

Risk factors in venous thromboembolism in hospitalized patients

Research Article

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Abstract: Venous thromboembolism (VTE) causes considerable morbidity and mortality. About half of all VTE cases in adults are related to recent hospitalization, in spite of the clinical guidelines regarding prophylaxis. We aimed to assess the frequency and the independent risk factors in VTE in hospitalized patients, and to compare the risk factors in medical versus surgical cases. A case-control study consisting of 732 patients (382 with VTE and 350 controls) was designed. At least one risk factor was found in 90.31% of VTE cases; more than half of the patients presented multiple risk factors, associated with a double risk comparatively to the intervention of only one factor. A similar distribution of the risk factors was found in both medical and surgical patients, except for congestive cardiac failure (predominant in medical cases) and respectively, varicose veins, previous episode of VTE and cancer (predominant in surgical VTE patients). The independent risk factors in VTE were the following: previous episode of VTE, obesity, chronic obstructive pulmonary disease, congestive cardiac failure, varicose veins and cancer. The study shows the importance of the risk factors in VTE and the need to detect hospitalized patients at risk in both medical and surgical cases.

Keywords: Deep venous thrombosis • Independent risk factors • Hospitalized medical patients • Surgical patients

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1. Introduction

VTE, the result of the interaction between genetic and acquired risk factors, occurs at an annual incidence of about 1 per 1000 adults [1]. Pulmonary embolism is the cause of 5%-10% of all in-hospital deaths, of which only 1 in 4 of these patients recently had surgery; although VTE is a major health problem, especially among elderly hospitalized patients, thromboprophylactic measures are still underutilized in about 40% of these cases [2-4]. Most hospitalized medical patients present at least one risk factor for VTE, which persists for several weeks after discharge [5]. Despite the existence of clinical guidelines regarding prophylaxis (available since 1986 and updated periodically) and over 300 randomized controlled trials that showed the importance of VTE

prevention, about half of all VTE cases occurring in adults are related to recent hospitalization [6,7].

The acquired risk factors in VTE include increasing age, acute respiratory failure, congestive heart failure, prolonged immobility, stroke or paralysis, previous VTE, cancer and chemotherapy, acute infection, dehydration, hormonal treatment, varicose veins, inflammatory bowel diseases, nephrotic syndrome, and recent surgery. Strong risk factors in VTE (associated with a 10-fold increased thrombotic risk) include: hip or leg fractures, hip or knee replacements, major general surgery, and spinal cord injury. Moderate risk factors (leading to a 2- to 9-fold higher risk of VTE) include: arthroscopic knee surgery, central venous lines, cancer and/or chemotherapy, congestive heart failure, respiratory failure, hormone replacement therapy or oral contraceptive therapy, stroke,

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pregnancy or postpartum, previous episode of VTE, and thrombophilia. Weak risk factors (associated with less than a double risk of VTE) include: bed rest for at least 3 days or prolonged immobility due to sitting, age, laparoscopic surgery, obesity, and varicose veins [8]. Among medical hospitalized patients, infection, being more than 75 years of age, cancer and previous VTE are associated with anVTE risk. Cardiovascular risk factors such as hypertension, diabetes mellitus, smoking, hypercholesterolemia, are also associated with VTE [8-10]. Recently, it was shown that major illnesses (liver disease, kidney disease, rheumatoid arthritis, multiple sclerosis, heart failure, hemorrhagic stroke, and arterial thrombosis) were associated with an increased risk of venous thrombosis. Furthermore, the risk was higher when any of these major illnesses was associated with immobilization or genetic factors [10].

The main aims of this study were to assess the frequency of the risk factors in VTE, in both medical and surgical hospitalized patients, and identify the associated risk and the independent risk factors.

2. Materials and methods

A case-control, observational study was performed, consisting of 732 subjects who were admitted consecutively for 3 years in two departments – Medical and Surgical – of a teaching hospital in Cluj-Napoca, Romania. These patients were divided into two groups: the first group consisted of 382 patients diagnosed with VTE, confirmed by Doppler ultrasound and/or venography, and the second group consisted of 350 sex- and age-matched controls without VTE. Patients with the clinical diagnosis/supposition of VTE without a confirmation by complementary examinations were excluded from the study.

The following data were registered for each participant:

- general data: sex, age
- the manifestation of VTE: deep venous thrombosis (DVT), pulmonary embolism (PE); the location of DVT (proximal DVT, distal DVT, a site other than the lower limbs)
- clinical data: obstetric history (pregnancy, postpartum, spontaneous abortions, use of oral contraception, or hormone replacement therapy), medical history regarding previous VTE; smoking; obesity (defined by body mass index $> 30 \text{ kg/m}^2$)
- co-morbidities/associated risk factors for VTE, considering diagnoses at the admission and documented past medical history: COPD (chronic obstructive pulmonary disease, all GOLD stages), congestive heart

failure (only grade III and IV), acute myocardial infarction, stroke with motor deficit, acute infection, nephrotic syndrome, inflammatory bowel diseases, vasculitis (Behcet's disease, antiphospholipidic syndrome—primary or secondary to collagenosis, thromboangiitis obliterans), neoplastic diseases, trauma, recent surgery (occurring within one month prior), central venous line, dehydration, hematological diseases (sickle cell anemia, paroxysmal nocturnal hemoglobinuria, thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, heparin induced thrombocytopenia, disseminated intravascular coagulation).

The statistic analysis consisted of: the univariate descriptive statistic for the risk factors, the bivariate inferential statistic for the assessment of the association between risk factors and VTE (using chi-square test, χ^2 , for qualitative variables), and the multivariate inferential statistic, with respect to logistic regression for the detection of the independent risk factors. The value of $p < 0.05$ was considered significant statistic. The program SPSS 15.0 for Windows (Statistical Package for the Social Sciences) was used for the data analysis.

3. Results

Patients with VTE presented a mean age of 58.62 years old with a standard deviation of 11.2 and a sex ratio male/female of 1.76:1; the controls presented a mean age of 59.59 years old with a standard deviation of 14.79 and a sex ratio male/female of 1.51:1. Patients with VTE were hospitalized with a slight higher proportion in the medical than surgical department, with 52.61% (201 patients) and 47.38% (181 patients), respectively. The demographical data are presented in Table 1.

Male sex was not significantly associated with VTE ($p = 0.403$, $\chi^2 = 0.727$, OR = 1.139, 95% CI: 0.835-1.552). No difference of thrombotic risk in medical versus surgical male patients was found ($p = 0.394$, $\chi^2 = 0.876$, OR = 0.819, 95% CI: 0.526-1.272).

The majority of the patients with VTE (82.98%) were more than 50 years old; however, age > 50 was not significantly associated with VTE ($p = 0.256$, $\chi^2 = 1.291$, OR = 1.241, 95% CI 0.855-1.802). Advanced age was a risk factor in VTE only for women ($p = 0.018$, $\chi^2 = 5.601$, OR = 1.905, 95% CI: 1.112-3.262), whereas no significant difference was found for men ($p = 0.092$, $\chi^2 = 2.837$, OR = 0.602, 95% CI: 0.332-1.091).

DVT was predominantly located in the lower limbs in 370 cases (96.85%); only 12 patients presented another site for thrombosis (10 in the upper limbs and 2 at the inferior cava vein). Proximal DVT occurred in 175 cases and distal DVT in 195 patients.

Table 1. Demographic characteristics of the medical and surgical patients with VTE, and the controls (non-VTE)

Parameter	Medical patients VTE	Surgical patients VTE	Controls
Mean age	57.85	58.57	59.59
Male (n=)	124	120	211
male <50	20	20	
male >50	104	100	
Female (n=)	77	61	139
female <50	15	10	
female >50	62	51	
DVT site (n=):			-
Proximal	85	90	
Distal	111	84	
Other sites	5	7	
DVT+ PE (n=)			-
male <50	1	2	
male >50	16	18	
female <50	1	1	
female >50	3	3	
Obstetrical history* (n=)	7	2	8
Hormonal therapy** (n=)	4	3	19
Previous VTE (n=)	37	20	14
Family history of VTE	40	30	66
Smoking (n=)	45	81	47

*obstetrical history: pregnancy, postpartum (up to 3 months after childbirth), spontaneous abortions

**hormonal therapy: use of oral contraception or hormonal replacement therapy

PE complicated DVT in 45 cases (11.78%), 37 men and 8 women, with a significantly higher distribution in patients older than 50 (40 cases) who presented a 2.7-fold increased risk compared to younger patients ($p=0.038$, $\chi^2=4.3$, 95% CI: 1.023-7.187). The risk of PE was almost triple in men compared to women ($p=0.008$, $\chi^2=7.442$, OR= 2.905, 95% CI: 1.249-6.994). No significant difference in the distribution of PE amongst medical and surgical patients was found ($p=0.429$, $\chi^2=0.725$, 95% CI: 0.391-1.486).

At least one risk factor was found in 345 VTE cases (90.31%), while multiple risk factors were found in 246 patients (64.39%). Obesity and immobility (>3 days in bed or cast) presented the highest frequency in VTE, 41.62% and 33.51%, respectively. A very low frequency of VTE (0.5%) was found in cases with: minor trauma, acute myocardial infarction, Chron's disease, hematological disorders, central venous line and dehydration; as a result, no further statistical analysis was performed on these factors. A significant association with VTE was found for the following factors: previous episode of VTE, obesity, COPD, congestive heart failure, stroke, varicose veins, cancer, surgery, prolonged immobilization, and smoking; all these factors were associated with a weak or moderate increase in thrombotic risk ($1<OR<9$). The frequency and the associated risk of VTE are shown in Table 2. The presence of at least one risk factor significantly associated with VTE, found

in 84.82% of cases, increased the risk by 6.263 times (95% CI: 4.416-8.886.3), whereas the presence of multiple risk factors, found in 56.02% of VTE, doubled the risk comparatively to the intervention of only one factor (OR=2.223, 95% CI: 1.516-3.260) and increased the risk by 8.865 times comparatively to the absence of any significant risk factor (95% CI: 5.981-13.139).

The distribution of the risk factors in medical versus surgical patients with VTE is shown in Table 3. A significant difference was found in the frequency of congestive heart failure, which were found predominantly in medical VTE cases, and the frequency of varicose veins (corresponding to OR=3.798, 95% CI: 2.344-6.170), previous episode of VTE (OR=2.278, 95% CI: 1.235-4.222), and cancer (OR=3.698, 95% CI: 1.767-7.864), which were found predominantly in surgical VTE patients.

The independent risk factors for VTE, using binary logistic regression, were the followings: previous episode of VTE, obesity, COPD, congestive cardiac failure, varicose veins, and cancer (Table 4).

4. Discussion

Literature shows that a risk factor could be detected in 75%-80% or even in 96% of VTE cases, which is reflected in our findings: at least one risk factor was found in 90.31% of cases, with 84.82% cases having

Table 2. The frequency and associated risk of factors in VTE

Risk factor	Frequency in VTE (%)	p	χ^2	Odds ratio (OR)	95% CI (lower– upper limit)
Obesity	41.62	0.00	91.782	6.219	4.167-9.281
Immobilization	33.51	0.00	40.48	3.249	2.236-4.720
Smoking	32.98	0.00	38.70	3.173	2.183-4.612
Varicose veins	32.2	0.00	61.675	5.066	3.291-7.798
Congestive heart failure	27.23	0.00	27.664	2.189	1.897-4.190
COPD	22.25	0.00	13.38	2.099	1.403-3.139
Family history VTE	18.32	0.172	1.865	1.315	0.887-1.951
Previous VTE	14.92	0.000	24.874	4.209	2.300-7.702
Cancer	11.78	0.023	5.185	1.814	1.080-3.046
Stroke	4.71	0.023	5.176	2.835	1.112-7.226
Acute infection	3.93	0.068	4.845	0.489	0.256-1.012
Vasculitis	3.4	0.366	0.818	1.506	0.617-3.678
Obstetrical history	2.35	0.426	0.635	1.486	0.558-3.955
Hormonal therapy	1.83	0.073	3.205	0.449	0.183-1.100
Nephrotic syndrome	0.78	0.715	0.246	0.685	0.152-3.081

Table 3. The distribution of the risk factors in medical versus surgical patients

Risk factor	Medical VTE cases (n=)	Surgical VTE cases (n=)	P	χ^2	Odds ratio (OR)	95% CI (lower– upper limit)
Obesity	79	80	0.351	0.939	0.818	0.533-1.255
Immobilization	57	71	0.101	2.849	3.249	0.920-2.285
Smoking	68	58	0.711	0.138	1.084	0.691-1.701
Varicose veins	38	85	0.00	34.338	0.263	0.162-0.427
Congestive heart failure	69	35	0.001	10.803	2.181	1.329-3.587
COPD	48	37	0.461	0.651	1.221	0.731-2.042
Family history of VTE	40	30	0.429	0.704	1.251	0.718-2.180
Previous VTE	21	38	0.005	8.112	0.439	0.237-0.810
Cancer	12	33	0.00	13.779	0.285	0.134-0.596
Stroke	11	7	0.481	0.547	1.439	0.503-4.214
Acute infection	7	8	0.793	0.222	0.780	0.249-2.426
Vasculitis	9	4	0.267	1.490	2.074	0.572-8.154
Obstetrical history	6	3	0.508	0.730	1.826	0.399-9.357
Hormonal therapy	4	3	1.00	0.059	1.205	0.225-6.874
Nephrotic syndrome	2	1	1.00	0.239	1.809	0.128-50.819

significant associations [9]. We found multiple risk factors in 64.39% of our patients, as reported data: about 50% in medical patients, respective 65% of all VTE cases [4,11].

Numerous studies have been performed to assess the independent risk factors for VTE. Different studies showed different independent factors: acute infection, age, cancer, previous VTE [12], immobilization, advanced age, previous VTE, trauma [13], hospital or nursing home confinement, surgery, trauma, cancer with/without chemotherapy, neurological diseases with

paresis, central venous catheter or pacemaker, varicose veins, and superficial vein thrombosis [14]. In our study, the independent risk factors were the following: previous VTE, obesity, COPD, heart failure, varicose veins, and cancer. We did not find an association with acute infections, especially since the majority of these cases were admitted to another department. We detected that age>50 was a risk factor for VTE in women; this might contradict data showing that younger women present a higher thrombotic risk [15]; however, other studies found similar frequencies in both sexes, except a two-fold

Table 4. Binary logistic regression to assess the independent risk factors for VTE

Risk factor	B	S.E.	Wald	df	Sig. (p)	OR	95% confidence interval	
							Lower limit	Upper limit
Previous VTE	1.379	0.339	16.553	1	0.000	3.970	2.043	7.714
smoking	-0.792	.971	0.666	1	0.415	0.453	0.068	3.036
Obesity	1.465	0.226	42.184	1	0.000	4.327	2.781	6.732
COPD	0.616	0.264	5.457	1	0.019	1.851	1.104	3.102
Congestive heart failure	0.837	0.228	13.487	1	0.000	2.309	1.477	3.608
stroke	0.643	0.609	1.115	1	0.291	1.903	0.577	6.277
Varicose veins	1.020	0.252	16.374	1	0.000	2.774	1.692	4.548
cancer	0.624	0.312	4.006	1	0.045	1.866	1.013	3.439
surgery	-0.400	0.320	1.560	1	0.212	0.670	0.358	1.256
Immobilization	1.247	0.959	1.693	1	0.193	3.481	0.532	22.790
Constant	-0.934	0.121	59.831	1	0.000	0.393		

higher rate in men aged >75 [16], and a slightly higher risk of DVT in old women and a lower risk for PE [17]. In our study, men were at a significantly higher risk for PE than women were, concordant with literature [18].

Although literature shows a 2- to 4-fold increase in thrombotic risk of hormonal therapy, we found no association with VTE, mainly due to the low prevalence (1.83% in VTE and 5.07% in women with VTE) and thus, we did not detail the analysis (according to the dose, route of administration) [8]. Smoking may represent a weak risk factor for DVT, especially in studies considering VTE events as the only outcome [19]; we found smoking to be relatively frequent in VTE (32.9%), but not enough to be independently associated with thrombotic risk. Family history is an independent risk factor for VTE, reflecting a hereditary thrombophilia [20]. However, our study indicated no association with VTE, which may be due to an underestimation of the frequency, since we considered only confirmed VTE of the siblings.

Our study shows a mild to moderate thrombotic risk associated with the other factors: obesity, prolonged immobilization, varicose veins, cancer, congestive heart failure, COPD, and stroke, which was similar to reported data in the literature [8].

The surgery in our study included major general surgery (>30-60 minutes in general anesthesia), which is associated with 15%-30% risk of VTE in the absence of thromboprophylaxis, as well as laparoscopic interventions. However, there were conflicting data about the incidence of VTE: 2%, 5%, 6.9%, and 50%; the risk of VTE in all these surgical cases could be comparable with the risk of medical hospitalized patients, which is 10%-30% [21-24]. Our hospitalized surgical patients included not only patients who suffered an intervention, but also cases admitted for the follow-up after a previous surgery. A recent Romanian study conducted in a

Surgical Clinic showed that almost half of the patients (45.5%) presented acquired risk factors requiring heparin thromboprophylaxis, except surgical intervention itself; the most common were the following: obesity, advanced age, smoking, and malignancies [25].

Some data showed that medical patients may present even higher risk probabilities in specific groups than surgical patients due to the influence of multiple factors. This data also revealed the importance of the following conditions: congestive heart failure, respiratory infections, cancer, chronic inflammatory state (lupus, inflammatory bowel diseases), coma, and nephrotic syndrome [26]. In our study, vasculitis and nephrotic syndrome occurred at a low frequency and thus, no associations with VTE were found.

Amongst our patients with VTE, only 38.74% correctly received thromboprophylaxis: 49.75% of medical patients and 44.75% of surgical patients. These findings were similar to reported data: nearly 40% of medical patients and about 50% of hospitalized patients at risk [3, 27-30]. However, we did not expand the analysis of prophylactic measures since it was not the aim of the study.

A limitation of the study was that we did not include cases with PE in the absence of the confirmed diagnosis of DVT in our group of patients because PE could only be detected during autopsy in some situations. This study showed the importance of the risk factors for VTE, in both surgical and medical hospitalized patients, requiring the correct implementation of prophylaxis.

Conflict of interest statement

Authors state no conflict of interest.

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