Prospective Evaluation of Patients Hospitalized with Venous Thromboembolism: Comparison between Cancer and Non-Cancer Patients

Albert Kolomansky MD[1], Ron Hoffman MD[1], Galit Sarig PhD[1], Benjamin Brenner MD[1] and Nissim Haim MD[2]

[1]Thrombosis and Hemostasis Unit, Department of Hematology and [2]Department of Oncology, Rambam Medical Center, Haifa, Israel
Affiliated to Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

Key words: thrombosis, cancer, activated protein C resistance, global C

Abstract

Background: Little is known about the epidemiology of venous thromboembolism in hospitalized patients in Israel. Also, a direct comparison of the clinical and laboratory features between cancer and non-cancer patients has not yet been reported.

Objectives: To investigate and compare the epidemiologic, clinical and laboratory characteristics of cancer and non-cancer patients hospitalized with venous thromboembolism in a large referral medical center in Israel.

Methods: Between February 2002 and February 2003, patients diagnosed at the Rambam Medical Center as suffering from VTE (deep vein thrombosis and/or pulmonary embolism), based on diagnostic findings on Doppler ultrasonography, spiral computed tomography scan or lung scan showing high probability for pulmonary embolism, were prospectively identified and evaluated. In addition, at the conclusion of the study period, the reports of spiral chest CT scans, performed during the aforementioned period in this hospital, were retrospectively reviewed to minimize the number of unidentified cases. Blood samples were drawn for evaluation of the coagulation profile.

Results: Altogether, 147 patients were identified and 153 VTE events diagnosed, accounting for 0.25% of all hospitalizations during the study period. The cancer group included 63 patients (43%), most of whom had advanced disease (63%). The most common malignancies were cancer of the lung (16%), breast (14%), colon (11%) and pancreas (10%). Of 122 DVT events (with or without pulmonary embolism) there were 14 upper extremity thromboses (12%). The most common risk factors for VTE, except malignancy, were immobilization (33%), surgery/trauma (20%) and congestive heart failure (17%). There was no difference in prevalence of various risk factors between cancer and non-cancer patients. During an acute VTE event, D-dimer levels were higher in cancer patients than non-cancer patients (4.27 ± 4.04 vs. 2.58 ± 1.83 mg/L respectively, $P = 0.055$). Relatively low values of activated protein C sensitivity ratio and normalized protein C activation time were observed in both cancer and non-cancer groups (2.05 ± 0.23 vs. 2.01 ± 0.33 and 0.75 ± 0.17 vs. 0.71 ± 0.22, respectively). These values did not differ significantly between the groups.

Conclusion: The proportion of cancer patients among patients suffering from VTE was high. Their demographic, clinical and laboratory characteristics (during an acute event) were not different from those of non-cancer patients, except for higher D-dimer levels.

IMAJ 2006;8:848–852

Venous thromboembolism is a common clinical disorder, carrying considerable morbidity and mortality [1]. Its annual incidence in the United States and Western Europe is 1.22/1000 [2] and 1.83/1000 [3], respectively. There are several well-known risk factors for VTE, including surgery, immobilization, inherited thrombophilia, and malignancy [3] which was first associated with thrombotic tendency back in 1865 [4]. Many clinical studies have described the epidemiologic, demographic and clinical characteristics of patients with VTE, including the impact and frequency of different risk factors. However, there is a large variability in the reported data, depending on location, study design, number of patients, etc. Moreover, only a few studies focused on the general hospital population and none directly compared cancer with non-cancer patients.

In the Worcester study [5], which was a large-scale retrospective registry, the incidence of VTE was 0.9%, but the proportion of objective diagnoses was low. Other studies, which were also retrospective, demonstrated that the incidence of deep vein thrombosis in general hospitals worldwide ranges between 0.1 and 0.78% [6-8], while that of pulmonary embolism is lower and ranges from 0.27 to 0.4% [9-11]. The percentage of cancer patients also varies widely – from 10.7% [12] to 32% [13], with most studies reporting 15–25% [1,14,15] – as does the prevalence and distribution of other risk factors. On the other hand, the proportion of patients with idiopathic VTE falls into the range of 19% [16] to 47% [17], depending largely on the definition of idiopathic versus secondary VTE and the timing of the studies in relation to the era of recently characterized and most common thrombophilic disorders such as factor V Leiden mutation, activated protein C resistance and prothrombin 20210A mutation [12,17,18]. Laboratory tests to reveal these abnormalities are now widely available and are usually performed several months after an acute event to avoid possible influences by coagulation imbalance and anticoagulant drugs. In fact, virtually no studies have investigated coagulation markers in patients during an acute venous thromboembolic event, except D-dimer which now has an important place in the workup of suspected VTE cases [19].

In order to investigate and compare the epidemiologic, clinical and laboratory characteristics of cancer and non-cancer patients suffering from VTE in a large referral medical center in Israel, we conducted a prospective clinical study of all patients diagnosed objectively as having acute venous thromboembolism during a 1 year period.

DVT = deep vein thrombosis
VTE = venous thromboembolism

Patients and Methods

Patients

Between February 2002 and February 2003, all patients diagnosed at the Rambam Medical Center as suffering from a venous thromboembolic event (deep vein thrombosis and/or pulmonary embolism), based on diagnostic findings on Doppler ultrasonography, high probability pulmonary scan or diagnostic spiral computed tomography scan for pulmonary embolism, were prospectively enrolled and evaluated. Patients were identified by ongoing records from corresponding imaging units of the hospital: ultrasonography unit, CT clinic and nuclear medicine department. In addition, spiral chest CT reports performed during that 1 year period were retrospectively investigated for missed cases of pulmonary embolism. All patients, except for those identified during a retrospective investigation of CT reports, were personally interviewed by one of the investigators according to a standard questionnaire that had been prepared before the beginning of the study; their medical records were also reviewed. Data from the remaining patients were collected from medical records only.

All patients hospitalized with a diagnosis of acute thromboembolic event were eligible for the study. Blood samples were drawn for laboratory analysis of coagulation profile upon patient approval, including written informed consent. The study was approved by the institutional ethics committee.

Imaging

The diagnosis of DVT was established using the Doppler ultrasound technique with an ALT 5000 US device (Philips, Advanced Technology Laboratories, Bothell, WA, USA). The following veins were examined by high frequency linear transducer (5–12 MHz): common and superficial femoral veins, popliteal vein and posterior tibial vein. The veins were examined with and without compression maneuver, and color and spectral Doppler were also applied. DVT was diagnosed if the vein was non-compressible and blood flow compromised.

A high probability lung scan for pulmonary embolism was defined when ventilation-perfusion mismatch was observed in two or more of the lung segments. Diagnosis of PE by spiral chest CT was based on direct visualization of a thrombus in one or more of the pulmonary arteries.

Laboratory methods

Blood samples were collected by venipuncture into 3.2% citrate tubes. Prothrombin time, activated partial thromboplastin time, fibrinogen, D-dimer, activated protein C sensitivity ratio and protein C global assay were performed on fresh platelet-poor plasma, prepared by centrifugation at 2000 g for 15 minutes. All the assays were measured on the STA-R analyz®, Innovin® (Dade Behring, Marburg GmbH, Germany) for PT assay, STA-PTT®, STA-FIBRINOGEN and STA-LIATEST® D-DI kits for PTT, fibrinogen and D-dimer assays, respectively (Diagnostica STAGO).

APC-SR was determined by the addition of activated protein C to activated PTT assay with a 1:5 factor V deficient plasma dilution, using a Coatest APC resistance kit (Chromogenix AB, Molendal, Sweden).

Global protein C assay was performed by ProC®Global kit (Dade Behring). The protein C activation time was measured either with Protac® (protein C activator) or buffer (to determine PCAT-0). Results were expressed as PCAT normalized ratio calculated by dividing the PCAT ratio (PCAT / PCAT-O) of patient's plasma by a PCAT ratio of lyophilized standard human plasma (ORKL, Dade Behring) and multiplying by a lot-specific sensitivity value defined by the manufacturer for each batch of standard plasma.

Normal values for PT-INR, APTT and fibrinogen were calculated from the mean values in 25 healthy volunteers ± standard deviations in accordance with the manufacturer's' recommendation and were found to be 0.75–1.3, 30–42 sec and 160–400 mg/dl, respectively.

For the D-dimer assay, normal values were considered bellow the cutoff level of 0.5 mg/L and for APC-SR and PCAT-NR; levels higher than 2.0 and 0.8, respectively, were referred to as normal.

Statistical analysis

Continuous variables were compared by means of the *t*-test, whereas categorical variables were compared by means of the chi-square test. Statistical significance was determined if P was ≤ 0.05.

Results

Altogether, 147 patients were identified (79 men and 68 women) and 153 acute thrombotic episodes were diagnosed during the study period, i.e., there were 6 in-study recurrent VTE episodes. Of the 147 patients, 132 were identified prospectively and the other 15 (10%) retrospectively (after reviewing spiral chest CT reports). Considering the number of hospitalizations in 2002, which closely corresponds to the study period, the incidence of VTE during the study period was 0.25% of all hospitalizations. (There were 60,009 hospitalizations in Rambam Medical Center in 2002, excluding newborns and hospitalizations in the neonatal intensive care unit and the psychiatric, pediatric and pediatric surgery wards). Of the 153 VTE episodes, 101 (65%) were DVT, of which 14 (12%) involved upper extremities; 31 (20%) were PE, including 3 massive events, and 21 were combined (DVT and PE).

The demographic and clinical characteristics of the patients are summarized in Table 1. The age range was 18–89 years. Sixty-three patients (43%) had cancer; 25 (17%) non-cancer and 13 (9%) cancer patients had recurrent VTE. The most common risk

PE = pulmonary embolism
PT = prothrombin
PTT = partial thromboplastin time

APC-SR = activated protein C sensitivity ratio
PCAT = protein C activation time
PCAT-NR = PCAT normalized ratio

Table 1. Demographic characteristics of the patients and distribution by type of VTE

	Cancer patients (n=63)	Non-cancer patients (n=84)	All patients (n=147)
Age (mean)	14 ± 64	20 ± 67	
Gender (M/F)	32/31	47/37	79/68
WHO performance status			
0–1(%)	37	49	44
PS 2(%)	19	18	19
PS 3(%)	34	20	26
PS 4(%)	10	13	12
Type of VTE	**No. of episodes**	**No. of episodes**	**No. of episodes (%)**
DVT only	49	52	101 (65%)
PE only	9	22	31 (20%)
DVT+PE	8	13	21 (15%)
Total	66	87	153

Table 2. Distribution of risk factors

	Cancer-associated episodes (n=66)	Non-cancer-associated episodes (n=87)	All episodes (n=153)
	No. (%)	**No. (%)**	**%**
Family history of VTE	2 (3)	(7) 6	5
Known inherited thrombophilia*	1 (2)	(8) 7	5
Surgery/trauma	13 (21)	(19) 16	20
Immobilization	24 (38)	(29) 24	33
Neurologic disorder**	6 (10)	(11) 9	10
Congestive heart failure	9 (14)	(19) 16	17
Pregnancy/puerperium	1 (2)	(1) 1	1
Hormone replacement therapy/Tamoxifen	4 (6)	0	3
Inflammatory bowel disease	0	(2) 2	1
Central venous catheter	10 (16)	(11) 9	13
Anticoagulants before event	10 (16)	(14) 12	15
No risk factors	22 (30)	) 3237)	

* Heterozygous prothrombin mutation, homo/heterozygous factor V Leiden mutation, homo/heterozygous MTHFR mutation

** Neurologic disorder with extremity weakness or paralysis.

Table 3. Cancer patients group

	No. of patients (%)
Type of malignancy	
Lung cancer	10 (16)
Breast cancer	9 (14)
Colon cancer	7 (11)
Pancreatic cancer	6 (10)
Bladder cancer	5
Primary brain tumor	5
Gynecologic cancer	4
Gastric and esophageal cancer	4
Other*	13
Total	63
Extent of disease	
Limited	23 (37)
Advanced**	40 (63)
Chemotherapy in previous 6 months	
Yes	24 (38)
No	39 (62)

* Other: primitive neuroendocrine tumor, chondroblastic osteosarcoma, non-Hodgkin's lymphoma, cancer of prostate, laryngeal cancer, cancer of parotis, melanoma, unknown primary with liver metastases, basal cell carcinoma, acute myeloid leukemia and multiple myeloma

** Stage III-IV.

Table 4. Laboratory findings (mean values)

	Cancer patients	Non-cancer patients	*P*
PT-INR	1.49 ± 0.77	1.56 ± 0.96	0.70
PTT (sec)	49.3 ± 17.1	45.5 ± 17.7	0.31
Fibrinogen (mg/dl)	450 ± 156	451 ± 138	0.97
D-dimer (mg/L)	4.27 ± 4.04	2.58 ± 1.83	0.055
APC-SR	2.05 ± 0.23	2.01 ± 0.33	0.44
PCAT-NR	0.75 ± 0.17	0.71 ± 0.22	0.40

APC-SR = activated protein C sensitivity ratio, PCAT-NR = protein C activation time normalized ratio.

factors for VTE, except malignancy, were immobilization (33%), surgery/trauma (20%) and congestive heart failure (17%) [Table 2]. Known inherited thrombophilia and family history were more common among non-cancer patients (13 vs. 3 patients), but this difference was not statistically significant. Likewise, there was no difference in prevalence of all other risk factors between cancer and non-cancer patients. Of the 87 non-cancer episodes, 32 (37%) were idiopathic, i.e., none of the risk factors listed in Table 2 were noted.

Cancers of the lung, breast, colon and pancreas were the most common malignancies (16%, 14%, 11% and 10%, respectively). Most patients (63%) had advanced disease (stage III and IV) and 38% of cancer patients had received chemotherapy in the preceding 6 months [Table 3]. No risk factors were noted in 22 cancer-associated VTE episodes [Table 2], of which 13 were associated with chemotherapy in the preceding 6 months, leaving only 9 cases with malignancy as a sole risk factor for VTE.

Of the 132 patients identified prospectively, 92 blood samples (70%) were available for investigation of the coagulation profile (36 and 56 in cancer and non-cancer groups, respectively). Blood samples were drawn between the first and fifth day after a diagnosis had been established. Mean values for different coagulation parameters are shown in Table 4. The mean D-dimer level was 4.27 ± 4.04 mg/L in the cancer group compared to 2.58 ± 1.83 mg/L in the non-cancer group ($P = 0.055$) (borderline significance). Two patients from each group had D-dimer levels lower than the cutoff (0.5 mg/L) (false negative)

Discussion

This prospective study provides a wide range of data on the epidemiologic, clinical and laboratory characteristics of VTE patients in a large referral medical center in Israel, with emphasis on the comparison between cancer and non-cancer patients.

The incidence of venous thromboembolic disease, based on the objective diagnosis only, provides a perspective on the frequency of this disorder in clinical practice in our region in recent years. We found that the estimated incidence of VTE in our facility (Rambam) was 0.25% of all hospitalizations, which is lower than reported from some medical centers in western countries. For example, in the Worcester study [5], which retrospectively reviewed all VTE cases in 16 hospitals diagnosed during an 18 month period (1985–86), the incidence of VTE was 0.9%, but the percentage of objective diagnoses was low, 84% for DVT and 54% for PE. More recent studies by Stein et al. [8,11] investigated the incidence of DVT and PE separately in a single medium-sized hospital and demonstrated corresponding rates of 0.78% and 0.27%. The percentage of objective diagnoses was much higher in these studies – almost 100% for DVT and 84% for PE. Therefore, a possible explanation for the relatively low incidence detected in the current study is that objective confirmation of diagnosis, and not only discharge diagnosis of VTE, was required.

We found that the percentage of cancer patients among all VTE patients was very high (43%), in fact one of the highest reported [5,13,14]. In a large multicenter prospective registry in the U.S. [13], which included 5451 DVT episodes with no exclusion criteria defined, as in our study, 32% of patients had cancer. In another multicenter international study known as ICOPER [16], which prospectively investigated pulmonary embolism cases, 22.5% of the patients had cancer. A possible explanation for the relatively high proportion of cancer-associated VTE in our study is the existence of large oncologic and hemato-oncologic clinics in this medical center, that serve a sizeable population living in the northern part of the country. In addition, direct interviewing could possibly have revealed more malignancies in the medical histories of the patients, as is the case with new immigrants for whom past medical records were not available.

A comparison between cancer and non-cancer patients in their demographic (age, gender, performance status) and clinical features, including the nature and number of risk factors for VTE, revealed no significant difference between the two groups. To date, no studies have focused on this kind of comparison.

The rate of idiopathic VTE episodes (32 of 84 non-cancer cases, 37%) was consistent with other studies [13-17]. On the other hand, the rate of spontaneous cancer-associated VTE – i.e., in the absence of any other risk factors including chemotherapy and tamoxifen [20] – was fairly low (9 of 63 cases, 14%). This finding is in contrast with the statement by Prandoni and colleagues [21] that most cancer-associated thrombotic episodes are spontaneous.

For coagulation studies, blood samples were available from two-thirds of the prospectively identified patients. We investigated several coagulation parameters, including APC-SR and global protein C, in an acute setting with most of the patients receiving active anticoagulant treatment, often combined. Despite this, we found that D-dimer levels were higher among cancer patients (though with marginal significance), which is consistent with other studies that demonstrated higher levels of this marker in different malignant processes even without thrombosis [22].

Low APC-SR in both cancer and non-cancer patients with acute thromboembolism (2.05 and 2.01, respectively) was not surprising and is consistent with the findings by Haim et al. [23] in their study in the same hospital. Although we did not carry out testing for factor V Leiden mutation, considering its prevalence among subjects with thromboembolism (10–20%) [12,17,18], which is much lower among subjects with both thromboembolism and cancer [23], it is reasonable to assume that in most cases the protein C resistance was acquired. Several mechanisms could explain low sensitivity to APC. First of all, in any thrombotic process there is continuing consumption of both procoagulant and anticoagulant factors, resulting in a state of relative deficiency of these factors including those involved in the protein C system. Secondly, anticoagulant medications could influence this system in two ways: the heparins diminish the generation of thrombin, while warfarin lowers protein C and protein S levels. In addition, in cancer patients, tumor-derived cytokines (such as tumor necrosis factor-alpha and interleukin-1 beta) induce the expression of tissue factor and down-regulate the expression of thrombomodulin [21]. Also, increased levels of coagulation factors V and VIII are potential mechanisms for acquired APCR in cancer patients [24].

Neither sensitivity to APC nor normalized PCAT values in the global protein C test differ between cancer and non-cancer patients, despite a seemingly more profound alteration of protein C activity in cancer-associated VTE. However, Goldenberg et al. [25] confirm this assumption by showing lower APC activity among cancer patients, though their study excluded subjects with known inherited thrombophilia, pregnancy, major surgery in the preceding month, recent chemotherapy, and anticoagulant treatment.

In conclusion, in a large referral medical center, which includes a cancer-treating center, the proportion of cancer patients among patients hospitalized with venous thromboembolism could be higher than reported by most studies, whereas their clinical features and most of the coagulation profile parameters (during an acute event) are not different from those of non-cancer patients, except for higher D-dimer levels.

References

1. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O' Fallon WM, Melton LJ III. Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. *Arch Intern Med* 1999;159:445–53.
2. Silverstein MD, Heir JA, Mohr DN, Petterson TM, O' Fallon WM, Melton LJ III. Trends in incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med* 1998;158:585–93.
3. Oger E. Incidence of venous thromboembolism: a community based study in Western France. *Thromb Haemost* 2000;83:657–60.
4. Trousseau A. Phlegmasia alba doleus. Lectures on clinical medicine, delivered at the Diew Paris. London: New Sydenham Society, 1872:281–95.

5. Anderson FA Jr, Wheeler HB, Goldberg RJ, et al. A population-based perspective of the hospital incidence and case fatality rates of deep vein thrombosis and pulmonary embolism: the Worcester DVT study. *Arch Intern Med* 1991;151:933–8.
6. Igbinovia A, Malik GM, Grillo IA, et al. Deep vein thrombosis in Assir region of Saudi Arabia: case-control study. *Angiology* 1995;46:1107–13.
7. Klatsky AL, Armstrong MA, Poggi J. Risk of pulmonary embolism and/or deep vein thrombosis in Asian-Americans. *Am J Cardiol* 2000;85:1334–7.
8. Stein PD, Patel KC, Kalra NK, et al. Deep vein thrombosis in a general hospital. *Chest* 2002;122:960–2.
9. Stein PD, IIenry JW. Prevalence of acute pulmonary embolism among patients and at autopsy. *Chest* 1995;108:978–81.
10. Stein PD, IIuang II, Afzal A, Noor HA. Incidence of acute pulmonary embolism in a general hospital: relation to age, sex and race. *Chest* 1999;116:909–13.
11. Stein PD, Patel KC, Kalra NK, et al. Estimated incidence of acute pulmonary embolism in a community/teaching hospital. *Chest* 2002;121:802–5.
12. Meyer G, Emmerich J, Helly D, et al. Factors V Leiden and II 20210A in patients with symptomatic pulmonary embolism and deep vein thrombosis. *Am J Med* 2001;110:12–15.
13. Goldhaber SZ, Tapson VF. A prospective registry of 5,451 patients with ultrasound-confirmed deep vein thrombosis. *Am J Cardiol* 2004;93:259–62.
14. Piccioli A, Prandoni P, Goldhaber SZ. Epidemiologic characteristics, management and outcome of deep venous thrombosis in a tertiary-care hospital: the Brigham and Women's hospital DVT registry. *Am Heart J* 1996;132:1010–14.
15. Kniffin WD Jr, Baron JA, Barrett J, Birkmeyer JD, Anderson FA. The epidemiology of diagnosed pulmonary embolism and deep vein thrombosis in the elderly. *Arch Intern Med* 1994;154:861–6.
16. Goldhaber GZ, Visani L, de Rosa M, for ICOPER. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry. *Lancet* 1999;353(9162):1386–9.
17. Rosendaal FR. Venous thrombosis: a multicausal disease. *Lancet* 1999;353:1167–73.
18. Rodengheiro F, Tosseto A. Activated protein C resistance and factor V Leiden mutation are independent risk factors for venous thromboembolism. *Ann Intern Med* 1998;130:643–50.
19. Wells PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N *Engl J Med* 2003;349:1227–35.
20. Sallah S, Wan JY, Nguyen NP. Venous thrombosis in patients with solid tumors: determination of frequency and characteristics. *Thromb Haemost* 2002;87:575–9.
21. Prandoni P, Falanga A, Piccioli A. Cancer and venous thromboembolism. *Lancet Oncol* 2005;6:401–10.
22. Bottasso B, Mari D, Coppola R, Santoro N, Vaglini M, Mannucci PM. Hypercoagulability and hyperfibrinolysis in patients with melanoma. *Thromb Res* 1996;81(3):345–52.
23. Haim N, Lanir N, Hoffman R, Haim A, Tsalik M, Brenner B. Acquired activated protein C resistance is common in cancer patients and is associated with venous thromboembolism. *Am J Med* 2001;110:91–6.
24. Sarig G, Michaeli Y, Lanir N, Brenner B, Haim N. Mechanisms for acquired protein C resistance in cancer patients. *J Thromb Haemost* 2005;3(3):589–90.
25. Goldenberg N, Kahn SR, Solymoss S. Markers of anticoagulation and angiogenesis in cancer-associated venous thromboembolism. *J Clin Oncol* 2003;21:4194–9.

Correspondence: Dr. A. Kolomansky, Dept. of Internal Medicine A, Tel Aviv Sourasky Medical Center, 6 Weizmann Street, Tel Aviv 64239, Israel.
Phone: (972-3) 697-3366
Fax: (972-3) 697-4989
email: alex_kolomansky228@yahoo.com