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Deep vein thrombosis: risk factors and location of thrombus

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Abstract. Objective: to determine a possible relation between different known medical risk factors for deep vein thrombosis and location of thrombus. Material and methods: we included consecutive patients diagnosed with deep vein thrombosis by the use of Doppler ultrasonography. Symptoms and signs, biochemical parameters and imagistic data were recorded and the presence or absence of comorbidities was noted. Results: a number of 192 patients were included in study. In univariate analysis, location of deep vein thrombosis was associated with age, immobility and unilateral calf edema. The multivariate analysis demonstrated the independent relation between location of thrombus and age (p=0.044), sex (p=0.014) and immobility (p=0.028). Conclusion: age, sex and immobility were correlated with location of deep vein thrombosis.
Key Words: deep vein thrombosis, proximal, distal, risk factors.

Rezumat. Obiectiv : determinarea unei posibile relaţii între diferiţi factori de risc medicali pentru tromboza venoasa profundă şi localizarea trombului. Material şi metodă : am inclus pacienţi consecutivi diagnosticaţi, prin ultrasonografie Doppler, cu tromboză venoasă profundă. Simptome şi semne, parametrii biochimici şi date imagistice au fost înregistrate şi prezenţa sau absenţa comorbidităţilor a fost notată. Rezultate : un număr de 192 pacienţi au fost incluşi în studiu. În analiza univariată, locaţia trombozei venoase profunde a fost asociată cu vârsta, imobilizarea şi edemul unilateral al gambei. Analiza multivariată a demonstrat relaţia independentă dintre locaţia trombului şi vârstă (p=0,044), sex (p=0,014) şi imobilitate (p=0,028). Concluzie : vârsta, sexul şi imobilizarea sunt corelaţie cu localizarea trombozei venoase profunde.
Cuvinte cheie: tromboză venoasă profundă, proximal, distal, factori de risc.

Introduction. Deep vein thrombosis is a disease with important mortality and morbidity, high social and economic costs. Most of thrombotic episodes are clinically silent, the symptomatic ones being only the tip of the iceberg. The most feared complication of deep vein thrombosis is the pulmonary embolism, which is, in many cases, the only clinical sign.

Deep vein thrombosis of lower limbs is defined as the forming of obstructive thrombus in the profound venous system of lower limbs. The onset of thrombus is caused by an imbalance of procoagulant and anticoagulant factors, accompanied by inflammatory response of vessel wall.

The first medical reference of a venous pathology is found in Ebers papyrus, dated 1550 B.C., in which it is noted that surgery for varicose veins has a probability for fatal bleeding (Besciu 2008). The first depiction of deep vein thrombosis appeared in the 13th century (Dexter et al 1974). In 1676, Richard Wiseman described the first case of deep vein thrombosis linked to postpartum period. Also he established a symptomatic treatment of thrombosis with the use of lace stocking as mean of compression (Wiseman 1676). In 1856, Rudolf Virchow defined the triad that can lead to vein thrombosis: stasis, injury of the vessel and a hypercoagulable state (Virchow 1856). In the same period of time, Armand Trousseau theoreticized that cancer can induce venous thrombosis (Trousseau 1865). In the beginning of 20th century, scientists proved that vein thrombosis has a hereditary component. The first valid treatment for thrombosis,

heparin, is introduced in medical practice in 1937, and in 1965 the deficit of antithrombin is described. In 1994, Bertina et al discovered the most frequent cause of thrombophilia known to this date: the mutation of in the factor V gene (a substitution guanine to adenine in nucleotide position 1691) that leads to synthesis of mutated factor V molecule (factor V Leiden) (Bertina et al 1994).

In present day there are several mutations, diseases or environmental factors that are linked to development of deep vein thrombosis: thrombophilia, hormone replacement therapy, oral contraceptive, pregnancy, age, immobilization, trauma of spine, fractures of pelvic or lower limbs bones, varicose veins, ankle edema, obesity, history of deep vein thrombosis, smoking, cancer, stroke, heart failure, sepsis, chronic obstructive pulmonary disease (COPD) and autoimmune diseases.

Proximal deep vein thrombosis poses a greater risk, than distal thrombosis, for pulmonary embolism. However distal thrombosis is still a risk for pulmonary embolism. Calf thromboses are difficult to diagnose because of many anatomic variants and small caliber of veins.

Aim. We studied the relation between different known medical (non-surgical) risk factors for deep vein thrombosis and location of thrombus, in order to find out which factor can predict distal or proximal thrombosis.

Material and method. We included consecutive patients hospitalized in the 5th Medical Clinic, Municipal Clinic Hospital of Cluj-Napoca, from November 2006 to January 2009, diagnosed with deep vein thrombosis.

The diagnosis of acute deep vein thrombosis was established by Doppler ultrasonography, using an Aloka SSD 4000 unit, with a transducer with variable frequency of 7-10 MHz. The criterion for an acute thrombosis was the incomplete compressibility of the vein (Torbicki et al 2008). Previous thromboses were diagnosed by the presence of a calcified thrombus or venous reflux. We examined patients that had a Wells score equal or higher than 2 (Wells et al 2006). Also we have taken into consideration, for ultrasonography, patients with a high score on risk for deep vein thrombosis assessment scale (available at http://www.crmhealthcare.net/docs/67450a_CapriniRiskAssesemntTool.pdf).

Doppler ultrasonography recorded the presence and extension of acute deep and superficial thrombosis, the presence of previous thrombosis or postphlebitic syndrome and the existence of varicose veins. Proximal deep vein thrombosis was defined as the presence of thrombus in common femoral vein, superficial femoral vein and popliteal vein. Distal deep vein thrombosis was characterized by the presence of thrombus in one or more calf veins: anterior tibial vein, posterior tibial vein, fibular vein and muscular calf veins (soleal and gastrocnemial veins (lateral and medial). Superficial thrombosis was confined in great saphenous or small saphenous veins. Based on the location of thrombus, we divided the patients in three groups: patients with distal deep thrombosis (group A), proximal thrombosis (group B) and patients with both proximal and distal deep thrombosis (group C).

For every patient we noted general data like age and sex. Anamnesis revealed the presence of comorbidities: COPD, arterial hypertension, heart failure diabetes, obesity, cancer, previous deep vein thrombosis or pulmonary embolism, immobility for more than 3 days, airplane or car travel more than 4 hours in the last month, fractures of lower limbs or pelvic bones in the last month, autoimmune and infectious diseases. From clinical exam, we noted the presence of pain in lower limb along distribution of deep venous system, acute unilateral calf edema, chronic bilateral ankle edema, calf swelling (over 3 cm more than other calf), local hyperthermia and skin color changes (cyanosis, erythema or paleness). Unilateral calf edema was defined as the edema that increased the circumference of the calf, but not over 3 cm than other calf. We did not have patients under treatment with chemotherapy or phenothiazine, patients that undergone major surgery in last month, patients with burns, stroke, polytrauma, nephrotic syndrome, cirrhosis, and lymphatic edema.

We measured a series of blood parameters: urea (normal values (NV) – 30-40 mg/dl), total cholesterol (NV – 140-200 mg/dl), triglycerides (NV – 50-150 mg/dl), high-density-lipoprotein cholesterol (HDL – NV > 40 mg/dl for males, > 50 mg/dl for females), low-density-lipoprotein cholesterol (LDL – NV - < 100 mg/dl). In some patients we determined the D-dimers (NV < 200 ng/ml).

The statistical analysis was performed using the SPSS software version 14. For univariate analysis we used the T test for independent variables (continuous variables with normal distribution on Kolmogorov-Smirnov test), Chi square test (dichotomic variables), and ANOVA test (ordinal variables). The multivariate analysis was performed with binary logistic regression and multinomial logistic regression (Tabachnik et al 1996; Whitley et al 2002; Băicuş 2007). The statistic significance was established by calculating the p parameter and a value less than 0.05 was considered statistically significant.

Results. We included 192 patients. 81 (42.2%) patients were in group A, 47 (24.5%) in group B and 64 (33.3%) in group C. Table 1 shows the location of thrombosis along the venous system for each lower limb.

Table 1

Location of deep and superficial thrombosis

Location of thrombosis	Right lower limb (N, %)	Left lower limb (N, %)
Common femoral vein	35 (18.2%)	44 (22.9%)
Superficial femoral vein (proximal one third)	35 (18.2%)	43 (22.4%)
Superficial femoral vein (middle one third)	33 (17.2%)	43 (22.4%)
Superficial femoral vein (distal one third)	36 (18.8%)	43 (22.4%)
Popliteal vein	51 (26.6%)	47 (24.5%)
Anterior tibial veins	14 (7.3%)	14 (7.3%)
Posterior tibial veins	38 (19.8%)	35 (18.2%)
Fibular veins	16 (8.3%)	32 (16.7%)
Soleal veins	17 (8.9%)	26 (13.5%)
Lateral gastrocnemial veins	1 (0.5)	8 (4.2%)
Medial gastrocnemial veins	10 (5.2%)	22 (11.5%)
Great saphenous vein	29 (15.1%)	24 (12.5%)
Small saphenous vein	11 (5.7%)	15 (7.8%)

N - number

The mean age was 66.8 (± 13), median 70, min 22, max 90. We applied an ANOVA test and found that the difference of means for age are statistically significant different as related to the location of thrombosis (p=0.019; figure 1). The major difference is significant when we compared group C to group A (table 2). 90 (46.9%) patients were men and 102 (53.1%) were women. We did not found an association between sex and location of thrombosis (chi square test; p=0.17).

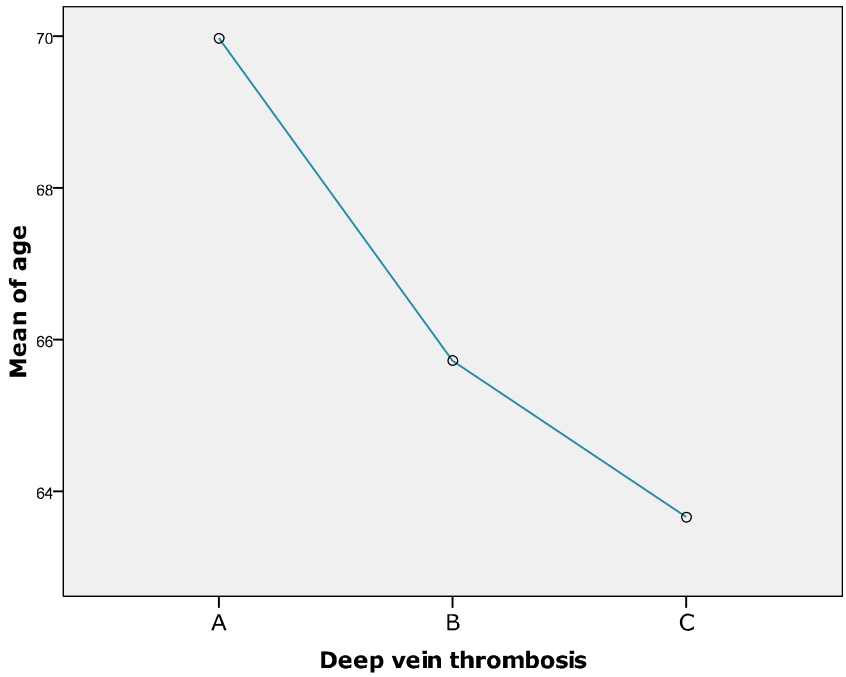

Figure 1. Relation between age and location of deep thrombosis.

Table 2

Post hoc analysis for age and location of thrombosis

Tukey HSD						
		Age				
(I)	(J)	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Group A	B	4.252	2.505	.209	-1.67	10.17
	C	6.319	2.285	.017	.92	11.72
Group B	A	-4.252	2.505	.209	-10.17	1.67
	C	2.067	2.625	.711	-4.13	8.27
Group C	A	-6.319	2.285	.017	-11.72	-.92
	B	-2.067	2.625	.711	-8.27	4.13

We recorded 14 (7.3%) deaths. There was no connection between death and location of thrombosis (chi square test; p=0.16).

COPD was present in 32 (16.7%) patients. 15 patients were in group A, 10 in group B and 7 in group C. There was no relation between the presence of COPD and location of thrombosis (chi square test; p=0.29).

Arterial hypertension was diagnosed in 88 (45.8%) patients. No connection between location of thrombosis and hypertension was established (chi square test; p=0.28).

71 (37%) patients suffered form obesity. 49 (25.5%) were overweight or in obese class I, 18 (9.4) were in obese class II and 4 (2.1%) were in obese class III. 32 patients were in group A, 14 in group B and 25 in group C. We did not found an association between obesity and location of thrombus (chi square test; p=0.5) or between obesity classification and location of thrombosis (chi square test; p=0.83).

Heart failure was diagnosed in 67 (34.9%) patients. 29 patients were in group A, 18 in group B and 20 in group C. No relation was found between the presence of heart failure and location of thrombosis (chi square test; p=0.72).

Cancer was present in 34 (17.7%) patients. 8 (4.2%) women presented ovary or uterus neoplasm, 4 (2.1%) gastric cancer, 2 (1%) liver cancer, 5 (2.6%) lung cancer, 10 (5.2%) men had prostate cancer and 5 (2.6%) other types of cancer. 13 cancers were in group A, 9 in group B and 12 in group C. There was not a correlation between the presence of cancer and the location of thrombosis (chi square test; p=0.87). The type of cancer did not predicted either the location of thrombosis (chi square test; p=0.36).

Previous deep vein thrombosis was detected in 82 (42.7%). 33 patients were in group A, 18 in group B and 31 in group C. No correlation was established between previous thrombosis and location of acute deep vein thrombosis (chi square test; p=0.5). Postphlebitic syndrome was found in 29 (15.1%) patients. There was no association between postphlebitic syndrome and location of thrombosis (chi square test; p=0.4).

Varicose veins were found in 82 patients. No correlation was described between the presence of varicose veins and location of deep vein thrombosis (chi square test; p=0.52). An association between superficial venous thrombosis and the presence of varicose veins was determined (chi square test; p=0.05).

Bilateral ankle edema was noted in 68 (35.4%) patients. 31 patients form group A presented ankle edema, 16 patients form group B and 21 from group C. We did not determine a correlation between the location of deep thrombosis and the presence of bilateral ankle edema (chi square test; p=0.77). Bilateral ankle edema could have multiple causes so we used a logistic regression in order to establish which factor is better linked to their presence (table 3). Only heart failure predicted independently the presence of bilateral ankle edema (OR – 1.6; p=0.002).

Table 3

Logistic regression for bilateral ankle edema

	B	*S.E.*	*Wald*	*df*	*Sig.*	*Exp(B)*	*95% C.I. for EXP(B)*	
							Lower	Upper
Sex	.030	.159	.035	1	.852	1.030	.754	1.407
Age	.018	.013	2.111	1	.146	1.019	.994	1.044
Postphlebitic syndrome	.171	.221	.595	1	.441	1.186	.769	1.829
Varicose veins	.213	.159	1.798	1	.180	1.238	.906	1.691
Heart failure	.518	.166	9.758	1	.002	1.679	1.213	2.324
Constant	-1.585	.881	3.237	1	.072	.205		

Another important risk factor for deep vein thrombosis is immobilization and 38 (19.8%) patients were immobilized for at least 72 hours. 16 of them were in group A, 15 in group B and 7 in group C. We found a statistically significant relation between history of immobility and location of deep vein thrombosis (chi square test; p=0.023). An ANOVA test revealed that the major difference is between group B and C (p=0.017; Figure 2).

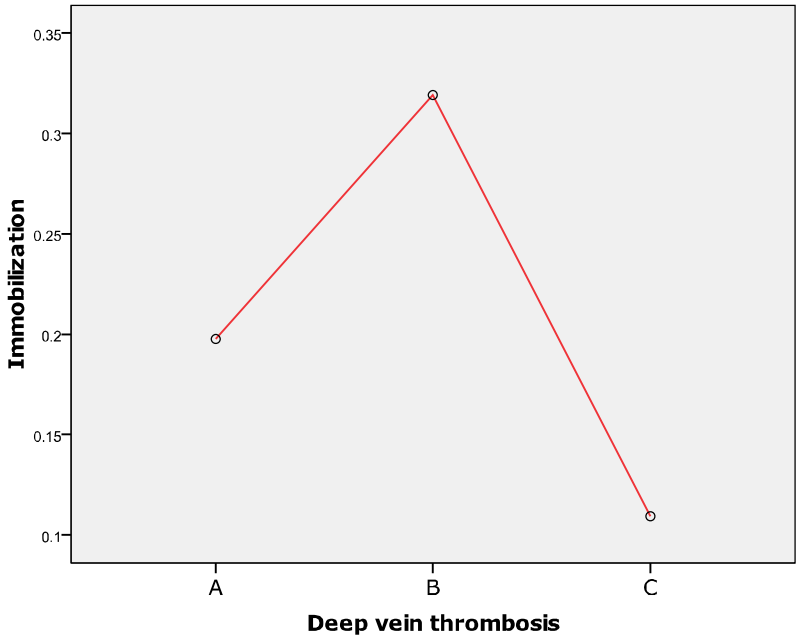

Figure 2. Relation immobility – location of deep vein thrombosis.

Three (1.6%) patients traveled by car or plane more than 4 hours in the last month. There was no association between history of long travel and the location of thrombosis (chi square test; p=0.3). History of lower limbs or pelvis fractures was present in 5 (2.6%) patient, but no association was found with the location of thrombosis (chi square test; p=0.17).

Infectious diseases were present in 33 (17.2%) patients. No relation was established between location of thrombosis and infectious disease (chi square test; p=0.5). Autoimmune diseases were diagnosed in 7 (3.6%) patients. We did not found any association between location of thrombosis and the presence of autoimmune disease (chi square test; p=0.28).

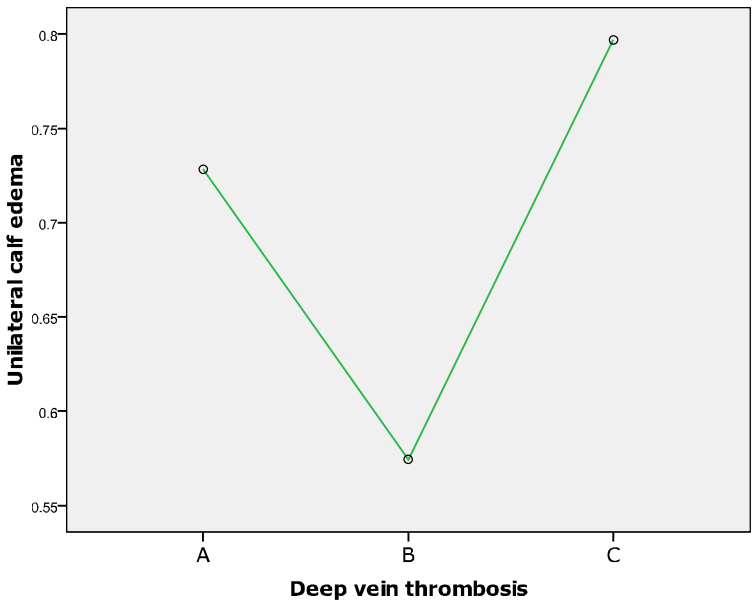

Figure 3. Relation unilateral calf edema – location of deep vein thrombosis.

Pain along the deep venous system was a frequent symptom, as it was described by 133 (69.3%) patients. Unilateral calf edema was the most frequent symptom present, as it was observed in 137 (71.4%) patients. Calf swelling was found in 42 (21.9%) patients. Cyanosis of the affected limb was described in 12 (6.3%) patients. 42 (21.9) patients presented erythema. Local hyperthermia was found in 18 (9.4%) patients. Pain (chi square test; p=0.64), calf swelling (chi square test; p=0.061), cyanosis (chi square test; p=0.084), local erythema (chi square test; p=0.51) and hyperthermia (chi square test; p=0.96) were not associated with location of thrombosis, but unilateral edema was (chi square test; p=0.035). An ANOVA test showed that the major difference was observed between group B and C (p=0.028; figure 3). We did not establish any association between the presence of concomitant superficial thrombosis and symptoms or signs recorded. 38 (20%) patients did not present signs or symptoms and were diagnosed with Doppler ultrasonography after scoring high on risk of thrombosis assessment scale.

We did not demonstrated a correlation between location of thrombosis and urea (ANOVA; p=0.14), total cholesterol (ANOVA; p=0.76), HDL-cholesterol (ANOVA; p=0.55), LDL-cholesterol (ANOVA; p=0.62) and triglycerides (ANOVA; p=0.16). We measured D-dimers in 98 (51%) patients and we found no relation between them and location of deep vein thrombosis (ANOVA; p=0.2), although their plasma levels increased evidently from group A to C (figure 4).

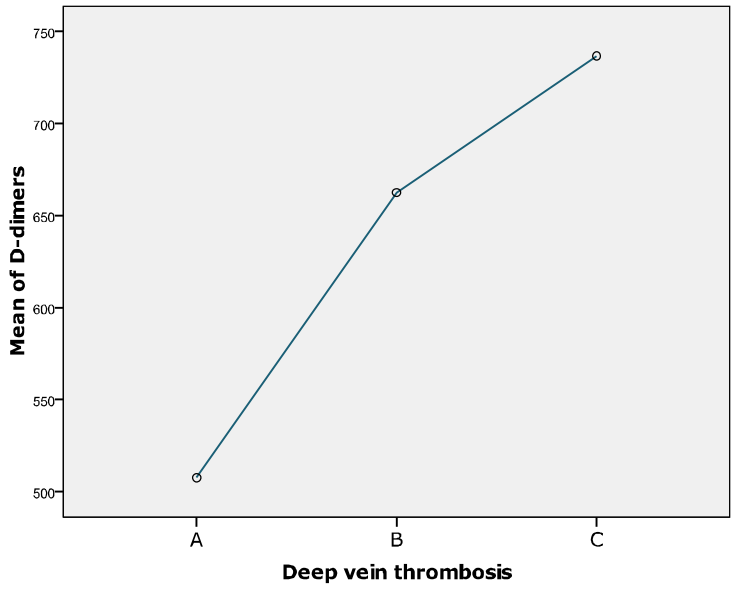

Figure 4. Relation D-dimers – location of deep vein thrombosis.

For the evaluation of concomitant effect of some parameters on the location of thrombosis we used a multinomial logistic regression. We used group C as a reference category. In order to use age in a multinomial regression we divided this parameter into four categories: under 40 years, between 40 and 59 years, between 60 and 74 years and over 75 years. We obtained statistically insignificant p (0.239) at the model fitting information, so the model with the parameters is different that the model without the parameters. At the pseudo R-square table we obtained a value for Cox and Snell test of 0.167, for Nagelkerke test of 0.189 and for McFadden test of 0.085. The parameters analysis (table 4) revealed that women have a slight tendency to present distal deep vein thrombosis (B=0.947; p=0.014), patients with age between 40 have a lower probability than older patients to develop distal thrombosis (B=-1.859; p=0.044) and the absence of immobility has a lower probability of proximal vein thrombosis than the presence of immobility (B=-1.296; p=0.028).

Table 4

Multinomial logistic regression for the location of deep vein thrombosis

		Parameter Estimates							
		B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
0	Intercept	-2.662	2.175	1.498	1	.221			
	[Sex=0]	.947	.387	5.990	1	.014	2.578	1.208	5.505
	[Sex=1]	0[b]	.	.	0	.	.	.	.
	[Age (<40)=0]	-1.859	.923	4.052	1	.044	.156	.026	.952
	[Age (40-59)=1]	-.477	.560	.725	1	.395	.621	.207	1.861
	[Age (60-74)=2]	-.227	.441	.266	1	.606	.797	.336	1.889
	[Age (>75)=3]	0[b]	.	.	0	.	.	.	.
	[Cancer=0]	.238	.470	.257	1	.613	1.269	.505	3.190
	[Cancer=1]	0[b]	.	.	0	.	.	.	.
	[COPD=0]	-.693	.553	1.572	1	.210	.500	.169	1.478
	[COPD=1]	0[b]	.	.	0	.	.	.	.
	[Immobility=0]	-.687	.558	1.517	1	.218	.503	.168	1.502
	[Immobility=1]	0[b]	.	.	0	.	.	.	.
	[HF=0]	.311	.405	.588	1	.443	1.365	.617	3.019
	[HF=1]	0[b]	.	.	0	.	.	.	.
	[Obesity=0]	-.232	.386	.363	1	.547	.793	.372	1.689
	[Obesity=1]	0[b]	.	.	0	.	.	.	.
	[Previous DVT=0]	.361	.366	.973	1	.324	1.435	.700	2.940
	[Previous DVT=1]	0[b]	.	.	0	.	.	.	.
	[Bilateral edema=0]	-.179	.398	.202	1	.653	.836	.383	1.824
	[Bilateral edema=1]	0[b]	.	.	0	.	.	.	.
	[Varicose veins=0]	.031	.369	.007	1	.932	1.032	.500	2.127
	[Varicose veins=1]	0[b]	.	.	0	.	.	.	.
	[Infection=0]	.821	.498	2.726	1	.099	2.274	.858	6.029
	[Infection=1]	0[b]	.	.	0	.	.	.	.
	[Autoimmune=0]	1.606	1.216	1.743	1	.187	4.982	.459	54.028
	[Autoimmune=1]	0[b]	.	.	0	.	.	.	.
	[Fractures=0]	1.342	1.570	.730	1	.393	3.826	.176	83.065
	[Fractures=1]	0[b]	.	.	0	.	.	.	.
1	Intercept	1.634	1.919	.725	1	.394			
	[Sex=0]	.259	.439	.349	1	.555	1.296	.549	3.061
	[Sex=1]	0[b]	.	.	0	.	.	.	.
	[Age (<40)=0]	.122	.838	.021	1	.884	1.130	.219	5.841

[Age (40-59)=1]	.006	.651	.000	1	.993	1.006	.281	3.600
[Age (60-74)=2]	-.126	.515	.060	1	.806	.881	.321	2.419
[Age (>75)=3]	0[b]	.	.	0	.	.	.	.
[Cancer=0]	-.032	.531	.004	1	.952	.968	.342	2.741
[Cancer=1]	0[b]	.	.	0	.	.	.	.
[COPD=0]	-.811	.604	1.803	1	.179	.445	.136	1.451
[COPD=1]	0[b]	.	.	0	.	.	.	.
[Immobility=0]	-1.296	.588	4.853	1	.028	.274	.086	.867
[Immobility=1]	0[b]	.	.	0	.	.	.	.
[HF=0]	-.182	.472	.148	1	.700	.834	.330	2.104
[HF=1]	0[b]	.	.	0	.	.	.	.
[Obesity=0]	.466	.463	1.012	1	.314	1.593	.643	3.946
[Obesity=1]	0[b]	.	.	0	.	.	.	.
[Previous DVT=0]	.456	.433	1.107	1	.293	1.578	.675	3.688
[Previous DVT=1]	0[b]	.	.	0	.	.	.	.
[Bilateral edema=0]	.024	.469	.003	1	.959	1.025	.409	2.569
[Bilateral edema=1]	0[b]	.	.	0	.	.	.	.
[Varicose veins=0]	.558	.421	1.758	1	.185	1.748	.766	3.988
[Varicose veins=1]	0[b]	.	.	0	.	.	.	.
[Infection=0]	.158	.539	.086	1	.769	1.171	.408	3.366
[Infection=1]	0[b]	.	.	0	.	.	.	.
[Autoimmune=0]	-.685	.907	.569	1	.451	.504	.085	2.986
[Autoimmune=1]	0[b]	.	.	0	.	.	.	.
[Fractures=0]	-.559	1.371	.166	1	.684	.572	.039	8.397
[Fractures=1]	0[b]	.	.	0	.	.	.	.

a. The reference category is: 2.

HF – heart failure; DVT – deep vein thrombosis

Discussion. The location and extension of deep vein thrombosis were associated with the following risk factors age, sex, and immobilization. One clinical sign, unilateral calf edema, was also linked to the location of deep vein thrombosis. In this particular study, bilateral ankle edema was independently associated with the presence of heart failure.

The epidemiology of deep vein thrombosis shows that its prevalence grows with the age. In children under 15 years the incidence of deep vein thrombosis is 5 cases in 100000 people per year. Between 70 and 79 years, the incidence is 0.5% and over 80 years it increases to 1% (Richard 2003). Oger et al found that age is a powerful determinant for asymptomatic deep vein thrombosis, in a population of elderly. Over 90% of thrombosis was limited to the calf (Oger et al 2002). Levels of procoagulant factors increase with age, as anticoagulant markers do not. Vein walls stiffen with age. Venous stasis is also often encountered in elderly (Karachi et al 2005; Young et al 2006).

Age was an important determinant of deep vein thrombosis in our study. The median age was 70 years. The data analysis revealed that younger patients (under 40 years) have low probability of developing distal thrombosis. This discovery is very important because

calf thrombosis is hard to detect and it shows us that if we diagnose femoral or popliteal thrombosis in people under 40, it is unlikely that we will find distal vein thrombosis.

In our study, women had a higher probability than men to develop distal vein thrombosis. Stain et al demonstrated that proximal thrombosis, followed by postphlebitic syndrome, has a tendency to appear in men (Stain et al 2005).

Immobility was an important risk factor of deep vein thrombosis in our study, being present in 20% patients. The absence of immobility was associated with lower risk of developing proximal vein thrombosis.

Immobilization interferes with a particular calf muscles activity, which is to pump blood through veins, against gravity. That process is achieved with the help of venous valves. The risk of deep vein thrombosis is greater in sitting position. In Second World War, during bombing of London, the incidence of pulmonary embolism increased by six times for people who were sitting on chairs. The risk decreased after replacing of chairs with beds. That fact shows the greater effect of gravity on venous stasis in sitting position (Rosendaal et al 2007). Landefeld et al determined that recent immobility is associated with proximal deep vein thrombosis (Landefeld et al 1990).

Limitations of our study: we could not determine markers of thrombophilia; we could not determine D-dimers in all patients; we had a small (or none) number of patients with important risk factors (autoimmune diseases, long distance travel, stroke, chemotherapy, pregnancy).

Conclusion. Age, sex and immobility were all independently associated with location of deep vein thrombosis.

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