

Kidney Histopathology Features of Suspected Intra-Kidney Venous Thromboembolism in Patients with Primary Glomerulonephritis

Hui Lu^a Zhao Cui^a Tang-li Xiao^b Su-xia Wang^b Ming-hui Zhao^{a,c}

^aRenal Division, Peking University First Hospital, Institute of Nephrology, Peking University, Key Laboratory of Renal Disease, Ministry of Health of China, Key Laboratory of Chronic Kidney Disease (CKD) Prevention and Treatment, Ministry of Education of China, Research Units of Diagnosis and Treatment of Immune-mediated Kidney Diseases, Chinese Academy of Medical Sciences, Beijing, China; ^bLaboratory of Electron Microscopy, Pathological Center, Peking University First Hospital, Beijing, China; ^cPeking-Tsinghua Center for Life Sciences, Beijing, China

Keywords

Kidney pathology · Intra-kidney venous thromboembolism · Venous thromboembolism · Scores · Glomerulonephritis

Abstract

Introduction: Renal vein thromboembolism is a severe complication of nephrotic syndrome. Small thrombus in the intra-kidney venous system cannot be recognized by ultrasonography. The current study was to investigate the kidney pathological features of intra-kidney venous thrombus and their values in clinical practice. **Methods:** Kidney pathological features of glomerular capillary dilatation and congestion, peritubular capillary dilatation and congestion, and intraglomerular neutrophil infiltration were screened and scored during kidney biopsy information interpretation. Eighty-four consecutive patients with these features and primary glomerulonephritis were analyzed, comparing to another 84 control patients without these features who were matched according to the pathological types of glomerulonephritis. **Results:** In the patients with pathological features of suspected intra-kidney venous thrombus, the levels of proteinuria (5.2 vs. 3.2 g/24 h, $p = 0.005$), serum creatinine (80.9 vs. 71.2 $\mu\text{mol/L}$, $p < 0.001$), platelet count (274.0 vs. $254.5 \times 10^9/\text{L}$, $p = 0.020$), D-dimer (0.2 vs. 0.2 mg/L, $p = 0.002$),

and fibrin degradation products (1.9 vs. 1.0 mg/L, $p = 0.003$) were significantly higher than those in control patients. The levels of serum albumin (24.2 vs. 28.6 g/L, $p = 0.003$) and eGFR (92.1 vs. 103.9 mL/min/1.73 m², $p < 0.001$) were significantly lower. The scores of these pathological features were positively correlated with the levels of D-dimer ($r = 0.21$, $p = 0.05$). During follow-up, 9 (10.7%) patients with pathological features of suspected intra-kidney venous thrombus developed venous thromboembolism, which was significantly more than that of control patients (0%, $p = 0.006$). **Conclusions:** Kidney pathological features could indicate intra-kidney venous thromboembolism, and their scores represent the possibility of thrombus. The notice of these features may provide clinical alerts for venous thromboembolism possibility.

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Introduction

Thromboembolism is one of the serious complications of nephrotic syndrome, which can be life-threatening in some cases [1–3]. Its overall incidence ranges from 5% to 62% according to different pathological types of glomerulonephritis and is highest in the patients with membra-

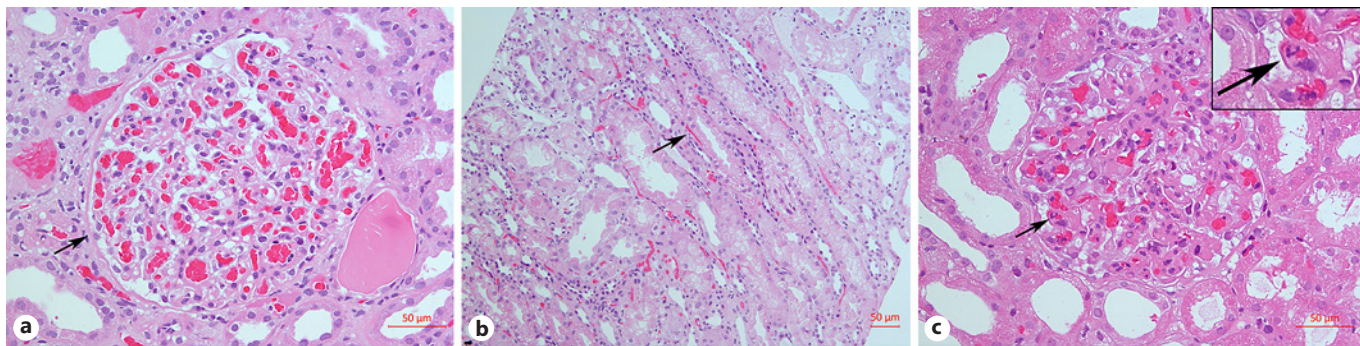


Fig. 1. Kidney biopsy findings in patients with pathological features of suspected intra-kidney VTE. **a** Glomerular capillary dilatation and congestion (arrow) (hematoxylin and eosin stain, original magnification, $\times 400$). **b** Peritubular capillary dilatation and congestion (arrow) (hematoxylin and eosin stain, original magnification, $\times 200$). **c** Intraglomerular neutrophil infiltration (arrow) (hematoxylin and eosin stain, original magnification, $\times 400$).

nous nephropathy (MN) or membranoproliferative glomerulonephritis [4, 5]. Changes in plasma proteins involving coagulation and fibrinolysis, elevated platelet count, enhanced platelet aggregation, reduced serum albumin, hyperviscosity, and hyperlipidemia are considered as factors contributing to thromboembolism [6–8]. Risk factors of venous thromboembolism (VTE) include lower serum albumin, higher urinary protein, and higher D-dimer value. Among them, serum albumin is the independent risk factor and is recommended for monitoring to guide prophylactic anticoagulation [9–11].

Timely detection of thromboembolism is crucial in clinical practice of nephrotic syndrome. Renal vein thrombosis is often silent, sometimes with pulmonary embolism being the first presenting sign [12]. The classic manifestation of acute renal vein thrombosis with gross hematuria, flank pain, and decreasing kidney function is uncommon. Doppler ultrasonography can visualize the actual venous flow, increased blood velocity, and turbulence in a narrowed vein or complete cessation of flow if the lumen is totally occluded. However, sonography is highly operator-dependent and has a low specificity (56%) despite a high sensitivity (85%) in experienced hands [13]. Usually, small thrombus in the intra-kidney venous system could not be recognized by ultrasonography.

Kidney biopsy is necessary for the pathological diagnosis of glomerulonephritis in adults. Besides, some pathological manifestations may provide important clues for the suspicious diagnosis of intra-kidney VTE. In the current study, we found that glomerular capillary dilatation and congestion, peritubular capillary dilatation and congestion, and intraglomerular neutrophil infiltration were

the pathological features of suspected intra-kidney VTE. We set up a semiquantitative scoring system and analyzed it in a large cohort of patients with primary glomerulonephritis, with the aim to investigate the clinical utilities of these pathological features to indicate hypercoagulability or thromboembolism in kidneys.

Materials and Methods

Study Design and Patients

In this study from January 2018 to April 2021, we retrospectively reviewed 84 consecutive patients with primary glomerulonephritis who had pathological features of suspected intra-kidney VTE on a kidney biopsy. We matched control patients without these pathological features 1:1 according to the different types of primary glomerulonephritis in the same period. All patients received a kidney biopsy at Peking University First Hospital. Patients with secondary glomerulonephritis, malignancy, atrial fibrillation, right heart failure, or left renal vein compression between the superior mesenteric artery and the aorta (nutcracker syndrome) were excluded [14].

Data Collection and Thromboembolic Events

Clinical data were collected at the time of the kidney biopsy and at every visit, including gender, age, thromboembolic events, pathological type, anticoagulation therapy, urinary protein, serum albumin, anti-PLA2R antibodies, serum creatinine, platelet count, mean platelet volume, hemoglobin, and hematocrit. The coagulation and fibrinolysis index included D-dimer, fibrin degradation products, prothrombin time, and activated partial thromboplastin time. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula [15]. Thromboembolic events were recorded according to vascular ultrasound, computed tomography, and ventilation and perfusion lung scanning, at the kidney biopsy and during follow-up.

Table 1. Scores of pathological features of suspected intra-kidney VTE

Definition	Variable	Severity	Score
Glomerular capillary dilatation and congestion	Percentage* of glomeruli involvement	0%	0
		1–25%	1
		26–50%	2
		>50%	3
Peritubular capillary dilatation and congestion	Percentage of cortical area involvement	0%	0
		1–25%	1
		26–50%	2
		>50%	3
Intraglomerular neutrophil infiltration	Percentage* of glomeruli involvement (A) plus number [#] of neutrophils per glomerulus (B)	A: 0%	0
		1–25%	1
		26–50%	2
		>50%	3
		B: 0	0
		1	1
		2	2
3	3		

* The glomeruli showing global sclerosis were excluded. [#]The number of neutrophils per glomerulus (mean) takes a single digit according to rounding.

Pathology Definitions and Scoring

Glomerular capillary dilatation and congestion were defined as global distention of glomerular capillaries plugged with intact red blood cells (Fig. 1a). Peritubular capillary dilatation and congestion were defined as distention of peritubular capillaries plugged with intact red blood cells (Fig. 1b). Intraglomerular neutrophil infiltration was defined as neutrophil lobulated nucleus infiltration in glomerular capillary loop (Fig. 1c).

Glomerular capillary dilatation and congestion, peritubular capillary dilatation and congestion, and intraglomerular neutrophil infiltration were the suspected pathological features of thromboembolism in the kidney venous system. The semiquantitative scoring system of these pathological indices are shown in Table 1, of which the number of neutrophils per glomerulus were calculated by dividing the total number of neutrophils by the number of glomeruli with neutrophil infiltration, and the result takes a single digit according to rounding.

Treatment and Follow-Up

All patients were treated and followed up for at least 6 months. They received renin-angiotensin-aldosterone system inhibitor therapies and/or immunosuppressant therapy according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for glomerulonephritis [16].

To evaluate therapeutic responses, complete remission was defined as urinary protein <0.3 g/24 h. Partial remission was defined as urinary protein reduction >50% from baseline and <3.5 g/24 h, with serum albumin concentration improvement or normalization and serum creatinine stable or elevated <30% from baseline. Patients who did not reach remission were considered as nonresponders. The recurrence of urinary protein >3.5 g/24 h after a period of remission was regarded as relapse [17–21].

For evaluation of kidney outcomes, the primary endpoint was ESKD with eGFR <15 mL/min/1.73 m², receiving dialysis or death. The secondary endpoint was eGFR reduction >30% from baseline.

Statistical Analysis

Statistical analysis was performed using SPSS 24.0 (IBM, New York, NY, USA). Normally distributed variables were described as mean ± standard deviation and compared using the *t* test or one-way analysis of variance. Data following a non-normal distribution were presented as median (interquartile range) and compared using the Kruskal-Wallis test or Mann-Whitney U test. Categorical variables were expressed as amount (percentage), and their differences were assessed by the χ^2 test. Correlations between pathological scores and clinical features were carried out using the Spearman test. Logistic regression analysis was performed to find potential risk or protective factors of treatment responses. All probabilities were two-sided, and a *p* < 0.05 was considered statistically significant.

Results

Clinical Characteristics

A total of 84 consecutive patients with primary glomerulonephritis and pathological features of suspected intra-kidney VTE were enrolled in the study. Another 84 patients without these features were matched at 1:1 according to the different pathological types of glomerulonephritis as the control group. Clinical and pathological features were presented in Table 2.

Table 2. Comparisons of clinical features of patients

Features	Pathological features of suspected intra-kidney VTE		
	positive (n = 84)	negative (n = 84)	p value
Gender, male, n (%)	60 (71.4)	43 (51.2)	0.007
Age, years	48.0 (37.0, 57.8)	40.5 (28.3, 51.8)	0.018
Proteinuria, g/24 h	5.2 (2.6, 9.3)	3.2 (1.8, 6.6)	0.005
Albumin, g/L	24.2 (18.8, 31.4)	28.6 (24.1, 35.0)	0.003
Nephrotic syndrome, n (%)	47 (56.0)	31 (36.9)	0.013
Positive anti-PLA2R antibodies in MN patients, n (%)	27/49 (55.1)	21/49 (42.9)	0.225
Serum creatinine, $\mu\text{mol/L}$	80.9 (68.8, 108.4)	71.2 (56.9, 82.2)	<0.001
eGFR, mL/min/1.73 m ²	92.1 (68.3, 106.3)	103.9 (90.2, 118.0)	<0.001
Platelet, 10 ⁹ /L	274.0 (241.0, 324.8)	254.5 (227.0, 293.8)	0.020
MPV, fL	8.2 (7.8, 8.8)	8.4 (7.9, 8.9)	0.346
Hemoglobin, g/L	147.5 (134.3, 155.8)	138.0 (125.3, 154.0)	0.059
Hematocrit, %	43.6 (40.0, 46.4)	41.5 (37.7, 45.9)	0.088
D-dimer, mg/L	0.2 (0.1, 0.6)	0.2 (0.1, 0.3)	0.002
FDP, mg/L	1.9 (0.9, 4.2)	1.0 (0.7, 2.0)	0.003
PT, s	10.6 (10.1, 11.0)	10.7 (10.3, 11.1)	0.244
APTT, s	32.9 (30.3, 36.8)	32.2 (29.5, 34.4)	0.108
Anticoagulation therapy, n (%)	30 (35.7)	14 (16.7)	0.005
Thromboembolism events, n (%)	13 (15.5)	0	<0.001
Intra-kidney microthrombus	7 (8.3)	0	0.021
VTE	9 (10.7)	0	0.006
Treatment responses			
Clinical remission, n (%)	58 (69.0)	59 (70.2)	0.867
Complete remission, n (%)	38 (49.4)	45 (53.6)	0.280
Partial remission, n (%)	20 (23.8)	14 (16.7)	0.249
Time to remission, months	3.0 (2.0, 9.0)	3.0 (1.0, 10.0)	0.285
Relapse, n (%)	16/58 (27.6)	13/59 (22.0)	0.487
No remission, n (%)	26 (31.0)	25 (29.8)	0.867
Follow-up, months	15.0 (11.0, 28.0)	20.0 (14.0, 25.8)	0.056
ESKD, n (%)	2 (2.4)	0	0.477
eGFR reduction >30%, n (%)	5 (6.0)	2 (2.4)	0.440
Death, n (%)	1 (1.2)	0	1.000

Normally distributed variables are shown as mean \pm SD. Non-normally distributed variables are presented as median (IQR). Categorical variables are shown as n (%). MPV, mean platelet volume; FDP, fibrin degradation products; PT, prothrombin time; APTT, activated partial thromboplastin time; VTE, venous thromboembolism; ESKD, end-stage kidney disease; SD, standard deviation; IQR, interquartile range.

In the 84 patients having pathological features of suspected thrombus, there were 60 (71.4%) male patients, and the median age was 48.0 (37.0, 57.8) years. The levels of proteinuria (5.2 [2.6, 9.3] vs. 3.2 [1.8, 6.6] g/24 h, $p = 0.005$) and serum creatinine (80.9 [68.8, 108.4] vs. 71.2 [56.9, 82.2] $\mu\text{mol/L}$, $p < 0.001$) were significantly higher, compared to the control patients. The levels of serum albumin (24.2 [18.8, 31.4] vs. 28.6 [24.1, 35.0] g/L, $p = 0.003$) and eGFR (92.1 [68.3, 106.3] vs. 103.9 [90.2, 118.0] mL/min/1.73 m², $p < 0.001$) were significantly lower in the thrombus group. The levels of platelet count (274.0 [241.0, 324.8] vs. 254.5 [227.0, 293.8] $\times 10^9/\text{L}$, $p = 0.020$), D-dimer (0.2 [0.1, 0.6] vs. 0.2 [0.1, 0.3] mg/L, $p = 0.002$), and fibrin degradation products (1.9 [0.9, 4.2] vs. 1.0 [0.7,

2.0] mg/L, $p = 0.003$) were significantly higher in the group with pathological features of suspected thrombus. There were 30 (35.7%) patients who received prophylactic anticoagulation therapy before the kidney biopsy in the thrombus group, which was higher than that in the control group (16.7%, $p = 0.005$).

Pathological Types of Glomerulonephritis

In the 84 patients with pathological features of suspected intra-kidney VTE, there were 49 (58.3%) patients of MN, 27 (32.1%) patients of minimal change disease (MCD), 5 (6.0%) patients of focal segmental glomerulosclerosis (FSGS), and 3 (3.6%) patients of IgA nephropathy. The patients with MN were older than those with

Table 3. Comparisons of patients with pathological features of suspected intra-kidney VTE, according to different pathological types of glomerulonephritis

Features	MN (n = 49)	MCD (n = 27)	FSGS (n = 5)	IgAN (n = 3)	p value*
Gender, male, n (%)	37 (75.5)	16 (59.3)	5 (100.0)	2 (66.7)	0.112
Age, years	51.4±14.4	42.4±17.0	32.8±18.3	44.3±6.4	0.007
Proteinuria, g/24 h	4.2 (2.4, 8.6)	7.2 (3.2, 10.1)	9.1 (8.1, 17.8)	1.55±0.8	0.032
Albumin, g/L	28.7 (21.6, 32.9)	19.2 (17.3, 24.0)	19.4 (17.2, 23.5)	40.8±4.0	<0.001
Serum creatinine, μmol/L	76.2 (65.0, 87.2)	93.5 (71.8, 148.1)	110.9 (84.1, 239.4)	104.4±14.8	0.003
eGFR, mL/min/1.73 m ²	95.2 (83.8, 106.5)	88.0 (36.1, 106.7)	61.9 (34.6, 101.5)	68.3±4.8	0.124
Platelet, 10 ⁹ /L	269.0 (228.5, 305.5)	288.0 (256.0, 327.0)	349.0 (212.0, 382.0)	270.0±103.3	0.099
MPV, fL	8.5±1.2	8.2±0.7	8.5±1.3	8.9±2.0	0.846
Hemoglobin, g/L	144.0 (128.5, 155.0)	151.0 (143.0, 155.0)	151.0 (130.0, 163.0)	147.0±10.8	0.390
Hematocrit, %	43.1 (37.9, 46.0)	45.3 (42.6, 46.9)	44.7 (40.4, 48.3)	43.2±4.5	0.134
D-dimer, mg/L	0.3 (0.1, 0.6)	0.2 (0.1, 0.5)	0.3 (0.2, 1.5)	0.1±0.1	0.548
FDP, mg/L	1.7 (0.6, 4.6)	2.1 (1.0, 3.5)	1.6 (1.6, 8.1)	0.9±1.0	0.555
PT, s	10.6 (10.0, 11.0)	10.6 (10.3, 11.2)	10.9 (9.9, 11.1)	10.6±0.5	0.520
APTT, s	32.4±4.4	37.5±6.4	32.0±1.2	31.7±1.9	0.001
VTE, n (%)	6 (12.2)	2 (7.4)	1 (20.0)	0 (0.0)	0.657

Normally distributed variables are shown as mean±SD. Non-normally distributed variables are presented as median (IQR). Categorical variables are shown as n (%). MN, membranous nephropathy; MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; MPV, mean platelet volume; FDP, fibrin degradation products; PT, prothrombin time; APTT, activated partial thromboplastin time; VTE, venous thromboembolism; SD, standard deviation; IQR, interquartile range. * The comparisons were among the patients with MN, MCD, and FSGS since the patients with IgAN were too scarce to do any statistical analysis.

MCD or FSGS (51.4 ± 14.4 vs. 42.4 ± 17.0 vs. 32.8 ± 18.3 years, $p = 0.007$). They had lower levels of proteinuria (4.2 [2.4, 8.6] vs. 7.2 [3.2, 10.1] vs. 9.1 [8.1, 17.8] g/24 h, $p = 0.032$), higher level of serum albumin (28.7 [21.6, 32.9] vs. 19.2 [17.3, 24.0] vs. 19.4 [17.2, 23.5] g/L, $p < 0.001$), and lower level of serum creatinine (76.2 [65.0, 87.2] vs. 93.5 [71.8, 148.1] vs. 110.9 [84.1, 239.4] μmol/L, $p = 0.003$) (Table 3).

Associations between Pathological Scores and Clinical Features

In each case, the pathological indices of suspected intra-kidney VTE were scored by two pathologists separately according to the semiquantitative scoring system (Table 1). The distributions of scores are shown in Figure 2. Among the 84 patients with pathological features of suspected thrombus, there are 32 (38.1%) patients showing scores ≤5 and 52 (61.9%) patients showing scores ≥6. Positive correlations between pathological scores and the level of D-dimer ($r = 0.21$, $p = 0.05$) were observed (Table 4). The D-dimer level was significantly higher in the patients with pathological scores ≥6 than that in the patients with scores ≤5 (0.3 [0.2, 0.8] vs. 0.2 [0.1, 0.3] mg/L, $p = 0.018$).

Among the 84 patients with pathological features of suspected thrombus, 13 (15.5%) patients had thrombo-

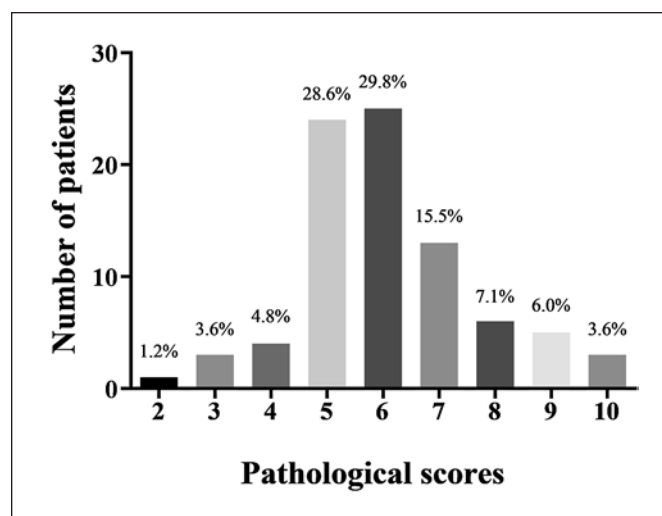


Fig. 2. Frequency of pathological scores in patients with pathological features of suspected intra-kidney VTE.

embolism events, including seven (8.3%) patients who presented with intra-kidney microthrombus (Fig. 3) and 9 (10.7%) patients who developed VTEs (3 patients had both), which were higher than those in the control group (15.5 vs. 0%, $p < 0.001$; 8.3 vs. 0%, $p = 0.021$; 10.7 vs. 0%, $p = 0.006$, respectively) (Table 2). Among patients with

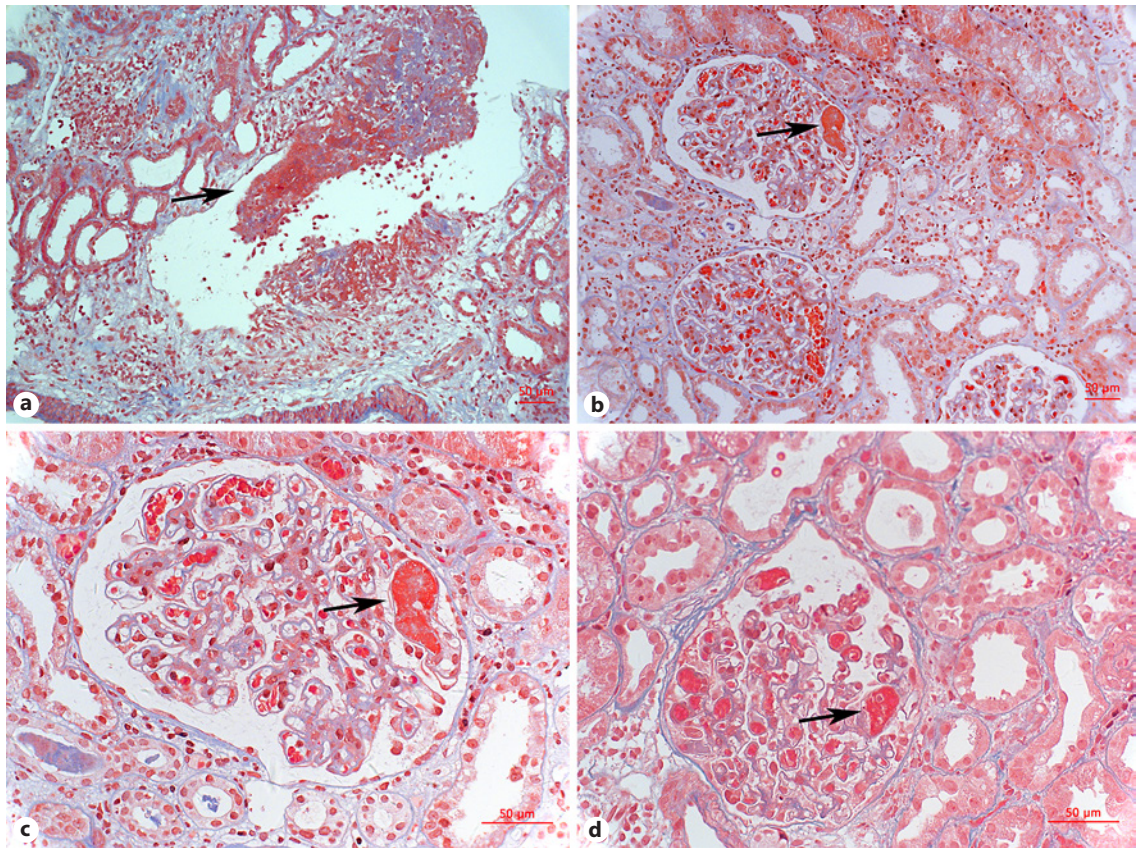


Fig. 3. Evidence of intra-kidney microthrombus in patients with pathological features of suspected intra-kidney VTE. **a** Renal vein thrombosis (arrow) (Masson trichrome stain, original magnification, $\times 200$). **b** Intracapillary microthrombus (arrow) (Masson trichrome stain, original magnification, $\times 200$). **c, d** Intracapillary microthrombus (arrow) (Masson trichrome stain, original magnification, $\times 400$).

VTEs, 6 patients had VTE on lower extremities, 1 patient had pulmonary embolism, 1 patient had thrombosis in renal vein, and 1 patient had both pulmonary and renal vein thromboembolism.

Treatment Responses and Kidney Outcomes

After treatments, in the 84 patients with pathological features of suspected intra-kidney thrombus, there were 58 (69.0%) patients who achieved clinical remission, including 38 (49.4%) patients of complete remission and 20 (23.8%) patients of partial remission, with the time from treatment to remission as 3.0 (2.0, 9.0) months. There were 26 (31.0%) patients not achieving remission. The treatment responses were comparable to those of patients without pathological features of suspected thrombus ($p > 0.05$) (Table 2).

Univariate logistic regression analysis showed that the pathological type of glomerulonephritis was a risk factor to treatment failure in this cohort. Compared to MCD

Table 4. Associations between pathological scores of suspected intra-kidney VTE and clinical features

Features	Pathological scores	
	correlation coefficient	<i>p</i> value
Age, years	-0.04	0.73
Proteinuria, g/24 h	0.17	0.11
Albumin, g/L	-0.17	0.12
Serum creatinine, $\mu\text{mol/L}$	0.10	0.35
eGFR, mL/min/1.73 m^2	-0.06	0.58
Platelet, $10^9/\text{L}$	0.15	0.17
MPV, fL	-0.05	0.64
D-dimer, mg/L	0.21	0.05
FDP, mg/L	0.18	0.11

MPV, mean platelet volume; FDP, fibrin degradation products.

patients, MN patients were more difficult to get clinical remission (odds ratio [OR] = 8.62, 95% confidence interval [CI] = 2.88–25.77, $p < 0.001$).

During the follow-up period of 15.0 (11.0, 28.0) months, in the group with pathological features of suspected thrombus, there were 2 (2.4%) patients progressing to ESKD and 5 (6.0%) patients having eGFR reduction $>30\%$ from the baseline. Two patients were dead, including 1 patient who died of cardiac arrest after ESKD and 1 patient who died of pulmonary infection during treatments. These outcomes were comparable to the patients without pathological features of suspected thrombus ($p > 0.05$) (Table 2). Univariate logistic regression analysis showed that older age (OR = 1.07, 95% CI = 1.02–1.13, $p = 0.005$), lower level of eGFR (OR = 0.98, 95% CI = 0.96–1.00, $p = 0.033$), and VTE event (OR = 5.96, 95% CI = 1.04–34.12, $p = 0.045$) were risk factors to kidney dysfunction outcome in this cohort.

Discussion

To our knowledge, this is the first study to examine the clinical values of the pathological features of suspected intra-kidney VTE in glomerulonephritis. We found that the glomerular capillary dilatation and congestion, peritubular capillary dilatation and congestion, and intraglomerular neutrophil infiltration were pathological features highly suggested intra-kidney VTE. Patients with these features presented with higher levels of proteinuria, serum creatinine, and platelet count and lower levels of serum albumin and eGFR. 15.5% of these patients developed thromboembolism events, including visible intra-kidney VTE and VTEs in the period of follow-up. We further created a semiquantitative scoring system for these pathological features and found that the scores were positively correlated with the level of D-dimer. All these findings imply that these pathological features are good indicators for intra-kidney VTE which could not be detected by ultrasonography. The notice of these features during the kidney biopsy information interpretation might provide clues for the thromboembolism complication in glomerulonephritis, which is associated with the kidney outcomes and needs more intensive clinical intervention. The current findings need to be validated prospectively in a larger cohort with a longer follow-up period.

Although invisible on ultrasound, intra-kidney venous thrombus could induce pathological features on microscopy. The renal venous hypertension led to paren-

chymal congestion and presented with glomerular capillary dilatation and congestion. The rise in kidney interstitial pressure would affect the capillary bed and tubules [22]. The pressure change in the tubules was transmitted to the peritubular capillaries and led to their dilatation and congestion [23]. Platelet and neutrophil recruitment were mutually promoted in hypercoagulability [24]. Mac-1 on neutrophils was a critical molecular link between thrombosis and inflammation [25]. After activation, neutrophils adhere to capillary endothelial cells with the aid of specific adhesion molecules [26, 27], which presented with intraglomerular neutrophil infiltration.

The patients with these pathological features had higher levels of platelet count, serum creatinine, and proteinuria and lower levels of serum albumin and eGFR. All these clinical characteristics have been identified as risk factors for VTE in previous studies. Mahmoodi et al. [9] found that the severity of proteinuria was associated with VTE, with the level ≥ 8.2 g/day (hazard ratio 5.2, $p = 0.03$). Serum albumin showed an inverse relationship with VTE. The enhanced platelet-vessel wall interaction and platelet aggregation were revealed in the development of thromboembolism in nephrotic syndrome [2]. eGFR was also an independent predictor for VTE risk. Wattanakit et al. [28–30] found that individuals with chronic kidney disease stage 3 or 4 had a 28% higher risk of VTE compared with those with normal kidney function. Actually, in our group of patients with pathological features of suspected thrombus, there were 10.7% of patients developing VTE in the period of follow-up, while in the control group, no patient underwent VTE later on. Furthermore, in the 7 patients who had visible intra-kidney microthrombus on the biopsy, 3 (42.9%) patients developed VTE. Therefore, these pathological features of suspected intra-kidney thromboembolism were closely related with the clinical risk factors of VTE, and the patients having these features did undergo many more VTE events. These findings imply that these pathological features were important alert of hypercoagulability or thromboembolism for clinical practice.

We set up a semiquantitative scoring system to evaluate the severity of these pathological features and found that the scores were positively correlated with the level of circulating D-dimer. D-dimer units are generated by action of factor XIIIa on fibrin monomers and polymers when the endogenous fibrinolytic system degrades cross-linked fibrin. It is the most frequently used laboratory marker of coagulation and fibrinolysis activation, and its levels parallel the extent and burden of thromboembolism [31, 32]. All our patients were screened negative of

pulmonary embolism, renal vein thrombosis, and lower extremity venous thrombosis before they received the kidney biopsy. Therefore, it is reasonable to presume that the higher level of D-dimer in the patients with pathological features of suspected intra-kidney thrombus may represent the higher possibility of intra-kidney thrombus. The positive relationship of pathological scores and D-dimer levels implies that this semiquantitative scoring system could reveal the possibility of intra-kidney VTE.

The current cohort is composed of patients with different types of primary glomerulonephritis. Under consecutive enrollment, patients with MN accounted for 58.3% of all patients with pathological features of suspected intra-kidney venous thrombus. Compared to the patients with MCD or FSGS, the patients with MN presented with milder proteinuria and better kidney function, yet they were still the most common patients in this cohort. These findings are consistent with the reports that MN patients are more prone to have thromboembolic complication [2, 33]. The disease-specific mechanisms leading to thrombophilia in MN need further investigations [7, 12, 34].

In conclusion, we discovered the kidney pathological features that indicated intra-kidney VTE. Its scores could represent the possibility of thrombus. The notice of these features during kidney biopsy information interpretation may provide clinical clues for the hypercoagulable state of patients and the possibility of VTE events.

Acknowledgments

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Statement of Ethics

The research followed the Declaration of Helsinki and was approved by the Ethics Committee of Peking University First Hospital (2017 [1280]). Written informed consent was obtained from each patient.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

Hui Lu collected and analyzed the data. Hui Lu and Zhao Cui interpreted the results and wrote the manuscript. Tang-li Xiao and Su-xia Wang reviewed the renal biopsies independently. Su-xia Wang and Ming-hui Zhao contributed to the revision of the manuscript. Zhao Cui and Su-xia Wang are the co-corresponding authors and were involved in the study design. All the authors contributed to the article and approved the submitted version.

Data Availability Statement

All data generated or analyzed during this study are included in this published article. Further inquiries can be directed to the corresponding author.

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