# Risk Factors, Locations of the Thrombus, Prophylaxis, and Treatment of the Deep Venous Thrombosis Patients in the İzmir City and Aegean Region: Results of a Multicenter Study

## Ege Bölgesi ve İzmir İlinde Derin Ven Trombozlu Hastalarda Trombus Yerleşimleri, Risk Faktörleri, Profilaksi ve Tedavileri: Çok-Merkezli Çalışma Sonuçları

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Geliş Tarihi/*Received:* 22.09.2010
Kabul Tarihi/*Accepted:* 05.03.2011

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**ABSTRACT Objective:** To determine whether there is a relationship between the risk factors and the locations of the thrombi, pharmacological prophylaxis, and the treatment modalities in patients with deep venous thrombosis (DVT) in the İzmir City and Aegean Region. **Material and Methods:** We enrolled 531 consecutive patients with DVT which are confirmed by Doppler ultrasound and reviewed records of 13 hospitals in the Izmir City and Aegean Region, in this multicenteric cross-sectional study. The data of the patients were recorded on a questionnaire form and analyzed by using confidence intervals for odds ratios, Chi-square test and Student-t tests. **Results:** 85.3% of the patients were outpatients while 14.7% were inpatients. The most frequently encountered medical risk factors were chronic venous insufficiency-varices, immobilization and family history respectively. The most frequently seen surgical risk factors were lung cancer surgery and knee surgery, followed by gastrointestinal surgery in the surgical group. While DVT were seen more frequent in males who had lung cancer, chronic obstructive pulmonary disease and under chemotherapy receiving patients for a malignancy; otherwise, DVT was seen more frequently in females who were obese and had a hip fracture. **Conclusion:** Advanced age is a crucially important risk factor in population for DVT and be able to treat with low molecular weight heparin without hospitalization as outpatient settings especially, for pregnant or mothers in lactation period. Malignity and its related surgery are at the forefronts of DVT causes. The obese females are in danger for DVT if any surgery is planned. The population-based studies are needed to be planned to detect for the true prophylaxis rates.

**Key Words:** Venous thrombosis; risk factors

**ÖZET Amaç:** İzmir ili ve Ege bölgesinde trombüslerin yerleşimi, risk faktörleri, farmakolojik profilaksi ve derin ven trombozlu (DVT) hastalarda tedavi modaliteleri arasında bir ilişki olup olmadığını belirlemek amaçlanmıştır. **Gereç ve Yöntemler:** Çok-merkezli kesitsel bu çalışmada, İzmir ili ve Ege bölgesinde 531 ardışık, Doppler ultrasonografi ile doğrulanmış derin ven trombozlu olgu çalışmaya alınarak 13 hastanedeki kayıtlar incelendi. Hastaların verileri bir anket formunda kayıt edilerek olasılık oranları için güven aralıkları, ki-kare testleri ve Student-t testleri kullanılarak istatistik analizleri yapıldı. **Bulgular:** Hastaların %85.3'ü ayaktan başvuranlardan, %14.7'si ise yatan hastalardan oluşuyordu. En sık gözlenen medikal risk faktörleri sırasıyla kronik venöz yetmezlik-varisler, immobilizasyon ve aile öyküsü idi. Cerrahi girişim öyküsü olan grupta en sık karşılaşılan cerrahi risk faktörleri ise, akciğer kanser cerrahisi, diz cerrahisi ve bunların arkasından da gastrointestinal cerrahi idi. Erkek olgularda DVT daha çok akciğer kanseri, kronik obstrüktif akciğer hastalığı ve malignite nedeniyle kemoterapi alanlarda görülürken, kadın olgularda ise obes ve kalça fraktürü olanlarda daha sık gözlendi. **Sonuç:** İleri yaş, DVT için önemli bir risk faktörüdür ve düşük moleküler ağırlıklı heparin tedavisi özellikle gebeler ve emziren annelerde ayaktan tedavide uygun bir seçenektir. Malignite ve bu nedenle yapılan cerrahi girişimler DVT için önde gelen risk faktörleridir. Obez kadınlar özellikle de cerrahi girişim planlananlar DVT yönünden ciddi risk altındadırlar. Doğru profilaksi değerlerini saptamak için toplum tabanlı çalışmalara ihtiyaç vardır.

**Anahtar Kelimeler:** Venöz tromboz; risk faktörleri

**Turkiye Klinikleri J Cardiovasc Sci 2011;23(2):115-20**

Deep venous thrombosis (DVT) hampers the prospects of many for a long and full life and claims more lives each year than AIDS.[1] In North America and Europe, the annual incidence is approximately 160 per 100 000 for DVT, 20 per 100 000 for symptomatic non-fatal pulmonary emboli (PE) and 50 per 100 000 for fatal autopsy-detected PE.[2] The most serious complication of DVT is PE, which has a 3-month mortality rate as high as 17%.[3] It is often necessary for at least two factors to coexist for venous thromboemboli (VTE) to occur. Principal clinical predisposing influences are immobilization, trauma, surgery, infection and the postpartum period.[4] Other predisposing influences are age, obesity, malignancy, previous history of venous thrombosis, varicose veins, dehydration and hormone therapy.[5] In the background for all of these is predisposition due to thrombophilia.[6]

The purpose of the present study was to determine whether there is a relationship between the risk factors and the locations of the thrombi, pharmacological prophylaxis, and the treatment modalities in patients with deep venous thrombosis in the İzmir City and Aegean Region.

## MATERIAL AND METHODS

We enrolled 531 consecutive patients with DVT with or without pulmonary emboli (PE) which is confirmed by Doppler ultrasound (US) and CT scan at 13 hospitals in the İzmir City and the Aegean Region, in this multicenteric cross-sectional prospective study. The maximum enrollment period was 10 months (from July 1, 2008, to April 30, 2009) of all appoinments to outpatient's clinic. We classified nearly 100000 patients as outpatients including those seen in the emergency department and cardiovascular surgery clinic for outpatients or inpatients in different clinics based on their status at the time of DVT diagnosis. The interviews were performed by using a survey method in outpatients who were able to respond to a questionnaire, were willing and gave fully informed consent and the data was recorded on the "Venous Thrombosis Evaluation Form". The data in inpatients' files and their findings of Doppler US were attached to these forms. All these forms were collected at a single center for the evaluation of statistical analysis. Thrombus status of the patients with DVT was classified by radiologic classification into three groups as acute, subacute and chronic phases. Comorbities were prespecified in our protocol. There were no exclusion criteria to obtain the data of real-world situation.

### STATISTICAL ANALYSIS

Software programs were used to analyze demographic and clinical data (*SPSS 12.0 for Windows, SPSS Inc. Chicago, IL, USA*) and statistical calculations (*Omega Research Company, İstanbul, Turkey*). Descriptive statistics were used for numeric variables, whereas, frequency tables were used for categorical variables. Chi-square test was used for the comparison of categorical variables and student-t test was used for the comparison of the numeric variables within the groups. Confidence intervals for odds ratios were used that the incidence or frequency of some outcome is assessed in two groups of individuals defined by the presence or absence of some characteristic. Statistical significance level was accepted as $p< 0.05$.

## RESULTS

### POPULATION DEMOGRAPHICS

We identified 531 patients with venous thromboembolism (VTE): 245 men (46.1%) and 286 women (53.9%) overall 501 patients (94.3%) had DVT alone and 30 (5.7%) had concomitant PE and DVT. We enrolled all patients of whom 85.3% (n= 453) were outpatients and 14.7% (n= 78) were inpatients. The mean age was 53.7+ 16 years (11-97). Mean diameter of limbs was 3.9cm (SD: 2.8). The difference of extremity diameter was not statistically significant (R: 3.98 SD= 2.80; L: 3.93 SD= 2.68, $p= 0.887$).

### SEX AND RISK FACTORS

There were more women than men > 70 years of age in 103 patients ($p< 0.003$). The differences between the locations of DVT and sex were not significant ($p= 0.486$). While DVT were seen more frequent in males who had lung cancer (5.6%),

chronic obstructive pulmonary disease (7.3%) and in patients receiving chemotherapy for a malignancy (11.9%), otherwise DVT was seen more frequently in females who were obese (14.6%) and had hip fracture (3.6%).

## LOCATIONS OF THROMBUS

Lower extremity DVT was detected in 95.9% of patients (n= 509) (233 right, 290 left, 8 bilateral) and upper extremity DVT was seen in 22 patients (4.1%). DVT were seen at Doppler US at crural 92.5%, popliteal 87.6%, femoral 54.5%, external iliac and common iliac veins 13.9% respectively. When we compared the patient's risk factors with the patients who were in surgical risk group as well, regarding to external iliac vein occlusion; patients who had urological cancer surgery, with a diagnosis of chronic venous insufficiency and in patients using oral contraceptives were statistically significant.

When we compared the patient's risk factors with the patients who were in surgical risk group as well, regarding to femoral vein occlusion; patients who had chronic renal insuffiency (p= 0.033), with a diagnosis of chronic venous insufficiency (p= 0.0021) and in patients who had underwent varicose vein surgery (p= 0.0040) were statistically significant.

When we compared the patient's risk factors with the patients who were in surgical risk group as well, regarding to patients with popliteal vein obstruction; patients with a diagnosis of chronic venous insuffiency (p< 0.001) was statistically significant.

## MEDICAL RISK FACTORS

Risk factors by status at time of DVT diagnosis in descending order of frequency were listed at the Table 1. The most frequent medical risk factors were chronic venous insufficiency-varices (n= 135, 25.4%), immobilization (n= 130, 24.5%) and family history (n= 82, 15.4%) respectively. DVT rates of immobilized patients were significantly higher than other patients who had medical risk factors (p= 0.033). The three most frequent risk factors of the upper extremity DVT were seen in malignity (n= 6, 28.6%), immobilization more than 3 days (n= 4, 19%) and polytrauma (n= 2, 9.5%) respectively. Two hundred fifty (47.1%) patients had more than one medical risk factor.

**TABLE 1:** Risk factors observed in 531 consecutive patients treated for DVT and/or PE.

| Risk Factors | n | % |
|---|---|---|
| 1- Chronic venous insufficiency-varices | 135 | 25.4 |
| 2- Immobilization(>3 days) | 130 | 24.5 |
| 3- Family History | 82 | 15.4 |
| 4- DVT History | 77 | 14.6 |
| 5- Obesity | 77 | 14.6 |
| 6- Malignity | 63 | 11.9 |
| 7- Chemotherapy | 59 | 11.1 |
| 8- Travelling (>6 hours) | 59 | 11.1 |
| 9- COPD* | 39 | 7.3 |
| 10- Radiotherapy | 30 | 5.6 |
| 11- Lung Cancer Surgery | 30 | 5.6 |
| 12- Knee Arthroplasty | 27 | 5.1 |
| 13- Hypercoagulability | 26 | 4.9 |
| 14- Oral contraseptive usage | 26 | 4.9 |
| 15- Gastrointestinal surgery | 23 | 4.3 |
| 16- Pulmonary Emboli History | 21 | 4.0 |
| 17- Hip Arthroplasty | 19 | 3.6 |
| 18- Stroke | 19 | 3.6 |
| 19- Polytrauma | 15 | 2.8 |
| 20- Acute Coronary Syndrome | 15 | 2.8 |
| 21- Pregnancy | 15 | 2.8 |
| 22- Varicose vein surgery | 13 | 2.4 |
| 23- Gynecologic surgery | 12 | 2.3 |

* Chronic Obstructive Pulmonary Disease.

## SURGICAL RISK FACTORS

The most frequently seen DVT was after lung cancer surgery (5.6%) and after knee surgery (5.1%), gastrointestinal surgery (4.3%) in surgical group respectively. The urological cancer surgery was statistically significant in patients who had external iliac vein obstruction (p= 0.007). There was no relation between sex and surgical risk factors in surgical patients group. Medical risk factors and surgical risk factors simultaneously were detected in females slightly higher than males (OR= 0.726 (95% CI: 0.4-1.3) for female:, OR= 0.520 (95% CI: 0.3-1) for male: OR= 0.616 (95% CI: 0.4-0.9) for all patients (Figure 1). Orthopedic surgery and med-

ical risk factors simultaneously was detected in females two times higher than males (OR= 0.613 (95% CI: 0.3-1.4) for female, OR= 0.398 (95% CI: 0.2-0.8) for male, OR= 0.487 (95% CI: 0.3-0.8) for all patients (Figure 2). Sixteen patients (3.0%) had more than one surgical risk factor. DVT without any risk factor was detected in 52 patients (9.8%). DVT was seen at 176 (67.4%) patients who had no surgery history within 3 months and 55 (20.9%) patients who had no medical risk factors before diagnosis. 193 (36.3%) had a surgery history in the last 3 months and 435 (81.9%) had a medical risk factors simultaneously.

### TREATMENT AND PROPHYLAXIS

Two hundred and forty-five (92.2%) patients received low molecular weight heparin (LMWH) or warfarin treatment. Warfarin and LMWH administered together at 72.7% of the patients (n=386). Twenty four (4.51%) patients were treated with only LMWH. The patients in this group were pregnant or mothers in lactation period and most of them had the distal DVT. Warfarin, LMWH and compression therapy together was used in 253 (47.6%) patients . Three (0.56%) patients underwent placement of a vena caval filter alone. Two (0.37%) patients received systemic thrombolysis and 2 (0.37%) patients underwent open femoral vein thrombectomy and pulmonary arterial embolectomy. Four hundred eighty three (91%) patients did not received LMWH or other treatment modalities for the pharmacologic prophylaxis.

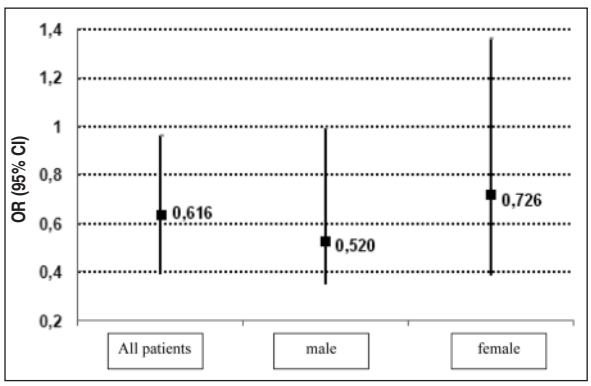


**FIGURE 1:** Orthopedic surgery and the medical risk factors simultaneously were detected more in females.

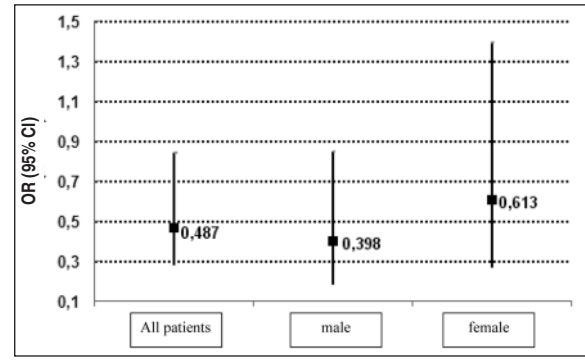


**FIGURE 2:** Medical risk factors and the surgical risk factors simultaneously were detected in females slightly higher.

## DISCUSSION

A study from Olmsted County during the 25-year study after screening 9046 potential cases, incidence rates were higher in females during their childbearing years, and the incidence rates were generally higher in men older than 45 years. Incidence rates increased markedly with age for both DVT and PE. Their study further demonstrates that VTE is predominantly a disease of older age.[7] In our study, there were more women than men >70 years of age in 103 patients (p< 0.003). Our study demonstrates that advanced age is a crucially important risk factor in population.

VTE incidence was determined 17.46/10.000 in 1996 and 22/10.000 in 2004 in a study from India. Total 722 DVT were detected in 438.667 patients. The clinical importance of our study lies in the fact that, in the future. The essential points in our data has been shown in a previously mentioned study from India.[8] Since 531 DVT were determined nearly in 400.000 screened patients in İzmir and the Aegeon region.

Heit et al reported that a 4-fold increased risk of VTE among patients with malignant neoplasm alone. In our study, the most frequently seen DVT was after lung cancer surgery in all patients who underwent surgery, and malignity is one of the most frequent risk factor of the upper extremity DVT. Our study demonstrates that malignity is increased risk of VTE and fairly common among the patient population.[5]

Kageyama et al indicated the highest frequency of crural-type DVT especially at the soleal vein, and the soleal vein, acting as a storage vein. In our study, the distal DVT was seen at 43% and proximal DVT 57% of the patients as well.[9] To our knowledge, detailed Doppler US studies are needed for evaluation this vein to avoid from PE resourced from soleal vein in DVT patients.

Heit et al reported that their study is the first to identify superficial vein thrombosis and varicose veins as independent risk factors for VTE. For example, 45 year-old patients with varicose veins had a 4-fold increased risk of VTE compared with a 2-fold increased risk for 60-year-old patients and no increased risk for 75-year-old patients.[5] Our study dealed with the same points thoroughly, with the most frequent medical risk factors were chronic venous insufficiency and varicose veins. To some extent, the varicose veins are responsible for DVT.

RIETE Study contains data from over 24 000 patients, followed-up for at least 3 months, from 186 hospitals. RIETE provides data on the treatment of VTE in a real-world situation with an unselected patient population, in contrast to the rigorously controlled conditions of randomized clinical studies.[10] Similarly, in our study, the real-world data were reflected without any exclusion criteria.

Overweight individuals, whether defined by weight or body mass index, may be at increased risk, but the association of excess weight with VTE is a weak one.[11] Our study demonstrated that DVT was seen more frequent in females who were obese and had hip fracture. In spite of this coincidence spontaneously occur, the hip or joint arthroplasty of the obese females could be complicated by deep venous thrombosis. Baykal et al determined that many of these risk factors are very frequent, among which several have been recently identified, such as resistance to activated protein C by factor V Leiden, hyperhomocysteinemia, high levels of factor VIII, as well as acquired risk factors, such as surgery and malignancies. When more than one of these risk are present simultaneously the risk of thrombosis is increased.[12]

DVT is one of the most common complications after total joint arthroplasty patients who are morbidly obese (average BMI of 35.2 for the low-risk group).[13] 193 (36.3%) had a surgery history in the last 3 months and 435 (81.9%) had medical risk factors simultaneously in our study. If there are medical risk factors in patients, surgical interventions in these patients, creates a major risk for DVT.

With simplified dosing and no need for coagulation monitoring, LMWH is ideal for out-of-hospital use. Compared with heparin, LMWH derivatives also exhibit (a) less binding to platelet factor 4, which results in a decreased risk of heparin-induced thrombocytopenia, and (b) reduced binding to osteoblasts and osteoclasts with a resultant lower risk of osteoporosis with long-term administration. Vitamin K antagonists (VKA) continue to be widely used for secondary prevention of VTE.[14] Warfarin and LMWH were used more widely as a treatment of choice instead of the standard heparin as an outpatient setting in our study population.

## CONCLUSION

Advanced age is a crucially important risk factor in population for DVT and be able to treat with exploitation of LMWH without hospitalization as outpatient settings especially, for pregnant or mothers in lactation period. The crural and popliteal vein DVT are seen more frequently. Medical risk factors are more important than surgical risk factors and in some patients had no any risk factors. Malignity and its related surgery are at the forefront of DVT causes. The obese females are in danger for DVT if any surgery is planned. Direct instrumentation of external iliac, femoral and popliteal vein obstructions may bring on DVT and they are crucial locations. The population-based studies are needed to be planned to detect for the true prophylaxis rates.

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