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Incidence and risk factors of venous thromboembolism in kidney transplantation patients: a prospective cohort study

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Abstract

To investigate the incidence and explore the risk factors of venous thromboembolism (VTE) within 6 months after kidney transplantation. Total of 331 kidney transplant recipients were assessed by venous ultrasonography for VTE at 14 days, 1 month, 3 months, and 6 months post-transplantation. Cox forward regression were used to identify the independent risk factors of VTE. This study registration number is ChiCTR1900020567 and the date of registration was 2019/01/08. The cumulative incidence of VTE was 2.72% (9/331) within 6 months after transplant. 77.8% (7/9) of VTEs occurred in the first 3 months post-transplantation. 88.9% (1/9) of VTEs were asymptomatic, 66.7% (6/9) of VTEs were mural thromboses and in the right lower extremity. Central vena catheterization (HR = 6.94) and severe pulmonary disease (including pneumonia) (HR = 57.35) were the risk factors for VTE in kidney transplantation recipients. KT patients are the high risk population of VTE. Future interventions should be strengthen for KT patients to receive a minimum of 3-month of precautionary measures for VTE, including infection prevention, and strengthening thromboprophylaxis on the CVC or transplanted side of lower extremity.

Keywords Venous thromboembolism · Kidney transplantation · Incidence · Deep venous thrombosis · Risk factor

Highlights

- Central vena catheterization (HR = 6.94) and severe pulmonary disease (including pneumonia) (HR = 57.35) were the risk factors for VTE in kidney transplantation recipients.
- KT patients are the high risk population of VTE.

Introduction

Venous thromboembolism (VTE) is a condition in which a blood clot forms in a vein, commonly referred to as deep venous thrombosis (DVT) or pulmonary embolism (PE). The incidence of VTE and associated unexpected death during the perioperative period is increasing in both developed and developing countries [1, 2]. Kidney transplantation (KT) involves the surgical implantation of a functional graft into patients with end-stage kidney disease (ESRD). According to the Virchow's triad, KT patients are at high risk for developing VTE [3]. Previous studies have shown that the incidence of VTE in KT patients is 7.1–7.9 times higher than that of the general population [4, 5]. However, the reported incidence of VTE in KT recipients varies between 1 and 24%, depending on the studied populations and duration[6]. In Korea, the incidence of VTE in KT recipients was lower than that in of Western countries due to differences in the risk factors [7–9]. Furthermore, several special factors in KT patients, including cytomegalovirus infection [10], immunosuppressant therapy [11], donor source [12], and biochemical immune factors, such as elevated levels of serum fibrinogen and serum creatinine [13–15], have been associated with VTE.

In fact, low awareness of VTE and a significant gap between best evidence and practice have hindered efforts to prevent VTE [2, 16]. In KT patients, VTE not only increases the risk of rejection and renal allograft failure, leading to

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longer hospitalizations and higher medical cost [4, 17], but also can lead to unexpected sudden death [1]. A better understanding of the incidence and risk factors of VTE in KT patients is essential for developing effective preventive strategies. However, there is a paucity of studies on the incidence and risk factors of VTE in KT patients in China, leaving uncertainty about how to bridge the gap between evidence and practice. Therefore, a prospective cohort study was designed to investigate the 6-month incidence of VTE in KT patients and explore the risk factors of VTE. The findings of this study might provide valuable insight for risk assessment and adapting prevention strategies of VTE in KT patients.

Methods

The prospective cohort study was approved by the Ethical Committee of West China Hospital of Sichuan University (NO. 2019135) and registered with the number ChiCTR1900020567.

Patients

KT patients were recruited from a single-center kidney transplantation center at a tertiary and teaching hospital from April 2019 to February 2020 in Chengdu, Sichuan, China. The inclusion criteria were patients over 18 years of age who was planning to have their first KT surgery. Exclusion criteria included patients who had lower extremity DVT based on ultrasonography before surgery, those who canceled their surgery, refused follow-up ultrasonography, or were lost to follow-up more than twice. The sample size was determined based on the reported incidence of thrombosis after renal transplantation. The formula is $n=\frac{\left(Z_{\alpha}\sqrt{2\overline{pq}}+Z_{\beta}\sqrt{p_0q_0+p_1q_1}\right)^2}{\left(p_1-p_0\right)^2}$ ($\alpha=0.05$, $\beta=0.01$, $p_0=8.9\%$, $p_1=1.5\%$ [4]). The sample size was calculated to be around 330 cases, taking into account a 10% loss rate.

Form April 2019 to February 2020, all patients received the VTE prophylactic protocol, which consist only of general precautions (such as VTE prophylactic education, VTE risk assessment, early motion and surveillance examination), without any mechanical prevention and routine chemoprophylaxis. Rehydration was administered to all recipients post-surgery based primarily on urine output per hour. Patients were instructed to begin drinking fluids 2 h after awakening from general anesthesia, and were directed by nurses to perform ankle pump exercises for 15 min at least twice a day. All recipients stood and walked within 24 h of surgery, gradually increasing their walking time each day under the guidance of a therapist. The use of anticoagulants as a prophylactic treatment route is avoided due to previous experiences of bleeding incidents. Anticoagulant therapy was only administered to patients who exhibited clinical symptoms or underwent thrombosis. Consider the practical and economic aspect, intermittent pneumatic compression (IPC) and graduated compression stockings was not used during our study period.

Data collection

Participants provided oral informed consent and signed a written consent prior to surgery. Nurses used the WeChat platform or phone to inform patients at scheduled intervals to complete vascular ultrasonography. To increase patients compliance and reduce withdrawal bias, a team consisting of three nurses and one doctor provided a complimentary 6-month follow-up nursing service through the WeChat platform. The nurses proactively reminded patients about their the doctor issued orders for vascular ultrasonography, which were then scheduled by the nurses. Additionally, funding from scientific sources covered the cost of vascular ultrasonography in the 3rd month. To minimize loss to follow-up, patients were allowed to undergo venous ultrasonography at other tertiary hospitals.

General information

General information on KT patients are showed in Table 1, including gender, ethnic group, marital status, dialysis modalities (hemodialysis, peritoneal dialysis, no dialysis, both hemodialysis and peritoneal dialysis) and duration, use of anticoagulant post-transplantation and pathogenesis of ESRD. Unfortunately, the etiology of ESRD was unknown in most patients without biopsy. This data was collected from the hospital information system.

Table 1 General information of kidney transplant recipients

Items	Classification	Frequency	Percentage (%)
Gender	Man	231	69.8
Ethnic group	Han	282	85.2
	Ethnic minorities	49	14.8
Marital status	Married	231	69.8
	Unmarried	85	25.7
	Divorced or widow	15	4.5
Dialysis modalities	No dialysis	4	1.2
	Hemodialysis	296	89.4
	Peritoneal dialysis	24	7.3
	Both	7	2.1
Anticoagulant	Unused	312	94.3
	Used	19	5.7

Table 2 The number and site of DVT in KT patients

Time	Number	Site
0–14 days	4	1 right MCVT, 1 right SSVT, 1 right FVT, 1 left CFVT
15 days–1 month	3	1 right MCVT,1 right FVT, 1 left MCVT
1–3 months	2	1 right calf DVT, 1 left FVT

MCVT muscular calf vein thrombosis, *SSVT* small saphenous vein thrombosis, *FVT* femoral venous thrombosis, *CFVT* common femoral venous thrombosis, *DVT* deep venous thrombosis

VTE potential risk factors

VTE potential risk factors were identified based on common risk factors from Caprini risk assessment model [18] and KT VTE-related special factors from previous studies, as shown in Table 2. KT VTE-related factors included donor source (deceased donor, living donor), immunosuppressive therapy, cytomegalovirus infection, special biochemical immune factors [serum fibrinogen, platelets, hemoglobin, hematocrit, serum creatinine, serum albumin and cholesterol and estimated glomerular filtration rate (eGFR)]. All recipients had open surgery with different surgical incision length from about 5 to 15 cm. This data was collected from the hospital information system, and obtained laboratory test results was closest to the surgery.

Caprini's risk assessment model includes some risk factors, such as Leiden V and prothrombin 20210A gene mutations, that are rarely reported in the Asian population [19–21]. Therefore, these gene mutations were not analyzed in this study. We systematically excluded unknown factors and incorporate all available variables in our calculation of the Caprini2010 score, and the score classified patients as very low (0 point), low (1–2 point), moderate (3–4 points) and high risk (≥ 5 points). All patients received a similar immunosuppressive therapy, including induction therapy (basiliximab or rabbit anti-human thymocyte immunoglobulin) and maintenance therapy (tacrolimus, mycophenolate sodium or mycophenolate mofetil and prednisone).

VTE events

VTE events included asymptomatic and symptomatic DVT, PE, and graft renal vein thrombosis (GVT). Routine ultrasonography examinations were conducted before surgery and at half a month, 1st month, 3rd month and 6th month after KT surgery, to detect DVT and GVT. In case of suspicious of DVT or GVT, patients were examined by venous ultrasonography one more time. PE suspicious was diagnosed using radionuclide pulmonary perfusion examination, though no cases of PE were observed in this study.

Bleeding events

Bleeding events were defined as fatal bleeding, decreased hemoglobin by at least 20 g/L, required at least 2 units of red cells or whole blood transfusion, or surgical intervention [22]. They were monitored during the hospital stay.

Statistical methods

SAS 9.0 was used for statistical analysis. Quantitative data is described as mean ± standard deviation or median (interquartile range), and qualitative data is described as a percentage (%). Univariables were analyzed using *T* test or ANOVA. Cox forward stepwise regression was used to analyze the risk factors of VTE events, with $P < 0.2$ of the independent univariables used for regression equations. $P < 0.05$ indicates a significant difference.

Results

KT patients

A total of 341 KT patients recruited, with 331 patients completed the study. Ten patients were lost to follow-up, of which 1 patient died due to postoperative infection, and 9 patients only finished ultrasonography 1 or 2 times. The average age of the participants was 36.02 ± 10.43 years old, and the average BMI was 21.48 ± 3.22 kg/m^2. Of the participants, 69.8% were male, and 85.2% were of Han nationality. Married status was 69.8%. Hemodialysis was the most type of dialysis modalities, with a median dialysis time of 18 (12,36) months. Only 5.8% of participants used anticoagulants.

Incidence of VTE

The cumulative incidence of venous thromboembolism (VTE) was 2.72% (9/331) within 6 months post-transplantation. Among the cases, 4 (44.4%), 3 (33.3%), 2 (22.3%) and 0 cases occurred at half a month, and 1st, 3rd and 6th month, respectively (Table 2). Mural thromboses accounted for 66.7% of total VTEs cases, with two-third of occurrence in the right lower extremity. Only one case of symptomatic DVT presented as lower extremity swelling. No cases of graft vein thrombosis (GVT) or PE, nor bleeding events, were observed within 6 months post-transplantation.

Risk factors of VTE

The univariable analysis shows that central vena catheterization (CVC, a catheter inserted through femoral vein, with its tip located in the superior or inferior vena cava,

Table 3 Univariable analysis of VTE in kidney transplant recipients

Factors	VTE group	NO VTE group	t/F	*P*
Age (years)	38.67 ± 11.5	35.94 ± 10.4	−0.773	0.440
BMI (kg/m$^{2)}$	20.60 ± 1.8	21.51 ± 3.2	1.448	0.180
Duration of surgery (hours)	2.25 ± 0.35	2.50 ± 0.49	2.072	0.068
Caprini score	3.78 ± 1.20	3.57 ± 1.26	−0.449	0.618
CVC	4 (44.4%)	50 (15.5%)	5.418	0.021
SPD	2 (22.2%)	2 (0.6%)	37.934	0.000
Varicose veins of lower leg	0 (0%)	1 (0.3%)	0.028	0.868
Leg swelling	0 (0%)	2 (0.6%)	0.056	0.813
Oral contraceptives	0 (0%)	8 (2.5%)	0.228	0.633
Bed time ≥ 72 h	0 (0%)	7 (2.2%)	0.199	0.656
History of VTE	0 (0%)	11 (3.4%)	0.316	0.574
Family history of VTE	0 (0%)	3 (0.9%)	0.084	0.772
Blood transfusion within 1 month	1 (11.1%)	4 (1.2%)	5.797	0.017
Acute MI within 1 month	0 (0%)	1 (0.3%)	0.028	0.868
Hemodialysis	8 (88.9%)	288 (89.4%)	0.004	0.949
Dialysis duration	36 (24.5,36)	18 (12,36)	0.837	0.361
Anticoagulant	1 (11.1%)	18 (5.6%)	0.491	0.484
Living donor	4 (44.4%)	213 (66.1%)	1.826	0.178
Cytomegalovirus infection	1 (11.1%)	15 (4.7%)	0.790	0.375
Fibrinogen	2.35 ± 0.79	2.96 ± 0.98	2.264	0.051
Platelet	186 (160,202)	145 (116,189)	1.797	0.181
Hemoglobin	107.00 ± 27.20	104.66 ± 20.09	−0.341	0.733
Hematocrit	0.34 ± 0.08	0.33 ± 0.06	−0.509	0.611
eGFR	10.39 (5.14,17.9)	11.68 (6.55,19.53)	0.969	0.326
Serum creatinine	483 (343,939)	471 (307,723)	0.465	0.496
Serum albumin	34.47 ± 3.89	38.39 ± 5.48	2.217	0.034
Cholesterol	2.26 (1.95,2.91)	3.31 (2.79,3.93)	1.797	0.181

CVC central vena catheterization, *SPD* severe pulmonary disease (including pneumonia), *MI* myocardial infarction

for hemodialysis or infusion), severe pulmonary disease (including pneumonia), blood transfusion within 1 month and serum albumin were significantly different between the VTE group and the no VTE group ($P < 0.05$) (Table 3). Meanwhile, duration of surgery ($P = 0.068$) and fibrinogen ($P = 0.051$) was close to the threshold value (Table 3). The remaining factors in Table 3 were not significantly different ($P > 0.1$). Table 4 shows the dummy variables of dependent univariables with a P value less than 0.2. The Cox regression shows that central vena catheterization (HR = 6.94) and severe pulmonary disease (including pneumonia) (HR = 57.35) were the independent risk factors of VTE (Table 5). The value of χ^2 is 15.224 ($P < 0.001$).

In this study, several hypothesized factors did not occur, including inflammatory bowel disease, pulmonary abnormalities such as COPD, congestive heart failure, stroke, sepsis, malignant tumor or chemotherapy, fracture with plaster fixation, 1 month prior to surgical history, pregnancy or within 1 month after delivery, and female history of habitual abortion.

Table 4 Dummy variable of VTE-related dependent variables

Dependent variable	Dummy variable
Age (years)	< 40 = 0, 40–59 = 1, 60–75 = 2, ≥ 75 = 3
BMI (kg/m^2)	≤ 25 = 0, > 25 kg/m^2 = 1, BMI > 30 kg/m^2 = 2
Surgery time	< 2 h = 0, 2–3 h = 1, ≥ 4 h = 2
CVC	Yes = 1, no = 0
SPD	Yes = 1, no = 0
Blood transfusion within 1 month	Yes = 1, no = 0
Donor source	Living donor = 1, deceased donor = 2
Fibrinogen	> 5 g/L = 1, ≤ 5 g/L = 0
Platelet	> 400 × 10^9/L = 1, ≤ 400 × 10^9/L = 0
Serum albumin	< 30 g/L = 1, ≥ 30 g/L = 0
Cholesterol	> 5.17 g/L = 1, ≤ 5.17 g/L = 0

CVC central vena catheterization; *SPD* severe pulmonary disease (including pneumonia)

Table 5 Risk factors of VTE in KT patients: a Cox forward stepwise regression

	B	SE	Wald	*p*	HR	95%CI for HR	
						Lower	Upper
CVC	1.937	0.764	6.433	0.011	6.94	1.55	31.01
Severe pulmonary disease	4.049	0.917	19.506	< 0.001	57.35	9.51	345.90

CVC central vena catheterization, *SPD* severe pulmonary disease (including pneumonia)

Discussion

In this study, the 6-month cumulative incidence of VTE among KT patients was 2.72%, which is higher than the general population (1.6‰ [23]). The incidence is similar to previous case studies conducted by Li and Zhang (2.38–2.42%) [24, 25], but lower than the 2-week incidence of 3.8% in a study by Musso et al. [14], the 1-month incidence of 8% in a study by Pavord & Myers [26], the 3-month incidence of 1.9–4.6% in the studies of Ahn et al. [9]and Poli et al. [27], 6-month incidence of 3.4% in the study by Poli et al. [27]. The discrepancy in incidence could be attributed to difference in the definition of VTE and the study participants. Firstly, VTE includes DVT and PE, and can be symptomatic and asymptomatic. Studies by Kim et al. [20] and Poli et al. [27] reveal that asymptomatic DVT can account for up to 81.6% and 88.9% of all VTE cases. Our study only identified one symptomatic DVT, despite conducting four ultrasound examinations after transplant. Therefore, it remains unclear whether the diagnosed DVT cases in our study were potentially missed or not. Additionally, public awareness and clinical knowledge of VTE prevention is low in developing countries, including China [1, 2]. This leads to a tendency to focus on symptomatic VTE rather than asymptomatic cases, which the incidence of VTE can be underestimated. Secondly, while ESRD patients do suffer from coagulation disorders with thrombotic complications and bleeding complications [6, 28], DVT has a higher risk in individual with specific risk genes, such as Leiden V and prothrombin 20210A gene mutations. But these mutations are rarely found in the Asian population [19–21]. Therefore, KT patients in China have a lower risk of VTE due to racial difference. Then, mean of Caprini score in our participants was 3.57 ± 1.25, which indicates a moderate risk of VTE. In summary, KT patients are a high-risk population for VTE. We suggest that KT patients should receive at least 3-month precautionary measures of VTE from professionals.

This study found 77.8% of VTE cases occurred within the 1st month post-transplantation, which is likely due to the dual risk factors related to ESRD and KT surgery increasing the likelihood of VTE [29–31]. As renal function improves and recovery from surgery, the incidence of VTE decreases. However, some previous studies have found that the risk of VTE in KT patients remains persistently high and may not decrease over time [4, 27], potentially due to other complications such as infection or cardiovascular disease which are common risk factors of VTE [18]. This study found that the risk of VTE in KT patients increased 57.35-fold with severe pulmonary disease (including pneumonia). Pulmonary infection can trigger the formation of inflammation-induced thrombosis and endothelial damage, leading to VTE [32]. Infections, such as infection of cytomegalovirus [12, 14, 33] and COVID-19 [34], may also activate the hemostatic and thrombotic process. Hence, thromboprophylaxis in KT patients should consist of long-term precautionary measures such as adopting a health lifestyle and preventing infections.

An interesting finding in this study was that 2/3 of VTE cases occurred in the right lower extremity. This may be due to the new renal graft being transplanted in the right iliac fossa, which can affect venous reflux in the right lower extremity. Additionally, another risk factor for VTE in KT patients was CVC, with a 6.94-fold increase in risk. Femoral vein catheterization, which was the type of CVC used in the study, can cause endothelial impairment and interfere with the return of lower extremity blood, thereby increasing the risk of VTE [21]. To prevent VTE, it may be beneficial to consider early removal of CVC or strengthening thromboprophylaxis on the CVC or transplanted side of the lower extremity.

It is important to acknowledge some limitations of this study. Several risk factors may have been missed in this study. Firstly, it was conducted at a single center with similar surgery and immunosuppressant protocols. Moreover, in cases of patients safety, transplant would be delayed or terminated if patients were suffering malignant tumor or chemotherapy, sepsis or congestive heart failure. Additionally, only four vascular ultrasounds were performed, which may have underestimated or missed the 6-month incidence of VTE. Furthermore, some gene mutation were not tested in this study. Therefore, further studies are needed, ideally through a multi-center study.

Conclusions

In sum, the incidence of VTE in Chinese KT patients was found to be 2.72% with a higher risk within the 1st month after transplant. CVC and pneumonia were identified as

risk factors for VTE in KT patients. It is important for KT patients to receive a minimum of 3-month of precautionary measures for VTE, including infection prevention, and strengthening thromboprophylaxis on the CVC or transplanted side of lower extremity. Further studies should required to determine the incidence of VTE beyond 6 months after transplant and to investigate there will be any influence of general prevention, mechanical prevention or chemoprophylaxis on incidence of VTE and bleeding.

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Author contributions XS and QT performed research and analyzed the data; HC provided vital expertise; SZ and BG designed the research and wrote the manuscript.

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Data availability The included data is available if you can contact the corresponding author.

Declarations

Competing interests There are no competing interests to disclose.

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