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Pre-operative risk factors predicting missed diagnosis of renal vein tumor thrombus in renal cell carcinoma: a retrospective cohort study

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ABSTRACT

Purpose: Previous reports showed that some patients with renal cell carcinoma (RCC) and renal vein tumor thrombus (RVTT) were misdiagnosed pre-operatively. To improve the accuracy of this diagnosis, the clinical characteristics of RCC with missed RVTT diagnosis were analyzed.

Methods: We retrospectively reviewed RCC patients with RVTT between January 2000 and December 2015. The survival analysis was estimated using the Kaplan–Meier method. The Cox proportional hazard models were applied to identify risk factors.

Results: The missed diagnosis rate of RVTT in RCC was 30.5%. In multivariate analysis, maximal tumor diameter, tumor located in the middle part, renal vein contrast agents filling insufficiently and tumor with collateral vessels (odds ratio = 1.22, 1.35, 1.25, 1.22; and $p = .034, .003, .015$ and $.037$, respectively) were independent predictors of missed RVTT diagnosis. A missed-diagnosis score was presented as area under curve of 0.852 ($p < .001$). Moreover, the missed diagnosis group had favorable prognosis, and tumor with collateral vessels was an independent prognostic indicator of poor overall survival time (hazard ratio = 1.15, $p = .025$).

Conclusions: This was the first study exploring clinical features as predictors of missed RVTT diagnosis. The possibility of complicating tumor thrombus should be considered when there is pre-operative presence of tumor with large diameter, renal tumor in the middle part, renal tumor with collateral vessels and renal vein contrast agents filling insufficiently. Patients with three points in missed-diagnosis scoring suggested a high possibility of missed RVTT diagnosis, and tumor with collateral vessels indicated poor prognosis.

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Introduction

Renal cell carcinoma (RCC) accounts for approximately 2–3% of all malignant diseases in adults and has shown an increasing trend in China [1,2]. RCC has the tendency of invading blood vessels and about 10% lead to the formation of venous tumor thrombus (VTT) [3]. With the recent developments in imaging techniques, there has been an increase in the detection of RCCs involving VTT. Radical nephrectomy in combination with thrombectomy is the only treatment [4]. The long-term survival in patients with RCC involving VTT is relatively poor than that of localized RCC [5]. If the VTT detaches, it can cause life-threatening pulmonary embolism; hence, it is important to diagnose VTT in clinical practice.

Abdominal multi-parametric imaging, which can increase the chances of discovery of low-stage renal masses, can help identify the VTT in 4–10% of the patients [6]. Computed tomography (CT), magnetic resonance imaging (MRI) and vascular ultrasonography are the main diagnostic methods for RCC with VTT. For Mayo grades I–IV of VTT, the rate of missed diagnosis is low. However, it is easy to miss a VTT of grade 0, which is a




tumor thrombus only in the renal vein and a primary manifestation of renal vein invasion. There is currently no accurate pre-operative clinical method to avoid misdiagnosis of the renal vein tumor thrombus (RVTT). If the renal vein is treated too close to the RVTT intraoperatively, it will cause the RVTT to squeeze out and lead to pulmonary embolism.

Some RVTT cases were misdiagnosed pre-operatively in our institute [7]. To analyze the causes of missed diagnosis of RVTT, we reviewed those RCC cases with RVTT in our institute, wherein the clinical and imaging characteristics were investigated. Additionally, we evaluated the predicting factors that diagnosed RVTT with negative imaging diagnosis. These factors could help decrease the rate of RVTT misdiagnosis.

Materials and methods

Study population

This was a series study that focused on RCC and was approved by the Ethics Committee of National Cancer

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Center/Cancer Hospital, Chinese Academy of Medical Sciences (NCC/CHCAMS) (ID Num: NCC2016YJC-08). Patient consent was not required due to the retrospective study design. We focused on evaluating the features of missed diagnosis of RVTT in RCC patients and found approaches to reduce the rate of missed diagnosis.

We enrolled RCC patients with RVTT from the NCC/CHCAMS between January 2000 and December 2015. The medical records of each patient were retrospectively reviewed. The key inclusion criteria were patients who underwent either enhanced kidney CT or MRI for clinical staging, patients who underwent laparoscopic nephrectomy with complete pathological specimens, and histopathological confirmation of RCC with macroscopically visible RVTT (grade 0 tumor thrombus by Mayo classification). The patients meeting our inclusion criteria were classified and assigned to the 'missed diagnosis' group and 'diagnosis' group depending on whether the RVTT was misdiagnosed pre-operatively. Patients matched into pairs (1:1 statistical matching) in the same continuous period according to the demographic data (sex, age and nationality) and clinical features (BMI, KPS, paraneoplastic syndrome, tumor side and surgery method) were selected as control group ('no tumor thrombus' group; Figure 1).

Pre-operative assessment and surgical plan

We collected the imaging data, regarding the tumor location, maximal tumor diameter in the coronary plane, filling

circumstance of contrast agents and collateral vessels of tumor. Pre-operative MRI or CT data were reviewed by two radiologists, blinded to the patients' surgery information. Axial and coronal planes were combined to assess the status of contrast agents and collateral vessels. 'Insufficient filling' was defined when enhanced CT or MRI scanning of the renal vein phase appeared as regional heterogeneous density and the region area is not less than 30 mm² (Figure 2(A)). The criterion of collateral vessels around the tumor was at least one varicose vein around the tumor (Figure 2(B)).

Either lumbar or transabdominal laparoscopic radical nephrectomy was performed in all patients. After separating and clamping the renal artery during surgery, the upper and lower poles of the kidney were fully dissociated and the renal vein was explored. If a tumor thrombus was found, the renal vein was clipped or ligated with Hem-o-lok at the beginning of the renal vein, allowing complete removal of RVTT without tumor exposure.

Statistical analysis

Normally distributed continuous data were compared using the student's *t*-test, and the chi-square test was used to compare the difference of distribution data between the groups. Overall survival time (OS) were estimated by the Kaplan–Meier method and the log-rank test was used to compare different survival curves. Univariate and multivariate

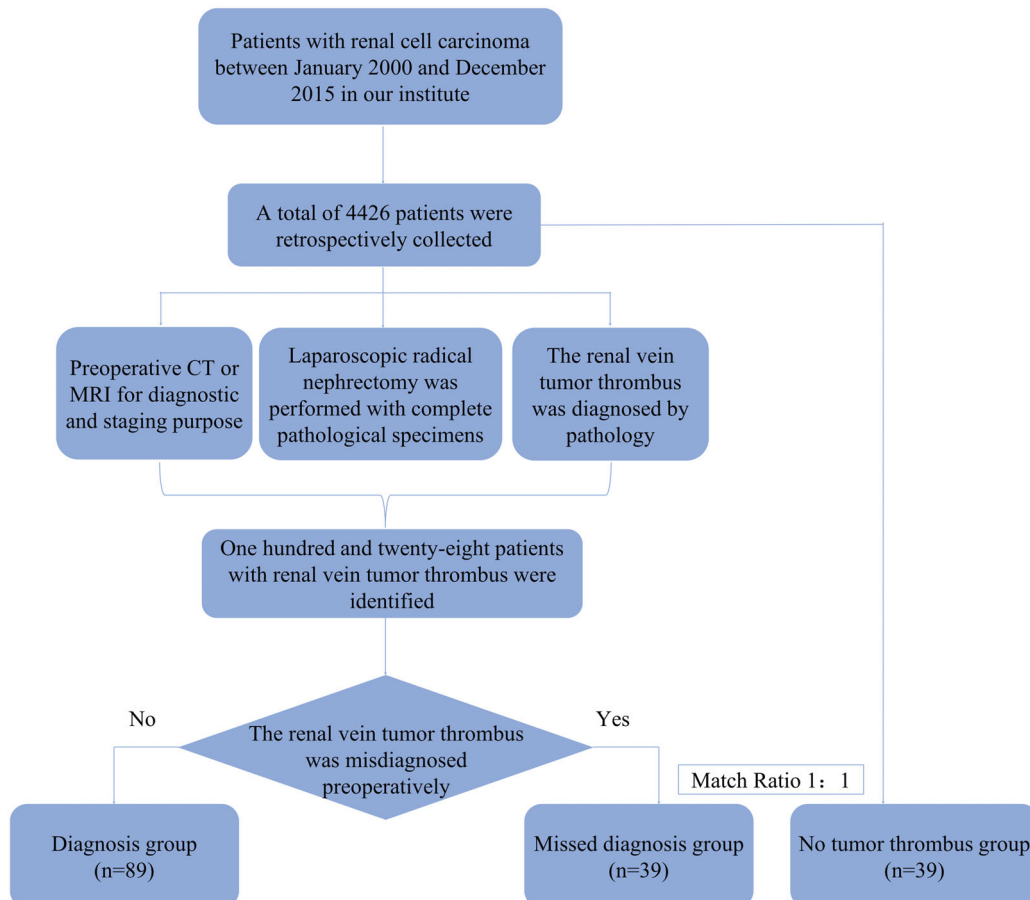


Figure 1. The process of screening patients for the diagnosis group, missed diagnosis group and no tumor thrombus group.

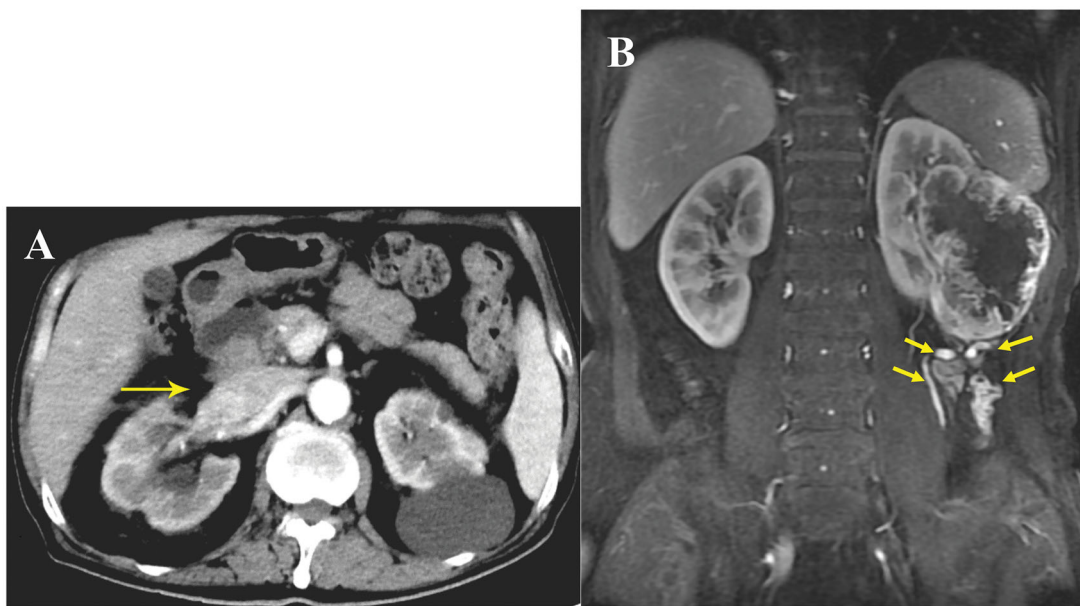


Figure 2. Appraisal of renal vein contrast agents filling insufficiently and tumor with collateral vessels. (A) Computed tomography imaging of insufficient contrast agent filling (arrow) in the renal vein; (B) magnetic resonance imaging of renal tumor with enlarged collateral vessels.

regression models were developed to find independent predictors for missed RVTT diagnosis. The receiver operating characteristic curve (ROC) was constructed, and area under the curve (AUC) analysis was performed to determine the prediction model. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS statistics for Windows, version 23.0; IBM Corp. Armonk, NY, USA), and differences were considered statistically significant if $p < .05$.

Results

Clinical characteristics of patients classified according to renal vein tumor thrombus

We retrospectively reviewed 4426 RCC patients at the NCC/CHCAMS, and screened 128 (2.9%) RCC patients based on the inclusion criteria. The chief complaint was hematuria in 41.4% cases, and 42.9% cases were diagnosed by routine physical examination. Among the 128 patients, 103 were males (80.5%) and 25 were females (19.5%) of median age 61 years (interquartile range [IQR], 52.0–68.7). Of these, 39 patients (30.5%) with RVTT, who were misdiagnosed pre-operatively by imaging, were assigned to the missed diagnosis group. The diagnosis group comprised of 89 patients (69.5%) diagnosed with RVTT by pre-operative imaging and confirmed by postoperative pathology. The 39 patients of the missed diagnosis group underwent 1:1 statistical matching and were assigned to the ‘no tumor thrombus’ group.

There were 22 cases (56.4%) of tumors located in the middle of kidney, 7 cases (18.0%) in the upper renal pole and 10 cases (25.6%) in the lower renal pole in the missed diagnosis group. All clinical parameters are summarized in Table 1. No postoperative complications associated with embolism occurred (Supplementary file 1). The missed diagnosis group was more likely to have a higher proportion of tumors located in the middle pole ($p = .012$), renal vein contrast

agents filling insufficiently ($p = .032$) and presence of collateral vessels ($p = .005$) as compared to the no tumor thrombus group. These features showed no differences between the missed diagnosis and diagnosis groups.

Development of the prediction model of missed diagnosis of renal vein tumor thrombus

The four pre-operative variables, including maximal tumor diameter (odds ratio [OR] = 1.37; 95% confidence interval [CI], 1.07–1.54; $p = .015$), tumor located in the middle part (OR = 1.89; 95% CI, 1.23–2.72; $p < .001$), renal vein contrast agents filling insufficiently (OR = 1.40; 95% CI, 1.19–2.62; $p < .001$) and tumor with collateral vessels (OR = 1.28; 95% CI, 1.01–1.86; $p = .026$), with $p < .05$ in univariable analyses were used in multivariable logistic regression analysis. These variables were significantly associated with missed diagnosis of RVTT, whereas body mass index, length of tumor thrombus, Karnofsky performance status, paraneoplastic syndrome and tumor side were not (Table 2).

Furthermore, multivariable logistic regression analysis demonstrated that maximal tumor diameter (OR = 1.22; 95% CI, 1.56–1.83; $p = .034$), tumor located in the middle part (OR = 1.35; 95% CI, 1.03–2.63; $p = .003$), renal vein contrast agents filling insufficiently (OR = 1.25; 95% CI, 1.01–1.65; $p = .015$) and tumor with collateral vessels (OR = 1.22; 95% CI, 1.12–2.04; $p = .037$) were independent predictors of missed RVTT diagnosis (Table 2).

Based on the final multivariable model, a missed diagnosis score was calculated by taking the sum of score of ‘1’ each for maximal tumor diameter, tumor located in the middle part, renal vein contrast agents filling insufficiently and tumor with collateral vessels (Figure 3). The sensitivity and specificity were 94.9% and 48.7% for patients with 2 score, 74.4% and 84.6% for patients with 3 score and 46.2% and 94.9% for

Table 1. Clinical characteristics between different groups.

Characteristics	Missed diagnosis group	No tumor thrombus group	Diagnosis group	P_1 value*	P_2 value*
Mean (SD)					
BMI, kg/m ²	26.74 (3.12)	23.68 (3.72)	25.12 (1.93)	0.172	0.677
Tumor diameter, cm	7.45 (3.28)	6.03 (3.74)	6.53 (1.87)	0.552	1.658
Length of tumor thrombus	1.44 (0.47)	–	1.63 (0.61)		0.083
N (%)					
KPS				0.556	0.911
<80	2 (5.1)	1 (2.6)	5 (5.6)		
≥80	37 (94.9)	38 (97.4)	84 (94.4)		
Side				0.365	0.399
Left kidney	17 (43.6)	21 (53.8)	46 (51.7)		
Right kidney	22 (56.4)	18 (46.2)	43 (48.3)		
Tumor location				0.012	0.056
Middle	22 (56.4)	11 (28.2)	34 (38.2)		
Upper and lower	17 (43.6)	28 (71.8)	55 (61.8)		
Paraneoplastic syndrome				0.556	0.452
Yes	1 (2.6)	2 (5.1)	5 (7.9)		
No	38 (97.4)	37 (94.9)	84 (92.1)		
Renal vein contrast agents filling insufficiently				0.032	0.860
Yes	18 (46.2)	9 (23.1)	38 (42.7)		
No	21 (53.8)	30 (76.9)	51 (57.3)		
Tumor with collateral vessels				0.005	0.834
Yes	13 (33.3)	3 (7.7)	28 (31.5)		
No	26 (66.7)	36 (92.3)	1. (68.5)		
Lymph node metastasis				0.692	0.345
Absent	35 (89.7)	36 (92.3)	84 (94.4)		
Present	4 (10.3)	3 (7.7)	5 (5.6)		
Fuhrman grade				0.645	0.654
I/II	15 (38.5)	17 (43.6)	38 (42.7)		
III/IV	24 (61.5)	22 (56.4)	51 (57.3)		
Tumor necrosis				0.411	0.981
Yes	10 (25.6)	7 (17.9)	23 (25.8)		
No	29 (74.4)	32 (82.1)	66 (74.2)		

* P_1 , Comparison between missed diagnosis group and no tumor thrombus group; P_2 , Comparison between missed diagnosis group and diagnosis group.

Table 2. Univariate and multivariate Cox analysis of the clinical factors predicting the missed diagnosis of renal vein tumor thrombus.

	Univariate			Multivariate		
	OR	95% CI	p Value	OR	95% CI	p Value
BMI, kg/m ²	0.35	0.17–2.05	.834	–	–	–
Maximal tumor diameter, cm	1.37	1.07–1.54	.015	1.22	1.56–1.83	.034
Length of tumor thrombus	0.73	0.94–1.65	.674	–	–	–
KPS, <80	0.47	0.27–1.07	.663	–	–	–
Paraneoplastic syndrome	0.58	0.24–1.56	.842	–	–	–
Tumor side (Left vs. Right)	0.37	0.13–0.82	.571	–	–	–
Tumor located in the middle part	1.89	1.23–2.72	<.001	1.35	1.03–2.63	.003
Renal vein contrast agents filling insufficiently	1.40	1.19–2.62	<.001	1.25	1.01–1.65	.015
Tumor with collateral vessels	1.28	1.01–1.86	.026	1.22	1.12–2.04	.037

patients with 4 score, respectively. The model presented an AUC of 0.852 (95% CI: 0.77–0.94, $p < .001$; Figure 4).

Correlation of clinical factors with outcomes of different groups

The median follow-up time was 47 months (7–186 months). The missed diagnosis group achieved longer OS than the diagnosis group and had similar survival time as that of the no tumor thrombus group (Figure 5).

Univariate and multivariate analyses for OS are summarized among patients with RVTT in Table 3. The univariate survival analysis revealed that presence of tumor with collateral vessels had a significant association with OS (hazard ratio [HR] = 1.61; 95% CI, 1.33–2.72, $p < .001$). The maximal tumor

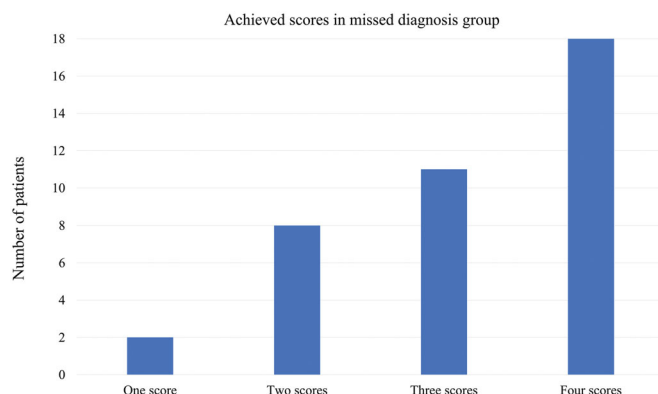


Figure 3. Sum scores for maximal tumor diameter, tumor located in the middle part, renal vein contrast agents filling insufficiently and tumor with collateral vessels (1 score for each feature).

diameter, tumor located in the middle and renal vein contrast agents filling insufficiently were not significantly associated with OS. However, in the model that included maximal tumor diameter, tumor located in the middle pole, renal vein contrast agents filling insufficiently and tumor with collateral vessels, only tumor with collateral vessels was an independent prognostic indicator of poor OS (HR = 1.15; 95% CI, 1.02–1.47, $p = .025$).

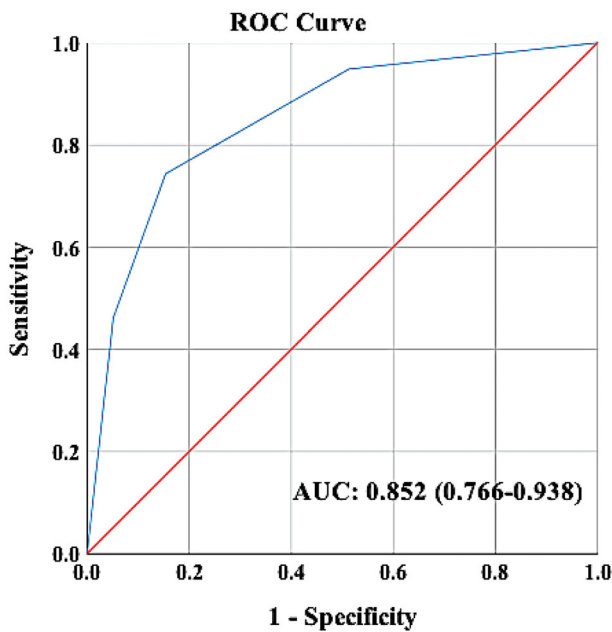


Figure 4. Scores based on final multivariable model assessed by the receiver operating characteristic curve.

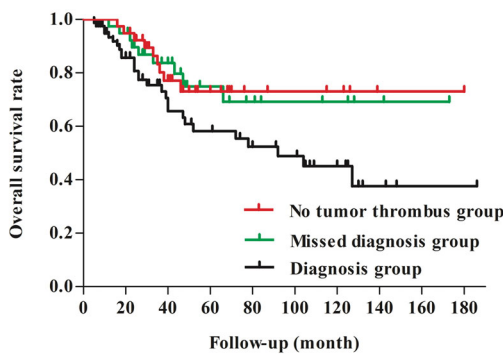


Figure 5. Correlation of overall survival between the three groups. Diagnosis group patients show poorer survival time as compared to the missed diagnosis group and the no tumor thrombus group ($p = .041$ and $p = .033$, respectively).

Discussion

We specially investigated the Chinese RCC patients with RVTT and constructed a risk model for long-term survival in these patients [7]. Based on our report of high rate of missed diagnosis of RVTT, we found that several features including maximal tumor diameter, tumor located in the middle part, renal vein contrast agents filling insufficiently and tumor with collateral vessels were associated with missed diagnosis of RVTT. These misdiagnosed patients had similar survival times as that of the no tumor thrombus group patients, which suggested that initially formed RVTT could be an unimportant prognosis factor.

According to the 8th edition of the American Joint Committee on Cancer’s tumor-node-metastasis staging system, RCC with VTT extending to the renal vein, extending to the sub-diaphragmatic inferior vena cava (IVC) or extending to the supradiaphragmatic IVC are classified as T3a, T3b or T3c, respectively. VTT destroys the integrity of blood vessels and changes the hemodynamics. Approximately 5–20% of RCC cases during initial diagnosis involved the renal vein, IVC or right atrial tumor thrombus. The probability of the VTT falling off and causing an embolism is between 1.2% and 6.0% [8]. The incidence rate is relatively low, the mortality rate is high and there is no clinical evidence to support that the implanted IVC filter can prevent pulmonary embolism [9,10]. RVTT belongs to T3a (locally advanced RCC) with poor long-term survival. Radical nephrectomy combined with tumor thrombectomy is the only treatment option that can cure non-metastatic RCC with VTT [11–13]. However, the 5-year cancer specific survival rate (CSS) was reported to be only 25–53% [5,14,15]. In our institute, the patients’ CSS with RVTT was 67.9% and 57.0% in the 5-year and 10-years follow-up, respectively [7]. In this study, we first investigated the prognosis of patients with missed diagnosis of RVTT pre-operatively. The result showed that these patients achieved longer survival than those not misdiagnosed with RVTT, and had similar survival time as that of the no tumor thrombus patients. We considered that this kind of RVTT could be a borderline status between obvious RVTT and initial formation of thrombus, which needs special attention, and further studies are necessary.

RVTT is usually stable, but there is a risk of squeezing and embolization in long, thin or fragile RVTT. Therefore, pre-operative diagnosis of RVTT is particularly important. The diagnosis of RVTT mainly depends on CT, MRI or vascular ultrasound, and the accuracy is approximately 85% [16–18]. The technical defects of imaging can contribute to missed diagnosis of RVTT, but it also has a possible correlation with the characteristics of primary tumor. In this study, the

Table 3. Univariable and multivariable Cox analysis of the clinical factors predicting the prognosis of renal vein tumor thrombus.

	Univariate			Multivariate		
	HR	95% CI	p Value	HR	95% CI	p Value
Maximal tumor diameter, cm	0.61	0.11–1.06	.748	0.87	0.16–1.72	.917
Tumor located in the middle part	0.25	0.11–0.81	.569	0.65	0.06–1.22	.514
Renal vein contrast agents filling insufficiently	0.18	0.09–0.57	.406	0.53	0.25–1.14	.835
Tumor with collateral vessels	1.61	1.33–2.72	<.001	1.15	1.02–1.47	.025

average tumor diameter in the missed diagnosis group was 7.45 cm. We found that there was no statistically significant difference in the maximum diameter of the tumor between the missed diagnosis group and the no tumor thrombus group. However, maximal tumor diameter was an independent factor associated with missed diagnosis. To some extent, the diameter of tumor was relatively large in patients undergoing radical nephrectomy, which tended to compress the renal vein and disturb the imaging observation and evaluation. Tumor size was reportedly of prognostic value and was not specially investigated in RVTT [19,20].

We also discovered that the proportion of tumors located in the middle part of the kidney in the missed diagnosis group was significantly higher than in the no tumor thrombus group. This could be because the middle kidney tumor is close to the renal pedicle vessels, and it was difficult or unclear to identify the renal portal vessels in imaging due to the inwardly growing tumor, renal vein invasion or tumor compression. There were also some RVTTs in the renal vein phase of CT or MRI enhanced scanning that showed insufficient contrast agent filling, which was sometimes found in the normal renal vein because of delayed filling. The identification was difficult, and required assistance by combination other factors. Chopra et al. [21] reported that a thorough understanding of collateral vessels was important for intraoperative safety of tumor thrombectomy in RCC. Bradley et al. [22] reported that the presence of enlarged perinephric collateral vessels was more likely to be at a stage over T3a. In this study, we discovered that patients with RVTT were prone to form collateral vessels, and that tumors with collateral vessels was not only a prognostic factor for RVTT, but also an important predictor of missed RVTT diagnosis. In summary, according to literature, no other study evaluated the presence of these clinical features as predictors of missed RVTT diagnosis. From the ROC curve, we found that patients with a score of 3 suggested higher possibility of missed RVTT diagnosis.

This study had the limitation of having a retrospective design and including only limited cases of certain groups. Future prospective studies are necessary to confirm the same.

In conclusion, the RCC imaging, including the characteristics of large tumor diameter, tumor located in the middle part, renal vein contrast agents filling insufficiently and tumor with collateral vessels were associated with missed diagnosis of RVTT. These characteristics may not be found in all cases, but even if one of the characteristics is recognized, it is necessary to suspect the possibility of the presence of RVTT. In the missed diagnosis scoring method, patients with a score of 3 had high sensitivity and specificity. Furthermore, missed diagnosis of RVTT could have relatively favorable prognosis, and the feature of perinephric collateral vessels was a prognostic factor for RVTT.

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Ethics approval and consent to participate

The research study was reviewed and approved by the Domain-Specific Review Board, Cancer Hospital Chinese Academy of Medical Sciences. Patient details were anonymized before analysis.

Patient study consent was not required due to the study's retrospective nature.

Availability of data and materials

The datasets used and/or analyzed data in the current study are available from the corresponding author on reasonable request.

Author's contribution

Study design and revision of manuscript: Changling Li, Jianhui Ma; data collection: Weixing Jiang, Chuanzhen Cao; data analysis: Dong wang, Li Wen; writing: Weixing Jiang; critical revision of manuscript and final approval of the version to be submitted: Hongzhe Shi, Jianzhong Shou; statistical analysis: Weixing Jiang, Chuanzhen Cao.

Disclosure statement

The authors report no conflicts of interest.

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