

Assessment of additional risk factors for deep vein thrombosis in patients with various malignancies

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Abstract. Abstract: Aim: to analyze the additional risk factors of deep vein thrombosis (DVT) in patients with a positive oncological history. Material and methods: The included 62 patients (29 (46.8%) women and 33 (53.2%) men) diagnosed with various cancers. The median age was 73.5 (68.75; 81) years. Patients were divided in two groups, the first group comprised 40 patients with DVT and the second group comprised 22 patients without DVT. The following risk factors for DVT were recorded for each patient: age, gender, varicose veins, history of bed rest longer than 3 days, bilateral lower limb edema, infections, chemotherapy, history of DVT, and other comorbidities such as: heart failure and diabetes mellitus. Results: History of DVT and the bed rest for more than 3 days were associated in univariate analysis with an increased risk of DVT in patients with cancer, and the prior enhanced the risk of DVT in multivariate analysis. Conclusion: History of DVT was an additional risk factor for DVT in patients with cancer.

Key Words: deep vein thrombosis, cancer, risk factors.

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Introduction

Venous thromboembolism (VTE) is an entity that encompasses two diseases: deep vein thrombosis (DVT), usually involving the lower limbs, and pulmonary embolism (PE). VTE is an important health and economic issue, affecting over 10 million people every year (Jha et al 2013). The mortality related to VTE events is high with over 300000 annual deaths in USA, and over 500000 in UE (Cohen et al 2008; Tapson 2008).

VTE due to deep vein thrombosis (DVT) is a common complication in patients with malignancies, for whom the risk of such an event is four- to six-fold higher than for age and sex matched controls (Bloom et al 2005). Since VTE is the second leading cause of death worldwide in oncological patients, the risk factors for DVT have been the object of many research groups looking to reduce the morbidity and mortality rate in these patients (Heit et al 2000). VTE is symptomatic in only 4-20% of cancer patients, but it is discovered in over 50% of autopsies (Khorana et al 2007).

There are several additional risk factors for DVT described in literature in oncologic patients. Some factors are related to the patient: advanced age, race (higher risk in Afro-Americans and lower in Asians) and comorbidities such as obesity, chronic obstructive pulmonary disease, previous DVT, thrombophilia. Other factors are linked to the cancer itself: primary location of the tumor, the first 3-5 months from diagnosis, presence of

metastases, chemotherapy, surgery related to the cancer, etc. (Lee&Levine 2003; Rosendaal 2005; Lyman et al 2015).

We aimed to analyze the additional risk factors of DVT in patients with a positive oncological history.

Materials and methods

This retrospective, analytical, observational, transversal, cohort study included 62 patients (29 (46.8%) women and 33 (53.2%) men) diagnosed with various tumor types (lung, digestive system, genitourinary tract and hematological malignancies). The median age was 73.5 (68.75; 81) years. The patients were recruited from those admitted to the internal medicine ward of the Municipal Clinical Hospital of Cluj-Napoca between September 2007 and September 2009. The patients were divided in two groups, the first group comprised 40 patients with DVT and the second group comprised 22 patients without DVT. The diagnosis of acute DVT was established using duplex ultrasonography by means of an Aloka SSD-4000 device with a linear transducer (7-10 MHz), according to the criteria in force. Patients having signs and symptoms that were evocative for acute DVT underwent ultrasound examination.

All patients completed a signed consent prior to the enrolment in the study. The study protocol was approved by the Ethics Committee of “Iuliu Hatieganu” University of Medicine and Pharmacy, Cluj-Napoca.

Patients receiving oral or intravenous anticoagulant therapy at the time of enrolment or did not signed the informed consent were not included in the study.

The following data were recorded for each patient: age, gender, BMI, varicose veins, history of bed rest longer than 3 days, bilateral lower limb edema, infections, chemotherapy, history of DVT, and other comorbidities such as: heart failure, diabetes mellitus and COPD.

Statistical analysis was performed using MedCalc Statistical Software version 15.5 (MedCalc Software bvba, Ostend, Belgium; <https://www.medcalc.org>; 2015). Data were classified as qualitative or quantitative. Nominal variables were described using frequency and percentage. The Kolmogorov-Smirnov test was used to determine if the continuous variables were normal distributed. Quantitative variables were described using the median and the 25th and 75th percentile. The chi-square test or Fisher's exact test were used to analyse the difference in frequency between two groups of nominal variables. Multivariate analysis was performed using binary logistic regression. The level of statistical significance was set at $p < 0.05$.

Results

Data recorded for the patients can be seen in table 1.

Table 1. Characteristics of patients with and without DVT

Variables	Patients with DVT	Patients without DVT	P	
Age (years)	74 (69; 82)	73 (65.76; 77.25)	0.1	
Gender	Female	21 (52.5%)	8 (36.4%)	0.3
	Male	19 (47.5%)	14 (63.6%)	
Environment	Rural	19 (47.5%)	13 (59.1%)	0.5
	Urban	21 (52.5%)	9 (40.9%)	
Heart failure	11 (27.5%)	6 (27.3%)	1	
Diabetes mellitus	4 (10%)	2 (9.1%)	1	
COPD	7 (17.5%)	2 (9.1%)	0.4	
Obesity	12 (30%)	3 (13.6%)	0.2	
History of DVT	14 (35%)	1 (4.5%)	0.01	
Bed rest for more than 3 days	8 (20%)	-	0.04	
Major surgery	1 (2.5%)	-	1	
Bilateral edema	10 (25%)	1 (4.5%)	0.07	
Varicose veins	13 (32.5%)	2 (9.1%)	0.08	
Chemotherapy	4 (10%)	-	0.2	

The different types of cancer are described in table 2. The location of the cancer was not related to the risk of DVT ($p=0.5$). A multiple logistic binary regression was used to determine the independent association between variables and DVT. The diagnosis of DVT was the dependent variable, while the following were introduced as independent variables: history of DVT, varicose veins and lower limb edema. The variable bed rest longer than 3 days was not included due to statistical concerns. These variables statistically significantly predicted the occurrence of

DVT, $R^2=0.19$. As seen in table 3, the factor with the most important contribution to the occurrence of DVT was the history of DVT (OR, 7.91; CI 0.91-68.73; $p=0.029$).

Table 2. Types of cancer

Type of cancer	Patients without DVT	Patients with DVT	Total
Brest/uterus	6	8	14
	27.3%	20.0%	22.6%
Digestive system	7	12	19
	31.8%	30.0%	30.6%
Other types	3	2	5
	13.6%	5.0%	8.1%
Pulmonary	2	7	9
	9.1%	17.5%	14.5%
Genitourinary	4	11	15
	18.2%	27.5%	24.2%

Table 3. The multiple logistic binary regression for DVT

Variables	B	P	OR	95% CI for OR	
				Lower	Upper
History of DVT	2.069	0.05	7.915	0.912	68.735
Bilateral edema	1.303	0.258	3.68	0.384	35.24
Varicose veins	1.252	0.145	3.498	0.649	18.854

Discussion

Cancer-associated thrombosis is a common problem in cancer patients. Patients with cancer which are not hospitalized do not require routine anticoagulation. Only patients with additional comorbidities or conditions that place them in the high risk percentile for DVT should receive thromboprophylaxis (Lyman et al 2015). Thus it is extremely important to identify which of the risk factors are associated with an increase chance of DVT onset. The occurrence of DVT in patients with cancer is due to concomitant action of several factors: inflammation caused by necrosis or release of acute phase proteins, stasis caused by external tumoral compression or vascular invasion. The tumors have the capacity of secreting specific substances (tissue factor, cytokines) which can inhibit the release of anticoagulation factors or can upregulate the procoagulant factors, and thus resulting a hypercoagulable state (Falanga et al; 1993; Falanga&Rickles 1999; Blow et al 2004).

In our study, the history of DVT was the strongest risk factor for onset of DVT (OR, 7.9; $p=0.05$). The risk of another DVT is lower in patients with transient risk factors like temporary immobility, estrogen therapy, and higher in those with permanent conditions (cancer, obesity, paralysis; thrombophilia) (Heit et al 2000a). Despite anticoagulation after the thrombotic episode, there is still a 5 to 7% chance of thrombosis recurrence within a year for cancer patients (Ginsberg 1996).

The bed rest for more than 3 days was the other factor associated with the onset of DVT. Due to the fact that there were no controls with bed rest, this parameter could not be included in the multivariate analysis, but this does not mean that it's not a strong risk factor. The long period of bed rest increase the chance of DVT, due to venous stasis (Weill-Engerer et al 2004). Limitations of the study include the small number of cases and controls, the absence of data regarding thrombophilia and the limited data regarding metastases.

Conclusion

The history of DVT and bed rest for more than 3 days increase the risk of an acute DVT in cancer patients.

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