

The Laterality of Deep Vein Thrombosis in the Pelvic and Lower Extremity Veins

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Purpose: This study aimed to determine whether deep vein thrombosis (DVT) predominantly occurred on a particular side in the pelvic and lower extremity veins.

Materials and Methods: Among 259 consecutive patients with leg swelling, 65 were confirmed to have DVT in the pelvis and lower extremities, and enrolled in this study. The serum levels of initial D-dimer, antithrombin III, tissue plasminogen activator, factor VIII, proteins C and S, anticardiolipin antibodies immunoglobulin (Ig) G and IgM and lupus anticoagulant were measured and analyzed retrospectively. Lower extremity venous system was divided into 11 anatomic segments on each side, and thrombotic involvement in each segment was recorded to determine the laterality of thrombotic involvement for each patient. The presence of thrombus in a specific vein was assigned using a Thrombus Scoring System (TSS) score of 1. Predominant direction was determined based on the TSS score for each side.

Results: Left-side predominant DVT (57%) was most frequent. Patients with both-side equivalent DVT had the highest total TSS score ($P=0.022$). The predominant side was significantly different between men (right 44.1%) and women (left 74.2%) ($P=0.022$). Patients with both-side equivalent DVT had the highest mean age (69.3 ± 9.9 years) as well as the highest mean levels of initial D-dimer (13.8 ± 20.7 $\mu\text{g/mL}$) and anticardiolipin antibody IgM (13.4 ± 22.8 MPL) indicating increased coagulability.

Conclusion: In the current study, left-side predominant DVT is most frequent in pelvis and lower extremities, and this phenomenon is more apparent in women. And both-side equivalent DVT is associated with the most advanced age and hypercoagulability.

Key Words: Venous thrombosis, Pelvis, Lower extremity

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INTRODUCTION

Previous studies have shown that deep vein thrombosis (DVT) predominantly develops unilaterally in the pelvic or lower extremity veins [1-5]. A well-known cause of unilateral predominance of DVT is an anatomical variant, known as May-Thurner syndrome in which the left common iliac vein (CIV) is compressed by the overlying right

common iliac artery (CIA) [1-6]. However, the definition of May-Thurner syndrome, extrinsic iliac venous compression by the arterial system against bony structure [7], is vague because there is a broad spectrum in the extent or degree of left CIV compression by the right CIA in patients with DVT [6,7]. Moreover, not all the patients with left CIV compression show clinical symptoms or signs of DVT. Indeed, it has been reported that 24% of patients out of

50 were asymptomatic in spite of the greater than 50% compression of the left CIV [8]. Recently, right side May-Thurner syndrome has also been reported [4]. In this study, regardless of the extent of iliac vein compression, onset time or etiology of DVT, we investigated whether thrombus formation developed preferentially on a particular side in DVT patients.

MATERIALS AND METHODS

From March 2010 to April 2013, 259 consecutive patients with signs and symptoms consistent with DVT of the lower extremities, such as pain, swelling, and tenderness on dorsiflexion of the foot, were studied. This study is a retrospective study from prospectively collected data including the thorough surveillance of thrombus in pelvic and lower extremity veins and coagulation-related blood tests. The DVT patients of this study were gathered regardless of the etiology or acuteness and/or chronicity of DVT, but those who underwent surgery or trauma within 3 months were excluded. The 6 orthopedic and 6 trauma patients did not have any anatomical sequelae or residual inflammatory lesions in their pelvis or lower extremities, which might affect the laterality of their DVT development.

Four colon cancers included 3 ascending colon and 1 transverse colon cancers, and there was no cancer that invaded or spread into the rectal cavity, which also might affect the laterality of DVT occurrence. After imaging studies, the patients with DVT in the inferior vena cava (IVC) were also excluded. Finally, the patients with DVT only in pelvic or lower extremity veins were included in this study. To avoid medication-related influences on blood levels, all blood tests were performed before the administration of any kinds of drugs including heparin or warfarin. For the diagnosis of DVT of the lower extremities, only the patients with positive D-dimer test were the candidates for imaging study, computed tomography (CT) venography or Doppler Ultrasound (US). Doppler US is known as the standard method for the diagnosis of DVT [7]. However, we use Doppler US as the first line method for the diagnosis of venous reflux disease such as varicose vein. But for DVT, we prefer CT venography because it can record every detail of small veins in the pelvis or lower extremities. However, for the patients with impaired renal function or allergy to radio-contrast dye, women of childbearing age, and those who refused CT venography, we utilized Doppler US. Patients also underwent blood tests to determine levels of antithrombin III, tissue plasminogen activator (t-PA), factor VIII, protein C, protein S, anticardiolipin antibody (Ab) immunoglobulin (Ig) G, anticardiolipin Ab IgM, and lupus anticoagulant. To evaluate the directional predominance of DVT in the pelvic and lower extremity veins, we devised

Table 1. Thrombosis Scoring System (TSS)

Veins containing thrombus	Score of right side	Score of left side
Common iliac vein	1	1
External iliac vein	1	1
Internal iliac vein	1	1
Common femoral vein	1	1
Superficial femoral vein	1	1
Deep femoral vein	1	1
Popliteal vein	1	1
Anterior tibial vein	1	1
Peroneal vein	1	1
Posterior tibial vein	1	1
Calf venous sinuses	1	1
Total score	11	11

If a thrombus is present in one specific vein, a TSS score of 1 is assigned.

and applied the Thrombus Scoring System (TSS) score, which was obtained by dividing the lower extremity venous system into 11 segments for each side based on the anatomical venous system. Each vein segment was given a TSS score of 1, and the maximal TSS score was 11 on each side of the pelvis and lower extremity (Table 1). The presence or absence of thrombus in each vein segment was determined based on formal radiology reports. In this study, for the definite diagnosis of DVT of the pelvis and lower extremities, the simultaneously positive results of D-dimer and imaging study were required. After finishing the blood tests and imaging studies, the patients who were definitely diagnosed to have DVT in the pelvis or lower extremities were treated with anticoagulation alone by unfractionated heparin and warfarin, and the target international normalized ratio (INR) was between 2.0 and 3.0. The determination of predominant side at which thrombosis occurred depended on the side with a higher TSS score in each patient. For statistical analysis, the patients were divided into right-side predominant, left-side predominant and both-side equivalent DVT groups according to the directional predominance of DVT, determined based on the TSS score. ANOVA and chi-square tests were used. The institutional review board of Inje University Haeundae Paik Hospital approved the study protocol (129792-2014-015), and written consent was obtained from each patient.

RESULTS

1) Included patients

Among the 259 patients, 138 patients (53.3%) were

Table 2. Distribution of deep vein thrombosis and Thrombus Scoring System (TSS) score

Deep vein thrombosis	Number of patients	Laterality	TSS score	Total TSS score	P-value ^a
Right-side predominant	22 (34)	Right	4.0±2.1	4.86±3.03	0.022
		Left	0.8±1.6		
Left-side predominant	37 (57)	Right	0.1±0.2	5.27±2.58	
		Left	5.2±2.6		
Both-side equivalent	6 (9)	Right	4.8±2.2	9.67±4.46	
		Left	4.8±2.2		

Values are presented as number (%) or mean±standard deviation.

Right, deep vein thrombosis in the veins of the right extremity and/or right pelvis; left, deep vein thrombosis in the veins of the left extremity and/or left pelvis; total TSS score=right TSS score+left TSS score.

^aANOVA; P-value, comparison of total TSS scores among 3 groups.

found to have elevated serum levels of D-dimer, and underwent imaging studies, including CT venography (113 patients) and Doppler US (25 patients). However, of the 138 patients, only 74 patients were diagnosed to have DVT in the pelvis or lower extremities by CT venography (65 patients) and Doppler US (9 patients). The 74 patients comprised 28.6% of the total of 259 patients who presented with clinical symptoms and signs consistent with DVT of the lower extremities.

From the 74 patients, 9 with thrombosis found in the IVC were excluded. Finally, 65 patients with DVT in the pelvis or lower extremities were enrolled in this study.

2) Associated diseases

DVT was most frequently associated with unknown conditions in 40 patients, cancer in 7 patients, orthopedic disease in 6 patients, trauma in 6 patients, gallbladder stones in 3 patients, nephrotic syndrome in 2 patients, and encephalitis in 1 patient. The cancers associated with DVT were stomach cancers in 4 patients and colon, liver, and breast cancer in 1 patient, respectively.

3) Distribution of DVT and TSS score

When we applied simple right, left or bilateral system to determine laterality, of the 65 patients with DVT in the pelvic and lower extremity veins that was proven through imaging studies and D-dimer test, there were 16 (25%) right, 35 (54%) left and 14 (21%) bilateral DVT patients. However, when we applied TSS score and predominant side system, the result was somewhat different.

Twenty two patients (34%) showed right TSS score of 4.0±2.1 and left TSS score of 0.8±1.6, and were classified as having right-side predominant DVT. Thirty seven patients (57%) revealed right TSS score of 0.1±0.2 and left TSS score of 5.2±2.6, and were classified as having left-side

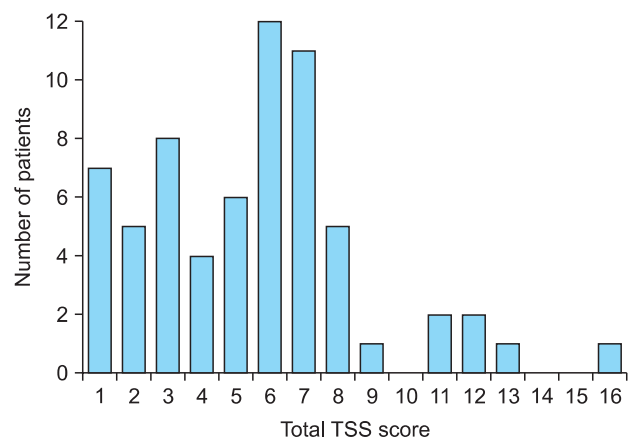


Fig. 1. Distribution of total Thrombus Scoring System (TSS) score.

predominant DVT. The remaining 6 patients (9%) showed TSS scores of 4.8±2.2 for both right and left legs, and were classified as having both-side equivalent DVT. Overall, the left-side predominant DVT was most frequent. Both-side equivalent DVT patients showed the highest total TSS score (9.67±4.46). Total TSS score revealed a significant difference among the 3 groups (P=0.022; Table 2).

4) Total TSS score

The mean and standard deviation of total TSS score of 65 patients with DVT was 5.54±3.18. The total TSS score ranged from 1 to 16, and the most frequent score was 6 (12 patients) (Fig. 1).

5) Comparison of right and left predominance between men and women

The most frequent predominant side of DVT in men was right (15 patients, 44.1%), whereas that in women was left (23 patients, 74.2%). The directional predominance of DVT was significantly different between men and women

Table 3. Comparison of directional predominance of deep vein thrombosis between men and women

Gender	Number of patients with deep vein thrombosis			P-value ^a
	Right-side predominant	Left-side predominant	Both-side equivalent	
Men	15 (44.1)	14 (41.2)	5 (14.7)	0.022
Women	7 (22.6)	23 (74.2)	1 (3.2)	

Values are presented as number (%).

^aChi-square test.

Table 4. Comparison of parameters among the patients with right- and left-side predominant and both-side equivalent deep vein thrombosis

	Laterality of DVT	Patient No.	Mean±SD	P-value ^a
Age (y)	1	22	52.4±18.0	0.005
	2	37	64.9±13.5	
	3	6	69.3±9.9	
Initial D-dimer (µg/mL)	1	22	3.3±2.4	0.006
	2	37	5.4±4.3	
	3	6	13.8±20.7	
Antithrombin III (%)	1	22	89.8±20	0.370
	2	37	96.3±12.9	
	3	6	90.4±26.1	
t-PA (ng/mL)	1	22	11.1±8.5	0.760
	2	33	10.0±3.9	
	3	6	9.6±2.1	
Factor VIII (%)	1	21	120.0±23.7	0.700
	2	32	123.9±23.5	
	3	6	128.9±16.5	
Protein C (%)	1	20	95.0±42.6	0.320
	2	33	102.7±31.2	
	3	6	78.8±47.6	
Protein S (%)	1	22	54.9±32.4	0.930
	2	34	57.1±27.7	
	3	6	59.3±23.3	
ACL IgG (GPL)	1	22	6.7±5.8	0.220
	2	34	10.6±14.0	
	3	6	3.6±2.5	
ACL IgM (MPL)	1	22	4.3±3.8	0.010
	2	35	3.2±3.7	
	3	6	13.4±22.8	
LA	1	22	3.6±8.8	0.160
	2	35	1.0±0.1	
	3	6	0.9±0.1	

DVT, deep vein thrombosis; SD, standard deviation; t-PA, tissue plasminogen activator; ACL, anticardiolipin antibody; GPL, IgG phospholipid unit; MPL, IgM phospholipid unit; LA, lupus anticoagulant.

Right-side predominant DVT=1, left-side predominant DVT=2, both-side equivalent DVT=3.

^aANOVA.

($P=0.022$; Table 3).

6) Comparison of parameters among the patients with right- and left-side predominant and both-side equivalent DVT

There were significant differences in age ($P=0.005$), levels of initial D-dimer ($P=0.006$) and anticardiolipin antibody IgM ($P=0.010$) among the 3 groups, and both-side equivalent DVT patients showed the highest values for these parameters (Table 4).

DISCUSSION

The clinical diagnosis of DVT of the leg is not easy, because many patients with the classic findings of DVT of the lower extremities such as painful and swollen legs finally turn out to be non-DVT patients [9,10]. In this study, we observed that only 74 patients (28.6%) out of 259 suspected pelvic or lower extremity DVT patients were true DVT patients. This result was comparable with previous studies that only the 25% to 37% of the suspected DVT patients had true DVT in their pelvis and legs [9,10]. Meanwhile, bilateral DVT patients of the pelvis and lower extremities have a broad spectrum of thrombus distribution in their pelvic and leg veins. Certain bilateral DVT patients may have large amount of thrombus burden bilaterally, but others may have only tiny amount of thrombus burden bilaterally. Furthermore, some bilateral DVT patients may have small amount of thrombus in one leg and large amount of thrombus in the contralateral leg. However, all these patients are classified simply as bilateral DVT. Therefore, we made a concept of "predominant side DVT" by devising the TSS score, in which the predominant side was determined by the higher TSS score. In this study, DVT of the pelvis and legs were not just classified into right, left or bilateral DVT, but classified into right- or left-side predominant and both-side equivalent DVT. There is some limitation in this study, being a single center study and with a small study population. Moreover, TSS is also limited in that all the large and small veins of the pelvis and legs are uniformly assigned the same score of 1. Thus, TSS score may not reflect the exact amount of thrombotic burden in each vein segment, but reflects the thrombus distribution in the pelvis and legs. However, the 11 vein segments are the basic anatomical units of the pelvic and lower extremity venous

structure, and are easy to be evaluated by Doppler US or CT venography. Therefore, we believe that, although TSS is not a perfect method, it is a simple and clinically useful method for the evaluation of thrombus distribution along the veins in the pelvis and lower extremities. We also think that if TSS is to be the more accurate and reliable method for evaluating thrombus burden, further studies are needed, especially on adopting a new computer software system which can calculate the exact amount of thrombus burden in each vein segment from the CT venography findings. Meanwhile, in the current study, TSS classification revealed that left-side predominant DVT was the most frequent type, and this phenomenon was more apparent in women. While men revealed similar distribution of predominant sides between right and left, women showed a markedly higher incidence of left-side predominant DVT than that of the right side. It has been shown that iliac vein compression associated with left DVT is more frequent in women than in men [5,6,11]. However, there has been no clear explanation for the higher prevalence of left-side predominance of DVT in women. Thus, further studies, including the anatomical and hormonal differences between men and women may be needed. It is known that advanced age is a significant risk factor for hypercoagulability owing to the increased levels of coagulation proteins such as fibrinogen, factors VII, VIII, IX, XIII, von Willebrand factor, and high molecular-weight kininogen, as well as increased platelet function [12-16]. Furthermore, advanced age has been reported as an independent risk factor for venous thrombosis [13,17].

In this study, patients with both-side equivalent DVT had the most advanced age, the highest values of total TSS score, initial D-dimer and coagulant anticardiolipin antibody IgM [18].

This result indicates that both-side equivalent DVT is associated with the most advanced age and hypercoagulability.

CONCLUSION

From these observations we conclude that in the current study, left-side predominant DVT is the most frequent type of pelvic and lower extremity DVT, and this phenomenon is more apparent in women. Furthermore, both-side equivalent DVT is associated with the most advanced age and hypercoagulability.

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