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Factors affecting the recurrence in patients with venous thromboembolism: A retrospective cohort study

Venöz tromboemboli olgularında nüks gelişimini etkileyen faktörler: Retrospektif kohort çalışması

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ABSTRACT

Background: The aim of the study was to evaluate the frequency of recurrence and the risk factors for recurrence in patients who were diagnosed with venous thromboembolism.

Methods: Between January 2005 and January 2015, a total of 412 venous thromboembolism patients (164 males, 248 females; mean age: 53.5±16.6 years; range: 19 to 95 years) were retrospectively analyzed. The demographics, underlying risk factors, comorbidities, imaging findings, and treatment data of the patients were recorded.

Results: At least one transient/permanent risk factor was found in 341 (82.7%) of the index events, and the other 71 (17.2%) were idiopathic. Recurrence developed in 76 (18.4%) of the patients. The duration of the treatment in the first event was significantly longer in recurrent cases (p=0.007). The recurrence rate in patients diagnosed with only deep vein thrombosis or patients diagnosed with pulmonary thromboembolism + deep vein thrombosis was significantly higher than the patients diagnosed with only pulmonary thromboembolism (24% *vs*. 14.2%, respectively; p=0.007). The rate of idiopathic venous thromboembolism was higher in recurrent cases than in non-recurrent cases (26.3% *vs*. 15.2%, respectively; p=0.028). At the end of the first year, the mean D-dimer levels were higher in recurrent cases (p=0.034). Hereditary risk factors were also higher in recurrent cases (39.5% *vs*. 19.3%, respectively; p=0.031). There was no significant correlation between recurrence and mortality.

Conclusion: The presence of deep vein thrombosis, idiopathic events, high D-dimer levels at the end of the first year and hereditary risk factors seem to be associated with recurrence.

Keywords: D-dimer, recurrence, risk factors, thrombophilia, venous thromboembolism.

ÖZ

Amaç: Bu çalışmada venöz tromboemboli tanısı konan hastalarda nüks sıklığı ve nüksün risk faktörleri incelendi.

Çalışma planı: Ocak 2005 - Ocak 2015 tarihleri arasında toplam 412 venöz tromboemboli hastası (164 erkek, 248 kadın; ort. yaş: 53.5±16.6 yıl; dağılım: 19-95 yıl) retrospektif olarak incelendi. Hastaların demografik özellikleri, altta yatan risk faktörleri, eşlik eden hastalıkları, görüntüleme bulguları ve tedavi verileri kaydedildi.

Bulgular: İndeks olguların 341'inde (%82.7) en az bir geçici/kalıcı risk faktörü bulunurken, 71'i (%17.2) idiyopatik idi. İndeks olguların 76'sında (%18.4) nüks gelişti. İlk ataktaki tedavi süresi, nüks gelişen olgularda anlamlı düzeyde daha uzundu (p=0.007). Tek başına derin ven trombozu veya pulmoner tromboemboli + derin ven trombozu ile tanılanan hastalarda nüks oranı, tek başına pulmoner tromboemboli ile tanılanan hastalara kıyasla anlamlı düzeyde yüksek idi (sırasıyla, %14.2'ye kıyasla %24; p=0.007). Nüks gelişmeyen hastalara kıyasla, nüks gelişen hastalarda idiyopatik venöz tromboemboli oranı daha yüksek idi (sırasıyla, %15.2'ye kıyasla %26.3; p=0.028). Birinci yılın sonunda ortalama D-dimer düzeyleri nüks gelişen hastalarda daha yüksekti (p=0.034). Nüks gelişen olgularda kalıtsal risk faktörleri de (sırasıyla, %19.3'e kıyasla %39.5; p=0.031) yüksek bulundu. Nüks ve mortalite arasında anlamlı bir ilişki saptanmadı.

Sonuç: Derin ven trombozu, idiyopatik olaylar, birinci yılın sonunda yüksek D-dimer düzeyleri ve kalıtsal risk faktörleri varlığının nüks ile ilişkili olduğu görülmektedir.

Anahtar sözcükler: D-dimer, nüks, risk faktörleri, trombofili, venöz tromboembolizm.

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Pulmonary thromboembolism (PTE) is a preventable disease with possible recurrence, higher mortality and morbidity.[1] The mortality rate in untreated patients is 25 to 30%; however, the rate decreases to 2 to 8% with appropriate treatment.[2] In recent years, mortality tends to increase.[2] Recurrence can be observed in 5 to 23%, despite treatment.[3] The recurrence risk of venous thromboembolism (VTE) peaks within the first four weeks, and the risk continues until two years after the discontinuation of treatment which gradually decreases over time.

In the literature, the cumulative recurrence rates have been reported as approximately 25% at five years and 30% at 10 years.[4] Recurrence rates are higher in patients with cancer, hereditary thrombophilia, and idiopathic.[5] The recurrence rate is higher in patients with higher D-dimer levels and residual deep vein thrombosis (DVT) after the discontinuation of anticoagulant therapy.[6] The risk of recurrence after a recent surgery is lower than the risk in patients with non-surgical risk factors (i.e., estrogen therapy, pregnancy, foot injury, or traveling a long distance). In addition, advanced age, male sex, post-thrombotic syndrome, obesity, chronic inflammatory bowel diseases, and some antipsychotic drugs are associated with the increased risk of recurrence after the discontinuation of the anticoagulant therapy.[7] Patients with a second VTE attack have a 1.5-fold higher risk of recurrence, compared to patients with the first attack.[8] Risk factors are possibly different from the risk factors in the first event as shown in the studies investigating the recurrence-related risk factors.[9] Recurrent PTE may result in death in about 4 to 9% of the patients.[3,7,10,11] In the present study, therefore, we aimed to evaluate the frequency of recurrence and the risk factors for recurrence in VTE cases.

PATIENTS AND METHODS

This single-center, retrospective cohort study was conducted at Istanbul University, Istanbul Medical Faculty, Department of Chest diseases, Pulmonary Thromboembolism outpatient clinic between January 2005 and January 2015. All patients who were diagnosed with VTE were evaluated using objective diagnostic methods and followed in the outpatient setting. Inclusion criteria were as follows: all patients who were diagnosed with venous thromboembolism and given treatment and followed up in the PTE outpatient clinic. Exclusion criteria were as follows: patients under the age of 18, patients who did not approve the voluntary consent form and patients whose follow-up data could not be accessed. Finally, a total of 412 VTE patients (164 males, 248 females; mean age: 53.5±16.6 years; range, 19 to 95 years) who fulfilled the eligibility criteria were included in the study. A written informed consent was obtained from each patient. The study protocol was approved by the Istanbul University, Istanbul Faculty of Medicine Ethics Committee (No: 2017/578). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Demographic data, risk factors, comorbidities, diagnostic methods, initial and follow-up D-dimer results, presence of DVT, and the treatment modalities were recorded. The first VTE attack was accepted as the index event. In this study, VTE which developed due to transient and reversible causes within the last three weeks or six months before diagnosis was evaluated as the provoked VTE, and VTE which developed with no risk factors was evaluated as the unprovoked VTE. Age of ≥70 years was accepted as advanced age. The clinical severity of PTE was classified as massive, submassive, and non-massive. The survival assessment was performed using the patient files, telephone queries, and death registration system.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were presented in mean ± standard deviation (SD) or median (min-max), while categorial variables were presented in number and frequency. The concordance of normal distribution of all variables was analyzed using the Shapiro-Wilk test. Non-parametric tests were used for dependent variables in the presence of non-normal distribution of the data. The Mann-Whitney U test or Student t-test was used in the comparison of the two groups. Categorical variables were compared using the chi-square test. In cross tables, the Fisher's exact test was performed, if more than 20% of the expected values were smaller than 5 or at least one of the values was smaller than 2. Multiple regression analysis was performed to analyze recurrence-associated variables. A p value of <0.05 was considered statistically significant.

RESULTS

Baseline demographic and clinical characteristics of the patients are shown in Table 1. Of the patients who had PTE (n=384), 44 (11.5%) had massive, 66 (17.2%) had submassive, and 274 (71.3%) had non-massive PTE. The diagnosis of PTE was performed using the contrast-enhanced computed tomography (CT) in 287

(69.6%) patients. The evaluation of the CT results showed a central thrombus in 27.2% (n=78/287) and a peripheral thrombus in 72.8% (n=209) of the patients. Bilateral thrombus was detected in 51.6% (n=148/287) of the patients. Deep vein thrombosis was detected using lower extremity Doppler ultrasonography in 171 patients at the time of index event. Fourteen (86.5%) of these patients were diagnosed with acute DVT and 13.5% (n=23) were diagnosed with chronic DVT. Proximal DVT was detected in 55.5% (n=95) of the patients. The evaluation of the risk factors showed that at least one of the risk factors was present in 82.8% patients and 17.2% were evaluated as idiopathic VTE (Table 1). Hereditary thrombophilia was detected in 39.3% patients. The most common hereditary thrombophilia was heterozygous Factor V Leiden (FVL) mutation (38.6%).

The mean duration of anticoagulant therapy at the first episode was 13.3±17.7 (range, 1 to 128) months. The mean follow-up was 25.3±24.5 (range, 3 to 138) months. Of all patients, 208 were treated in the hospital setting, and the mean length of hospital stay was 14.2±9.5 (range, 3 to 60) days. Thirty-nine patients (9.5%) were administered thrombolytic therapy (32 patients with massive, and seven patients with submassive PTE). Heparin resistance was detected in one (2%) patient, and inadequate anticoagulation therapy in five (1.6%) patients. Recurrence was detected in one (16.6%) of six patients. Mortality rate with all associated causes was found to be 17.2% (n=71). No mortality was detected in the acute VTE period.

Recurrence was detected in 76 (18.4%) of 412 patients diagnosed with VTE in the follow-up period. The mean number of recurrences was 1.1±0.33 (range, 1 to 3). The mean time to recurrence was 21.4±20.3 (range, 1 to 101) months. Recurrence developed in 28 (18.5%) of the 151 cases with PTE + DVT, 33 (14.2%) of 233 cases with only PTE in the beginning. The recurrence rate in the presence of only DVT or DVT + PTE was significantly higher than in the presence of only PTE (24% *vs*. 14.2%, respectively; p=0.007). The recurrence rate was higher in patients with PTE + DVT, compared to only PTE cases (18.5% *vs*. 14.2%, respectively); however, the difference between them was not statistically

Table 1. Demographic and clinical characteristics of patients (n=412)

	n	%
Age (year)		
<40	105	25.5
40-70	230	55.8
>70	77	18.7
Sex		
Males	164	39.8
Females	248	60.1
PTE	233	60.7
PTE + DVT	151	39.3
DVT	28	6.8
PTE severity (n=384)		
Massive	44	11.5
Submassive	66	17.2
Nonmassive	274	71.3
Idiopathic VTE	71	17.2
Presence of temporary and permanent risk factors	303	73.5
Single factor	167	40.3
Two factors	94	22.7
>2 factors	38	9.2
Presence of hereditary risk factors (n=242)	95	39.3

PTE: Pulmonary thromboembolism; DVT: Deep vein thrombosis; VTE: Venous thromboembolism.

Table 2. Risk factors of VTE in recurrent cases (n=76)

Risk factors	n	%
Idiopathic first VTE (n=71)	14	19.7
Age >70 years	8	10.5
Male sex	34	44.7
Family history of VTE (n=54)	10	18.5
Inadequate treatment (n=76)	1	1.3
Pregnancy (n=42)	6	14.3
Surgery	7	9.1
Oral contraceptive use	6	7.8
Longer travel	6	7.8
Immobilization	5	6.5
Cancer/chemotherapy	10	13
Vena cava filter	1	1.3
Antiphospholipid syndrome	1	1.3
Homozygous factor V leiden	2	3.5
Heterozygous factor V leiden	21	38.6
Homozygous prothrombin *G20210A*	1	1.7
Heterozygous prothrombin *G20210A*	5	8.6
Hyperhomocysteinemia	5	8.6

VTE: Venous thromboembolism.

Table 3. Comparison of the index event of recurrent and non-recurrent VTE cases

	Non-recurrent (n=336)			Recurrent (n=76)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Mean age (year)			54.2±16.6			50.8±15.9	0.116
Age <40	84	25		21	27.6		0.663
Age >70	58	17.3		8	10.5		0.169
Sex							
Males	130	38.7		34	44.7		0.364
VTE type							
PTE	204	60.7		33	43.4		1
PTE + DVT	119	35.4		28	36.8		1
DVT	13	3.9		15	19.7		0.014
Proximal	75/132	56.8		29/43	67.4		
PTE severity							
Massive	35/323	10.8		9/61	14.7		0.623
Submassive	57/323	17.6		9/61	14.7		0.635
Nonmassive	231/323	71.5		43/61	70.1		0.606
12th month follow-up D-dimer >500 µg/L	41/137	29.9		19/39	48.7		0.036
Number of temporary risk factors	259	77		43	56.6		<0.001
1	98	37.9		18	42.1		
>1	101	39.2		6	14.5		
Hereditary risk factor	65	19.3		30	39.5		0.031
Idiopathic VTE	51	15.2		20	26.3		0.028

VTE: Venous thromboembolism; SD: Standard deviation; PTE: Pulmonary thromboembolism; DVT: Deep vein thrombosis.

significant (p=0.198). Risk factors of the recurrent VTE cases are shown in Table 2. No risk factor was found in 26.3% (n=20) of recurrent cases. Transient/permanent risk factors were detected in more than half of the patients (n=44, 57.9%). In 29 (39.7%) of the patients with recurrent VTE, there was a newly established transient/permanent risk factor that was not detected in the first event. Nine of 76 recurrent patients died during follow-up. No reliable data were available for the causes of death.

There was no statistically significant difference in age, sex, radiologically extensive involvement, and the severity of PTE between the recurrent and non-recurrent cases (Table 3). Transient risk factors

Table 4. Comparison of recurrence with the index event of recurrent cases (n=76)

	Index event		Recurrence		
Recurrent cases	n	%	n	%	*p*
Type of VTE					
PTE	33	43.4	44	57.9	0.009
PTE + DVT	28	36.8	16	21	1
DVT	15	19.7	16	21	0.225
Severity of PTE					
Massive	9/61	14.7	6/60	10	0.564
Submassive	9/61	14.7	9/60	15	0.97
Nonmassive	43/61	70	45/60	75	0.445
Idiopathic	14/70	20	22/70	28.9	<0.001
Hereditary risk factor	30	39.5	26	34.2	<0.001

VTE: Venous thromboembolism; PTE: Pulmonary thromboembolism; DVT: Deep vein thrombosis.

were significantly higher in non-recurrent cases and hereditary risk factors were significantly higher in recurrent cases (p<0.001, p=0.031, respectively). The idiopathic VTE rate of the first episode was higher in the recurrent patients (p=0.028). The duration of treatment at the first event was significantly higher in recurrent patients (p=0.007). The D-dimer values at 1, 3, 6 and 12 months after the beginning of the treatment were available. However, only D-dimer values at 12 months were included in the analysis due to the scarcity of data. At the end of the first year, D-dimer levels were significantly higher in recurrent cases (p=0.036). No association was detected between recurrence and mortality. In the multiple regression analysis, the factor associated with recurrence was detected to have a hereditary risk factor.

Twenty-five (75.7%) of 33 recurrent cases with a first presentation of PTE had recurrence in the form of PTE again. Five of 28 recurrent cases (17.8%) with the first presentation of PTE + DVT had recurrence in the form of PTE + DVT once again. The rate of presence of transient or permanent risk factors in the first episode was higher, compared to the rate in the recurrent event (p=0.003, p<0.001, respectively). The rate of idiopathic event in recurrent cases was significantly higher (p<0.001). The comparison of the clinical features of index and recurrent VTE is shown in Table 4.

DISCUSSION

In the present study, we found recurrence in 18.4% of the VTE patients during follow-up. Presence of hereditary risk factors, idiopathic feature of the first events and D-dimer levels at 12 months were also significantly higher in recurrent patients. The only factor associated with recurrence in multiple regression analysis was the presence of hereditary risk factor.

There are conflicting results in the literature regarding the age as a strong risk factor for VTE.[10,12] In our study, no statistically significant difference was found in the rate of recurrence in different age groups. Only eight (10.5%) of our patients were older than 70 years. The majority of the patients (61.8%) were aged between 40 and 70 years.

Similarly, the effect of sex on VTE recurrence is still unclear. Male sex has been shown to be two to three-fold higher than female sex in large number of studies;[6,13] however, no significant association was demonstrated between recurrence and sex in another study.[14] The discrepancy between the studies can be attributed to the hormones, age, and DVT localization.[15] Although the ratio of men was higher in recurrent patients in our study, no statistically significant difference was found between the two sexes.

The presence of hereditary thrombophilia was related both to the first episode and the recurrence.[16-18] Homozygous FVL or prothrombin *G20210A* mutations have a higher risk of recurrence than heterozygous and the heterozygous combination of both factors has been shown to increase the risk.[18] Ho et al.[16] reported that, in 3,104 patients who had the first VTE attack, the risk of VTE increased by 1.41-fold in heterozygous FVL mutation carriers, and by 1.72-fold in heterozygous prothrombin *G20210A* mutation carriers. The presence of heterozygous FVL mutation was associated with an approximately 40% increase in VTE recurrence risk, and risk of recurrence was found to be higher in the heterozygous FVL mutation, compared to the risk in prothrombin *G20210A* mutation in a meta-analysis.[17] In our study, the hereditary risk factors were significantly higher in recurrent patients. Consistent with the literature, this risk was found to be higher in patients with heterozygous FVL mutations, compared to the risk in patients with heterozygous prothrombin *G20210A* mutations.

In previous studies, the risk of recurrence was significantly higher in unprovoked cases, compared to the risk in provoked cases.[7,18] In our study, similarly, the rate of unprovoked VTE was higher in recurrent patients.

The presence of persistent risk factors such as cancer, and antiphospholipid syndrome (APS) leads to a higher risk of recurrence. The risk of recurrence in cancer patients during and after anticoagulant therapy is reported to be two or four-fold higher, compared to the risk in other patients. Chemotherapy and metastasis increase the risk.[19,20] In our study, 13% of recurrent cases were diagnosed as having cancer and/or received chemotherapy. The risk of recurrent VTE in patients with APS was found to be 2.3 to 8.5-fold higher in different studies.[21-23] Recurrent VTE was detected in one of seven patients diagnosed with APS in our study.

The recurrence risk of patients diagnosed with proximal DVT was approximately two to five-fold higher, compared to the recurrence risk in patients with distal DVT.[7,12] In our study, we detected DVT in 46.1% of the index cases and in 56.5% of the recurrent cases, and the rate of proximal DVT was higher in recurrent patients.

Several studies have reported that the recurrence risk is two or four-fold higher, when the index

event is PTE, compared to the recurrence risk with the presence of only DVT.[3,10,24] In a study, the recurrence rate was found to be 17.2% in patients with symptomatic PTE and to be 9.5% in patients with DVT as the index event.[24] In our study, the recurrence rate in patients with PTE+DVT was found to be significantly higher than the risk in patients with only PTE (24%, 14.2%, p=0.007) as the first presentation. Researchers found that the initial clinical VTE type (symptomatic PTE or only DVT) was likely to be highly similar to the clinical type of recurrence.[3,10,24] In compliance with the literature, in our study, the recurrence in 75.7% of patients presenting with initial PTE was also PTE.

The VTE recurrence rates in patients with higher D-dimer levels following the discontinuation of anticoagulant therapy were found to be higher than the rates in patients with normal D-dimer levels. Following D-dimer levels may help to predict the risk of recurrence, and be useful to establish a period for optimal treatment.[8] In general, the D-dimer levels one month after the discontinuation of treatment were used in previous studies. In the current study, the D-dimer levels at 12 months were significantly higher in recurrent cases. However, some patients received long-term treatment, and D-dimer levels were studied during the treatment.

The main limitations of this study are its retrospective design and lack of reliable data on causes of death. The main strengths of the study are that it includes a large patient series and the data are real-life data of a tertiary healthcare institution.

In conclusion, the presence of deep vein thrombosis, idiopathic events, high 12th -month D-dimer levels, and presence of hereditary risk factors are associated with recurrence. However, further large-scale, long-term, prospective studies are needed to establish a definite conclusion.

Declaration of conflicting interests

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