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Analysis of risk factors for recurrence of deep venous thrombosis in lower extremities

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Background: Preventing relapse is a basic goal in the treatment of DVT and requires investigation of risk factors for recurrence of deep venous thrombosis (DVT) in the lower extremities.

Material/Methods: We recruited and retrospectively reviewed 218 patients with recurrent DVT in the lower extremities diagnosed in our hospital from 2001 to 2012.

Results: Univariate analysis showed the incidence of recurrent DVT in patients with concomitant malignancy was 3 times higher than that in patients without malignancy (P<0.01); the incidence of recurrent DVT in patients with inferior vena cava filter (IVCF) at initial treatment was increased by 4.3 times as compared to patients treated with other modalities. In addition, pathological types of DVT (*P*=0.047), diabetes (*P*=0.040), nephrotic syndrome (NS; *P*=0.040), systemic lupus erythematosus (SLE; *P*=0.031) and poor compliance after discharge (*P*=0.030) were closely related to increased incidence of recurrent DVT. However, age (t=–1.927, *P*=0.055), gender (*P*=0.664), primary hypertension (*P*=0.098), embolectomy (*P*=0.367), and anti-coagulation (*P*=0.338) at initial treatment were not associated with recurrence of DVT. Multivariate analysis revealed that the risk for recurrent DVT in patients with concomitant malignancy was 3.5 times higher than that in patients without malignancy (OR=3.494, *P*<0.05); the risk for recurrent DVT in patients with IVCF at initial treatment was increased by 4.6 times as compared to patients treated with other modalities (OR=4.658, *P*<0.05). Pathological types of DVT, concomitant diabetes, NS, SLE and poor compliance after discharge were not associated with the risk for recurrent DVT (P>0.05).

Conclusions: Concomitant malignancy and IVCF at initial treatment are independent risk factors for recurrent DVT in the lower extremities.

MeSH Keywords: Risk Factors • Vena Cava Filters • Venous Thrombosis

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Background

Deep venous thrombosis (DVT) in the lower extremities is a common disease with high morbidity in our Department of Vascular Surgery. Preventing relapse is a basic goal in the treatment of DVT The incidence of alternative occurrence of DVT in both lower extremities and deterioration of DVT of the initially involved extremities was 6% and 30%, respectively Rethrombosis occurred in the affected extremity with recanalization of 31% of patients [1]. Thus, to correctly understand the risk factors for recurrence, DVT is helpful to guide the prevention of DVT and is a key step in the early diagnosis and treatment of DVT. We retrospectively reviewed 1124 patients with DVT who were treated in our hospital from 2001 to 2012 to investigate the risk factors for recurrent DVT in the lower extremities.

Material and Methods

Patient data

DVT patients who were treated in our hospital from January 2001 to December 2012 were recruited according to following criteria. Inclusion criteria included: 1) Venography of deep veins of lower extremities or vascular color Doppler ultrasound examination confirmed the diagnosis of DVT; 2) patients received anti-coagulation therapy, thrombolysis, or surgery for DVT; 3) medical record and findings in follow-up showed a favorable response to treatments. A total of 1124 patients were recruited, including 691 males and 433 females with the mean age of 56±13 years (range: 19–83 years). The mixed, central, and peripheral types of DVT were found in 560, 325, and 239 patients, respectively. In addition, concomitant malignancy, diabetes, nephrotic syndrome (NS), systemic lupus erythematosus (SLE), and concomitant primary hypertension were noted in 246, 153, 213, 206, and 463 patients, respectively. At initial treatment, anti-coagulation therapy, implantation of permanent inferior vena cava filter (IVCF), and embolectomy were done in 937, 307, and 125 patients, respectively. Moreover, 155 patients had poor compliance to treatment (anti-coagulation therapy and wearing support hose).

Criteria for determination of recurrent DVT

After resolution of swelling, pain, increased temperature, superficial venous engorgement, and skin cyanosis of the lower extremities following anti-coagulation, thrombolysis or surgery for DVT, these symptoms occurred twice or more within 1 year and their severity was similar to or higher than that before treatment. Venography of deep veins of lower extremities or vascular color Doppler ultrasound examination confirmed the thromboses, which were defined as clinical relapse of DVT of the lower extremities.

Criteria for determination of poor compliance

According to the Guideline of the American College of Chest Physicians (ACCP-9) in 2012 [2], poor compliance is defined as when patients received anti-coagulation therapy for <3 months; patients with malignancy underwent anti-coagulation therapy for <6 months; or patients wear support hose for <12 months (a mean hospital stay of 18 days in our hospital).

Grouping

On the basis of whether DVT relapse was present, patients were divided into relapse group and non-relapse group. The age, gender, pathological types, history of diseases of internal medicine, history of malignancies, modalities at initial treatment of DVT, and compliance after discharging were recorded and their influence on the relapse of DVT was investigated.

Statistical analysis

Statistical analysis was done with SPSS version 13.0. Univariate analysis was done with chi-square test for qualitative data or t test for quantitative data. In the multivariate analysis, factors with statistical significance were included for logistic regression analysis. A value of $P<0.05$ was considered statistically significant.

Results

General information

Among these 1124 patients, 906 patients had no relapse (80.6%) with the mean age of 56±14 years and 218 patients had relapse of DVT (19.4%) with the mean age of 58±11 years. In the relapse group, there were 113 males and 105 females; mixed, central, and peripheral types of DVT were found in 96, 63, and 59 patients, respectively. Concomitant malignancy was found in 86 patients (lung cancer: n=16; prostate cancer: n=17; retroperitoneal soft tissue sarcoma: n=21; breast cancer: n=13; gynecologic cancer: n=19); at initial treatment for DVT, anti-coagulation therapy, implantation of IVCF and embolectomy were performed in 177, 116, and 25 patients, respectively; diabetes, NS, SLE, concomitant primary hypertension and poor compliance to treatment after discharging were found in 39, 52, 51, 79, and 39 patients, respectively.

Univariate analysis of risk factors for recurrent DVT

Univariate analysis showed the pathological types of DVT ($P=0.047$), concomitant malignancy ($P<0.05$), diabetes ($P=0.040$), NS ($P=0.040$), SLE ($P=0.031$), implantation of IVCF

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Table 1. Univariate analysis of risk factors for relapse of DVT.

Variates	Non-relapse (n=906) N (%)	Relapse (n=218) N (%)	RR	X^2	*P*
Gender			0.89	0.21	0.664
M	578 (63.80)	113 (51.83)			
F	328 (36.20)	105 (48.17)			
Pathological types				6.10	0.047
Mixed	464 (51.21)	96 (44.04)			
Peripheral	180 (19.87)	59 (27.06)			
Central	262 (28.92)	63 (28.90)			
Comorbidities					
Diabetes	114 (12.58)	39 (17.89)	1.51	4.21	0.040
NS	161 (17.77)	52 (5.74)	4.21	4.23	0.040
SLE	155 (17.11)	51 (23.39)	1.48	4.64	0.031
Primary hypertension	384 (31.35)	79 (36.24)	0.77	2.74	0.098
Malignancy	160 (17.66)	86 (39.45)	3.04	48.80	0.000
Modalities at initial treatment					
Anti-coagulation	760 (83.89)	177 (81.20)	0.83	0.92	0.338
IVCF	191 (21.08)	116 (53.21)	4.26	91.73	0.000
Embolectomy	97 (10.71)	28 (12.84)	1.23	0.81	0.367
Poor compliance	116 (12.80)	39 (17.89)	1.55	4.73	0.030

Univariate analysis showed the pathological types of DVT (*P*=0.047), concomitant malignancy (*P*<0.05), diabetes (*P*=0.040), NS (*P*=0.040), SLE (*P*=0.031), implantation of IVCF (*P*<0.05) and poor compliance after discharging (*P*=0.030) were risk factors for DVT (P<0.05). However, age (t=–1.927, *P*=0.055), gender (*P*=0.664), primary hypertension (*P*=0.098), embolectomy (*P*=0.367) and anti-coagulation at initial treatment (*P*=0.338) had no influence on the risk for DVT relapse (P>0.05).

(*P*<0.05) and poor compliance after discharging (*P*=0.030) were risk factors for DVT (P<0.05). However, age (t=-1.927, *P*=0.055), gender (*P*=0.664), primary hypertension (*P*=0.098), embolectomy (*P*=0.367) and anti-coagulation at initial treatment (*P*=0.338) had no influence on the risk for DVT relapse (P>0.05) (Table 1).

Logistic regression analysis of risk factors for DVT

Eight factors with statistical significance were included in logistic regression analysis. As shown in Table 2, logistic regression analysis showed that concomitant malignancy and implantation of IVCF at initial treatment were independent risk factors for DVT relapse (OR malignancy=3.5; ORIVCF=4.7, P<0.05). However, pathological types of DVT, concomitant diabetes, NS, SLE, and poor compliance after discharge had no influence on the risk for DVT relapse (P>0.05).

Discussion

The causes for relapse of DVT of the lower extremities twice or more within 6 months are very complex. In the present study, the gender, age, pathological types, concomitant malignancy, diseases of internal medicine, modalities at initial treatment for DVT, and post-discharge compliance to treatments were employed as risk factors for univariate analysis and multivariate analysis. Unlike common cardiovascular diseases, risk factors for the development of cardiovascular diseases such as higher systolic and diastolic blood pressure, BMI, blood levels of glucose, total cholesterol, and triglycerides were significantly higher in the group of patients with POAF, while HDL level was significantly lower in the same group [3]. Results showed the incidence of DVT relapse in patients with concomitant malignancy was significantly higher than that in malignancy-free patients (OR=3.4, *P*<0.05). Implantation of permanent IVCF at

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Table 2. Multivariate analysis of risk factors for relapse of DVT.

Variates	Wald	Odd risk (OR)	*P*	95% CI	
				Minimum	Maximum
Diabetes	1.084	1.294	0.298	0.797	2.100
Pathological types	3.075	0.838	0.080	0.688	1.021
Malignancy	49.643	3.494	0.000	2.467	4.948
IVCF	84.584	4.658	0.000	3.355	6.465
Poor compliance	0.939	1.269	0.333	0.784	2.054
NS	2.875	1.393	0.090	0.950	2.043
SLE	3.154	1.419	0.076	0.964	2.087

Logistical regression analysis showed concomitant malignancy and implantation of IVCF at initial treatment were independent risk factors for DVT relapse (ORmaliganncy=3.5; ORIVCF=4.7, P<0.05). However, pathological types of DVT, concomitant diabetes, NS, SLE and poor compliance after discharge had no influence on the risk for DVT relapse (P>0.05).

initial treatment for DVT also increased the incidence of DVT relapse (OR=4.6, *P*<0.05). Thus, we speculate that malignancy and implantation of permanent IVCF are independent risk factors for DVT relapse.

Malignancy as a risk factor for DVT of the lower extremities

It is reported that cancer patients have 4–7 times more venous thromboembolism than non-cancer patients, about 15% of cancer patients experienced at least 1 venous thromboembolism, 20% of patients with venous thrombosis had an active tumor [4]. Approximately 10% of patients who were admitted due to clinical manifestations of DVT had covert malignancy, but half of them were diagnosed and/or treated [5]. In the present study, 86 patients with DVT relapse had malignancy, and the incidence of DVT relapse in these patients was 3 times higher than in malignancy-free patients (RR=3.04, *P*<0.05). The risk for DVT relapse in patients with malignancy was also higher than that in malignancy-free patients (OR=3.494, *P*<0.05). Of these patients, 3 patients with lung cancer (3.5%), 4 patients with prostate cancer (4.7%), 2 patients with retroperitoneal soft tissue sarcoma (2.3%), and 3 patients with gynecologic cancer (3.5%) were admitted due to symptoms of DVT of the lower extremities, and they accounted for 14% of cancer patients with DVT. Thus, malignancy should be suspected in patients with DVT of unknown causes, DVT patients with poor response to treatment, and those with DVT relapse. In addition, we found that the proportion of DVT patients with retroperitoneal soft tissue sarcoma and gynecologic cancer was higher (24.4% and 22.1%, respectively) among DVT patients with malignancy. This might be because the compression of veins induced by these cancers is more obvious than that caused by other malignancies. In 1865, Trousseau et al found that malignancy patients had increased tendency to blood coagulation. Tissue factors, pro-coagulation factors, and mucilage in early malignancy may activate coagulation factor X, causing a hypercoagulable state [6–11]. The involvement of blood vessels by primary cancer or metastatic cancer may cause damage to the endothelial cells and compromise the anti-coagulation capability. Cancers may also activate platelets and reduce fibrinolytic activity [12–17]. The space-occupying effect of malignancies and enlarged lymph nodes may cause compression of veins, which then blocks the blood back flow and reduces the blood velocity. Chemotherapeutics such as tamoxifen, cyclophosphamide, and fluorouracil may reduce the activities of plasma protein C and protein S [18–23]. Time of surgical removal of cancers may be prolonged or the patient's position during surgery may cause compression of blood vessels. Cachexia in patients with advanced cancers affects patients who are confined to bed and reduces their activity. These factors may increase the risk of DVT relapse.

Implantation of IVCF as a risk factor for DVT relapse

IVCF has been used in clinical practice for more than 40 years [24]. The frequency of IVCF implantation has increased over time from 10%-32% in the early years [25–27]. It has been revealed that indications for IVCF implantation are strictly applied in only 51% of patients receiving IVCF implantation and 26% patients are actually not suitable for IVCF implantation [28]. There is evidence showing that implantation of IVCF has no influence on the PE-related mortality and total mortality, and 7–38% of patients receiving IVCF implantation develop DVT. In addition, a 2-year single-center randomized trial and a 5-year observational study showed the implantation of IVCF had no significant influence on the occurrence of symptomatic PE, but the relative risk for DVT relapse doubled, which is consistent with findings in an 8-year prospective, randomized, controlled PREPIC study. For spinal cord injury patients with prophylactic implantation of IVCF, 20.4% developed DVT [29]. Another meta-analysis showed the risk for DVT after IVCF

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implantation was increased by 1.6-fold as compared to other patients [30]. In the present study, the incidence of DVT within 6 months also supported this conclusion. In our hospital, the frequency of permanent IVCF implantation was 27.3% and the incidence of DVT relapse was 37.8%, which was significantly higher than that in patients treated with other modalities (RR=4.26, $P<0.05$). The risk for DVT relapse in patients receiving IVCF implantation was 4.6 times higher than that in patients treated with other modalities (OR=4.658, $P<0.05$). Patients with DVT relapse usually present with alternative occurrence of DVT of lower extremities or propagation of DVT of unilateral lower extremities into DVT of both lower extremities. Perhaps the vena cava outflow tract becomes stenotic after capture of thrombi by IVCF, causing poor blood back flow. The displacement and collapse of IVCF, damage to the inferior vena cava wall, and thrombosis of IVCF may also be factors causing DVT relapse. The Guideline of ACCP-9 does not recommend routine implantation of IVCF in DVT patients, but recommends the IVCF implantation in patients with proximal DVT and contradictions for anti-coagulation therapy. However, once the contradictions for anti-coagulation therapy resolve, anti-coagulation therapy should be performed [2]. Strict control of the indications for IVCF implantation is a key step to reduce the incidence of DVT relapse after IVCF implantation.

Pathological types of DVT, diseases of internal medicine, and poor compliance

The prevalence of mixed DVT is higher than that of peripheral and central DVT. Univariate analysis showed the incidence of mixed DVT was higher than that of peripheral and central DVT ($P=0.047$), and mixed DVT accounted for 44% of relapsed DVT. This might be attributed to the wide involvement of blood vessels by thrombi, more severe DVT and difficulty in recanalization, and the improvement of symptoms and signs more dependent on formation of collateral circulation. However, multivariate analysis showed mixed DVT was not a risk factor for DVT relapse. The fact that patients with concomitant diabetes, SLE, or NS are more likely to develop DVT has been widely accepted [31–33]. Univariate analysis showed the incidence of DVT relapse in patients with these internal diseases was about 1.5 times higher than that in other patients, but in regression analysis these diseases had no influence on the DVT relapse ($P_{diabetes}=0.298$; $P_{SLE}=0.076$; $P_{NS}=0.090$). In our study, the incidence of DVT relapse in patients with poor compliance to treatment after discharge was 25.2% and they accounted for 17.9% of patients with DVT relapse. However, poor compliance had no influence on the DVT relapse in multivariate analysis ($P>0.05$).

Age, gender, primary hypertension, anti-coagulation, and embolectomy

The mean age was 58±11 years in the relapse group and 56±14 years in the non-relapse group, showing no significant difference (t=–1.927, $P=0.055$). Univariate analysis showed the incidence of DVT relapse was comparable between males and females ($P=0.664$). In addition, our results showed primary hypertension, anti-coagulation therapy, and embolectomy had no influence on the DVT relapse ($P_{hypertension}=0.098$; $P_{anti\text{-}coagulation}=0.338$; $P_{embolectomy}=0.367$).

Conclusions

In summary, malignancy and IVCF implantation at initial treatment for DVT are 2 independent risk factors for DVT relapse within 6 months. Thus, early screening and treatment of malignancies and strict control of the indications for IVCF implantation are key measures to reduce the incidence of DVT relapse.

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