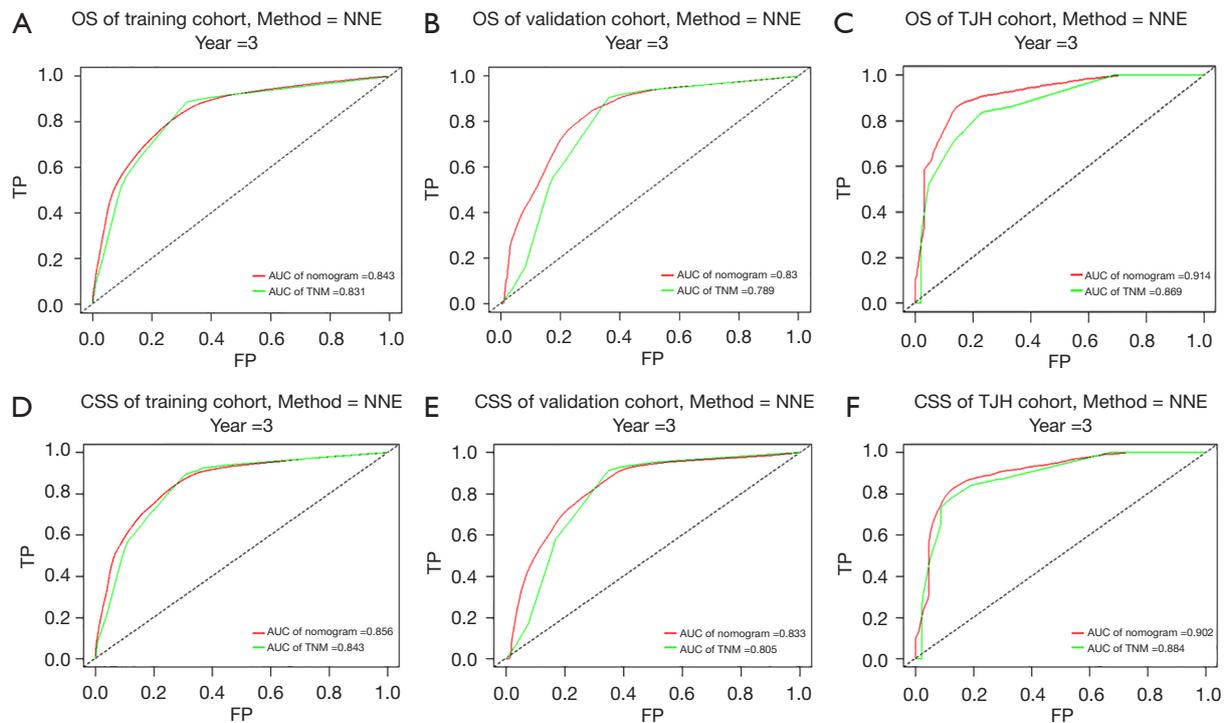


**Figure 3** The OS nomogram was validated in the training set, validation set, and TJH cohort. The abscissa is the survival predicted by the nomogram, and the ordinate is the actual survival. The grey straight line indicates the ideal model, and the calibration curves are all close to the grey straight line, indicating that the nomograms are reliable. (A-C) Calibration curve of OS nomogram predicting OS of 1-, 3-, and 5-year OS probabilities of the training cohort; (D-F) Calibration curve of OS nomogram predicting OS of 1-, 3-, and 5-year OS probabilities of the validation cohort; (G-I) Calibration curve of OS nomogram predicting OS of 1-, 2-, and 3-year OS probabilities of the Tongji Hospital cohort. OS, overall survival; TJH, Tongji Hospital.

example, patients in our institution is relatively younger, which may be mainly because our patients have been screened by local hospitals, and some elderly patients are more likely to choose conservative treatment in local hospitals. Another example is that patients in our institution have larger tumors and more advanced stage, which may be related to the lower frequency of routine

physical examinations. In addition, these demographics and clinicopathological parameters were also significantly correlated with receiving surgery, suggesting that urologists prefer to operate on patients with favourable conditions.

There are also some limitations in our study, due to the limitations of the database, we failed to obtain baseline information about the patients; physical condition such as



**Figure 4** Time-dependent ROC curves of the nomograms and the prognostic models based on TNM staging for predicting the 3-year OS (A-C) and 3-year CSS (D-F) rates of the training set, validation set, and TJH cohort. The green curves are generated by the TNM model, and the red curves are generated by the nomograms; the AUCs of the nomograms are greater than those of the TNM model. OS, overall survival; NNE, nearest neighbour estimation; TJH, Tongji Hospital; AUC, area under curve; TP, true positive rate; FP, false positive rate; CSS, cancer specific survival; TNM, tumor, node and metastasis; ROC, receiver operating characteristic.

the Eastern Cooperative Oncology Group (ECOG) score, body mass index (BMI), comorbidities, approaches of surgery, and concentration of haemoglobin and albumin. In addition, systemic treatments in the SEER database include chemotherapy, immunotherapy and targeted therapy. The systemic treatments and radiotherapy regimens, type of drugs and start times can't be identified which may bias the results of the study, and the clinical values of these features may be limited.

## Conclusions

Patients developed RCC and VTT in the United States and central China had comparable outcomes. Age at diagnosis, tumour size, location of VTT, histological classification, nuclear grade, N stage, M stage, surgery, and systemic treatments are the nine key prognostic factors for RCC

patients with VTT. The nomograms established based on key prognostic factors could predict the survival of patients in America and central China with reliable accuracy.

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## Footnote

*Reporting Checklist:* The authors have completed the TRIPOD reporting checklist. Available at <https://tau.amegroups.com/article/view/10.21037/tau-22-128/rc>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://tau.amegroups.com>).

[com/article/view/10.21037/tau-22-128/coif](https://doi.org/10.21037/tau-22-128/coif)). 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).

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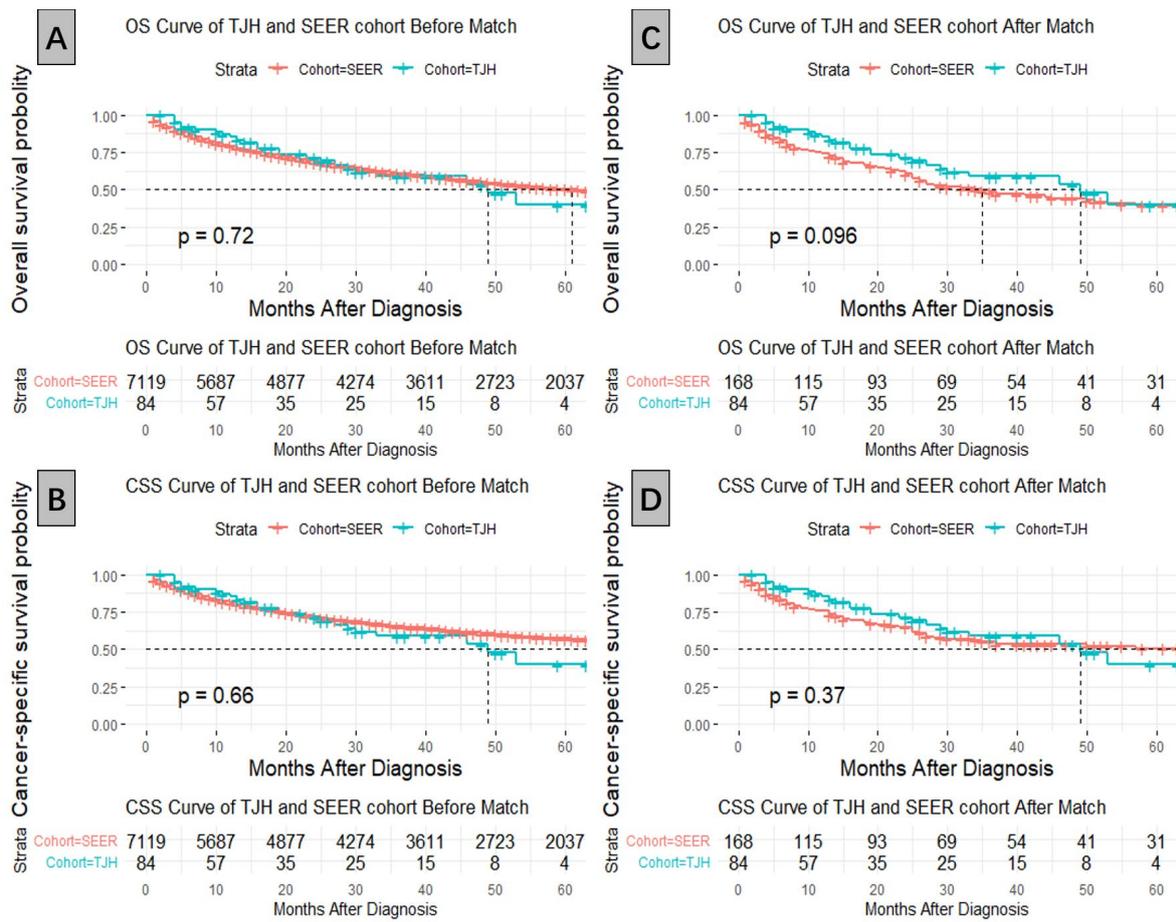
**Cite this article as:** Tian J, Zeng X, Guan W, Hu Z, Yang C. Prognostic indicators for survival in renal cell carcinoma with venous thrombus and development of predictive nomograms. *Transl Androl Urol* 2022;11(10):1374-1388. doi: 10.21037/tau-22-128

**Table S1** Comparison of characteristics before and after matching between TJH and SEER cases

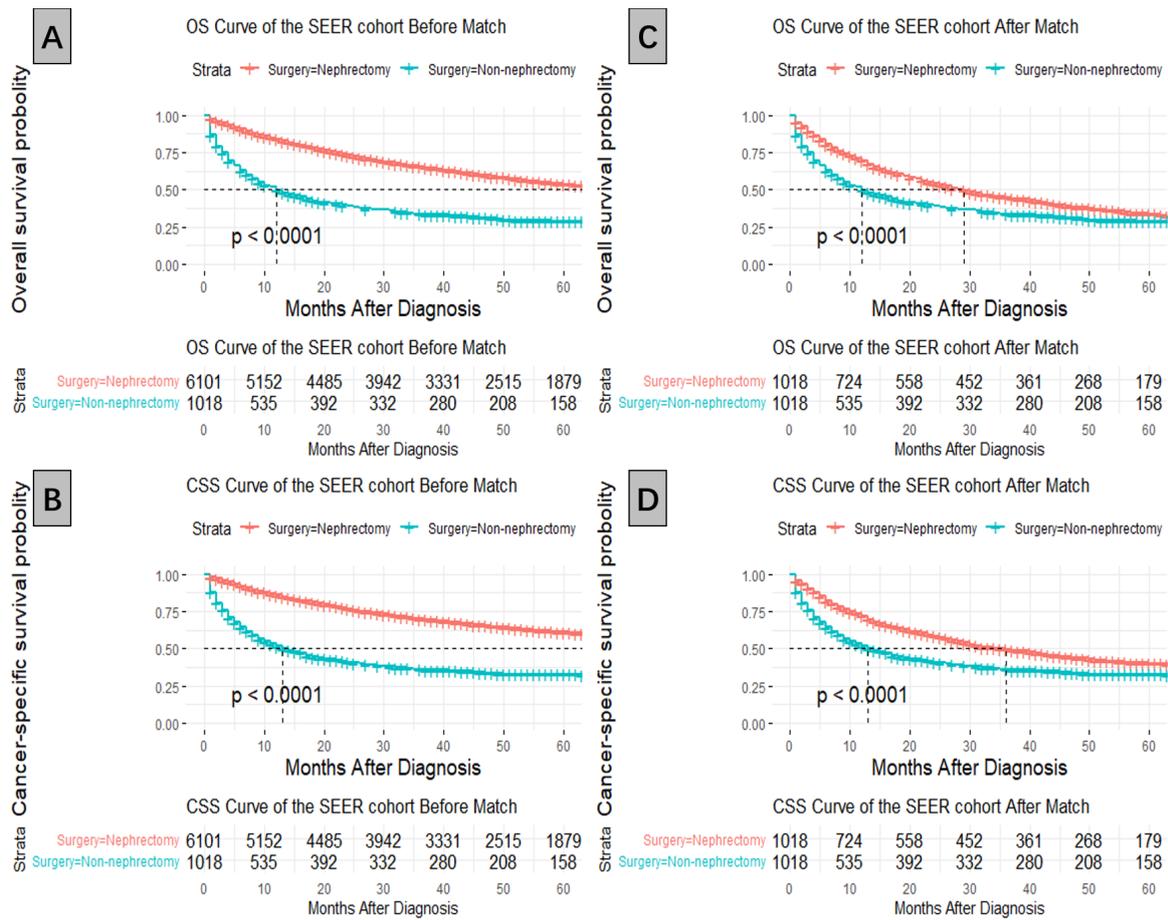
Characteristics	Before match			After match		
	SEER (n=7119)	TJH (n=84)	P	SEER (n=168)	TJH (n=84)	P
Age (years), median [IQR]	64.00 [56.00, 71.00]	59.50 [52.00, 65.00]	<0.001	56.50 [48.00, 64.00]	59.50 [52.00, 65.00]	0.251
Size (mm), median [IQR]	85.00 [60.00, 110.00]	85.25 [70.00, 100.75]	0.474	90.00 [65.00, 115.00]	85.25 [70.00, 100.75]	0.692
Race (%)			<0.001			<0.001
Black	514 (7.2)	0 (0.0)		19 (11.3)	0 (0.0)	
Other	509 (7.1)	84 (100.0)		11 (6.5)	84 (100.0)	
Unknown	40 (0.6)	0 (0.0)		0 (0.0)	0 (0.0)	
White	6056 (85.1)	0 (0.0)		138 (82.1)	0 (0.0)	
Sex (%)			0.479			0.661
Female	2236 (31.4)	23 (27.4)		52 (31.0)	23 (27.4)	
Male	4883 (68.6)	61 (72.6)		116 (69.0)	61 (72.6)	
Laterality (%)			0.014			0.950
Bilateral	25 (0.4)	1 (1.2)		2 (1.2)	1 (1.2)	
Left	3342 (46.9)	28 (33.3)		59 (35.1)	28 (33.3)	
Right	3752 (52.7)	55 (65.5)		107 (63.7)	55 (65.5)	
T (%)			<0.001			0.004
T3a	5310 (74.6)	22 (26.2)		33 (19.6)	22 (26.2)	
T3b	1165 (16.4)	41 (48.8)		114 (67.9)	41 (48.8)	
T3c	623 (8.8)	10 (11.9)		16 (9.5)	10 (11.9)	
T4	21 (0.3)	11 (13.1)		5 (3.0)	11 (13.1)	
N (%)			<0.001			0.767
N0	5772 (81.1)	49 (58.3)		92 (54.8)	49 (58.3)	
N1	1143 (16.1)	31 (36.9)		64 (38.1)	31 (36.9)	
NX	204 (2.9)	4 (4.8)		12 (7.1)	4 (4.8)	
M (%)			0.04			1.000
M0	5067 (71.2)	51 (60.7)		102 (60.7)	51 (60.7)	
M1	2052 (28.8)	33 (39.3)		66 (39.3)	33 (39.3)	
Location of VTT (%)			<0.001			0.362
Above diaphragm or invading the IVC wall	644 (9.0)	8 (9.5)		21 (12.5)	8 (9.5)	
Below the diaphragm	1165 (16.4)	53 (63.1)		114 (67.9)	53 (63.1)	
In the RV	5310 (74.6)	23 (27.4)		33 (19.6)	23 (27.4)	
Histology (%)			<0.001			0.561
ccRCC	5264 (73.9)	58 (69.0)		106 (63.1)	58 (69.0)	
ChRCC	117 (1.6)	0 (0.0)		0 (0.0)	0 (0.0)	
Other	1431 (20.1)	12 (14.3)		33 (19.6)	12 (14.3)	
PRCC	307 (4.3)	14 (16.7)		29 (17.3)	14 (16.7)	
Grade (%)			<0.001			0.755
Grade I	127 (1.8)	7 (8.3)		12 (7.1)	7 (8.3)	
Grade II	1660 (23.3)	27 (32.1)		59 (35.1)	27 (32.1)	
Grade III	2687 (37.7)	31 (36.9)		59 (35.1)	31 (36.9)	
Grade IV	1385 (19.5)	14 (16.7)		33 (19.6)	14 (16.7)	
Unknown	1260 (17.7)	5 (6.0)		5 (3.0)	5 (6.0)	
Radiation (%)			0.003			1.000
None/Unknown	6579 (92.4)	84 (100.0)		0 (0.0)	0 (0.0)	
Yes	540 (7.6)	0 (0.0)		168 (100.0)	84 (100.0)	
Systemic treatments (%)			0.065			1.000
No/Unknown	5536 (77.8)	58 (69.0)		117 (69.6)	58 (69.0)	
Yes	1583 (22.2)	26 (31.0)		51 (30.4)	26 (31.0)	
Surgery (%)			0.211			0.742
Nephrectomy	6101 (85.7)	68 (81.0)		132 (78.6)	68 (81.0)	
Non-nephrectomy	1018 (14.3)	16 (19.0)		36 (21.4)	16 (19.0)	

**Table S2** Characteristics of the training set and validation set cases

Characteristics	Training Cohort (n=1622)	Validation Cohort (n=414)	P
Age (years), median [IQR]	65.00 [58.00, 73.00]	64.00 [56.00, 72.00]	0.248
Size (mm), median [IQR]	81.00 [58.25, 107.00]	80.00 [54.00, 110.00]	0.460
Race (%)			0.043
Black	168 (10.4)	35 (8.5)	
Other	118 (7.3)	38 (9.2)	
Unknown	3 (0.2)	4 (1.0)	
White	1333 (82.2)	337 (81.4)	
Sex (%)			0.685
Female	560 (34.5)	138 (33.3)	
Male	1062 (65.5)	276 (66.7)	
Laterality (%)			0.904
Bilateral	18 (1.1)	5 (1.2)	
Left	749 (46.2)	188 (45.4)	
Right	855 (52.7)	221 (53.4)	
T (%)			0.349
T3a	1046 (64.5)	276 (66.7)	
T3b	378 (23.3)	83 (20.0)	
T3c	187 (11.5)	50 (12.1)	
T4	11 (0.7)	5 (1.2)	
N (%)			0.015
N0	981 (60.5)	230 (55.6)	
N1	532 (32.8)	165 (39.9)	
NX	109 (6.7)	19 (4.6)	
M (%)			0.192
M0	626 (38.6)	145 (35.0)	
M1	996 (61.4)	269 (65.0)	
Location of VTT (%)			0.345
Above diaphragm or invading the IVC wall	198 (12.2)	55 (13.3)	
Below the diaphragm	378 (23.3)	83 (20.0)	
In the RV	1046 (64.5)	276 (66.7)	
Histology (%)			0.204
ccRCC	1003 (61.8)	258 (62.3)	
ChRCC	23 (1.4)	7 (1.7)	
Other	523 (32.2)	121 (29.2)	
PRCC	73 (4.5)	28 (6.8)	
Grade (%)			0.647
Grade I	35 (2.2)	12 (2.9)	
Grade II	280 (17.3)	63 (15.2)	
Grade III	475 (29.3)	124 (30.0)	
Grade IV	277 (17.1)	78 (18.8)	
Unknown	555 (34.2)	137 (33.1)	
Radiation (%)			0.764
None/Unknown	1359 (83.8)	350 (84.5)	
Yes	263 (16.2)	64 (15.5)	
Systemic treatments (%)			0.501
No/Unknown	974 (60.0)	241 (58.2)	
Yes	648 (40.0)	173 (41.8)	
Surgery (%)			0.783
Nephrectomy	814 (50.2)	204 (49.3)	
Non-nephrectomy	808 (49.8)	210 (50.7)	



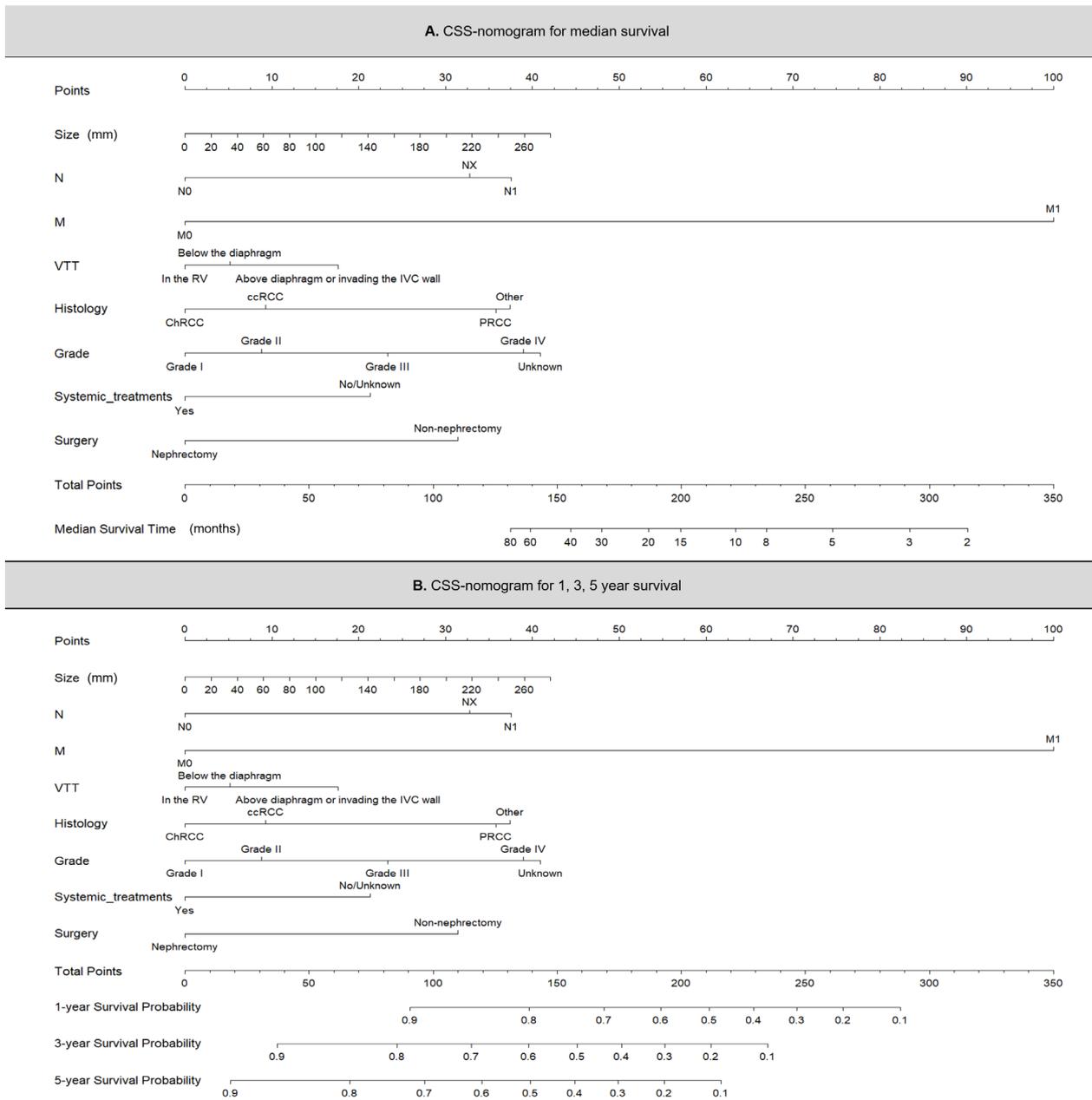
**Figure S1** OS and CSS curves of the SEER and TJH cases before and after PSM.



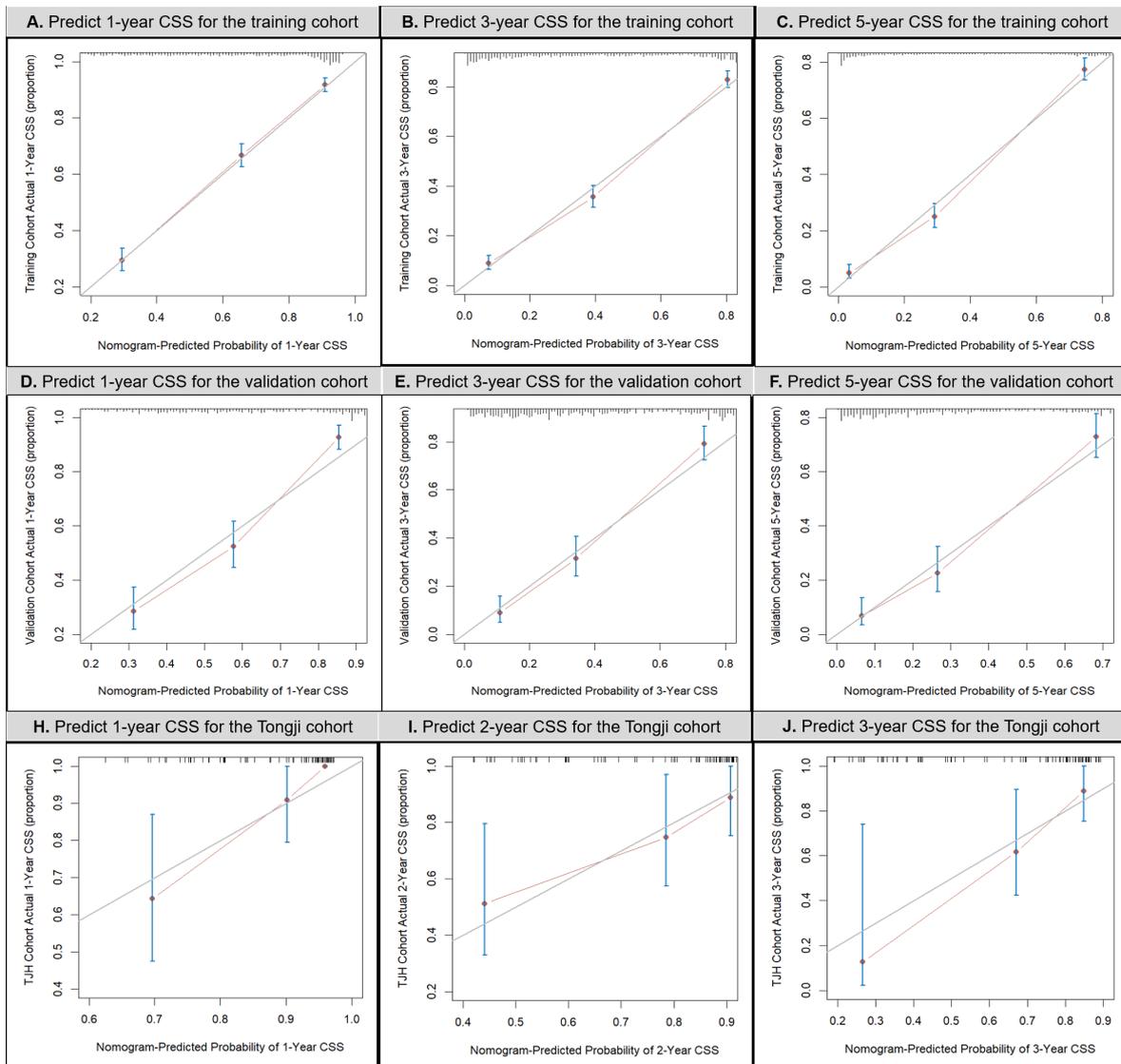
**Figure S2** The effect of surgery on OS and CSS before and after matching. After matching, the difference between OS (A-C) and CSS (B-D) in the nephrectomy group and the non-surgical group was reduced.

**Table S3** Univariate and multivariate Cox proportional hazards regression for CSS

Characteristics	Univariate			Multivariate		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Systemic treatments						
No	1 (Reference)			1 (Reference)		
Yes	2.19	1.92-2.49	<0.001	0.71	0.61-0.82	<0.001
Grade			<0.001			<0.001
Grade I	1 (Reference)			1 (Reference)		
Grade II	0.84	0.48-1.47	0.539	1.18	0.67-2.09	0.557
Grade III	1.32	0.77-2.26	0.314	1.48	0.85-2.56	0.161
Grade IV	2.36	1.37-4.06	0.002	1.89	1.08-3.31	0.026
Unknown	3.30	1.94-5.63	<0.001	1.93	1.12-3.33	0.017
Histology			<0.001			<0.001
ccRCC	1 (Reference)			1 (Reference)		
ChRCC	0.59	0.29-1.19	0.139	0.87	0.43-1.76	0.701
Other	2.53	2.21-2.89	<0.001	1.58	1.36-1.82	<0.001
PRCC	1.86	1.39-2.50	<0.001	1.54	1.14-2.09	0.005
M						
M0	1 (Reference)			1 (Reference)		
M1	5.99	5.05-7.12	<0.001	4.59	3.71-5.69	<0.001
N						<0.001
N0	1 (Reference)			1 (Reference)		
N1	3.66	3.19-4.2	<0.001	1.82	1.56-2.12	<0.001
NX	2.80	2.21-3.54	<0.001	1.66	1.30-2.11	<0.001
Race			0.018			0.765
Black	1 (Reference)			1 (Reference)		
Other	0.80	0.59-1.08	0.142	1.09	0.80-1.48	0.598
Unknown	1.42	0.35-5.77	0.620	1.35	0.33-5.55	0.679
White	0.73	0.60-0.89	0.002	1.11	0.91-1.37	0.307
Radiation						
None/Unknown	1 (Reference)			1 (Reference)		
Yes	2.09	1.8-2.44	<0.001	1.16	0.99-1.36	0.072
Size (per 1 mm)	1.01	1.01-1.01	<0.001	1.00	1.00-1.00	0.007
Surgery						
Nephrectomy	1 (Reference)			1 (Reference)		
Non-nephrectomy	1.47	1.29-1.67	<0.001	1.63	1.38-1.92	<0.001
Location of VTT			<0.001			0.021
Above diaphragm or invading the IVC wall	1 (Reference)			1 (Reference)		
Below the diaphragm	0.74	0.60-0.91	0.004	0.83	0.67-1.03	0.085
In the RV	0.43	0.36-0.52	<0.001	0.76	0.63-0.92	0.005



**Figure S3** CSS nomogram for predicting the median overall survival and the 1-, 3-, and 5-year CSS probabilities. (A) CSS nomogram for predicting the median CSS. (B) CSS nomogram for predicting the 1-, 3-, and 5-year CSS probabilities.



**Figure S4** The CSS nomogram was validated in the training set, validation set, and TJH cohort.