The predictive value of D-dimer measurement for cancer in patients with deep vein thrombosis

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Background and Objectives. Venous thromboembolism can be related to malignancy, but routine screening for cancer in patients with deep vein thrombosis (DVT) is not a recommended practice. The aim of this study was to evaluate the value of D-dimer concentration in predicting cancer in patients with DVT.

Design and Methods. D-dimer levels were measured in outpatients presenting with DVT. In a proportion of patients, D-dimer levels were measured daily for 4 days. The occurrence of malignancy was documented.

Results. Patients were followed for a median of 34 months. Fifty (23%) of 218 patients with thrombosis had cancer in the study period including 14 who developed cancer during the follow-up. High initial D-dimer levels (levels > 4000 μg/L) were associated with more cancer during follow-up than were lower D-dimer levels: 13% versus 4% (p=0.048). High D-dimer levels after 4 days of treatment were associated with a 15% prevalence of cancer whereas the prevalence in patients with lower D-dimer levels was 5% (p=0.1). The total cancer prevalence (including cancer diagnosed before thrombosis) in patients with initial D-dimer levels < 4000 μg/L was 16% compared to 32% in patients with higher levels (p=0.009, RR=2.0). After 4 days of treatment, total cancer prevalences were 14% and 46%, respectively (p=0.02, RR=3.4). In patients aged < 60 years, initial D-dimer levels of < 4000 μg/L were associated with a cancer prevalence of 3% whereas higher levels were associated with a prevalence of 23% (p=0.001, RR=8.6). After 4 days of treatment, the prevalences associated with lower and higher levels of D-dimer were 0% and 100%, respectively (p=0.003). There was no difference in older patients.

Interpretations and Conclusions. High D-dimer concentrations at presentation or during the first days of treatment are indicators of an increased probability of overt or occult forms of cancer, especially in patients under 60 years old.

Key words: D-dimer, cancer, deep vein thrombosis.

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The development of venous thromboembolism is associated with transient risk factors for thrombosis, such as surgery or trauma, and permanent risk factors, such as factor V Leiden, the prothrombin mutation, protein C and S deficiency, antithrombin deficiency, lupus anticoagulant and hyperhomocysteinemia. Venous thromboembolism can also be related to malignancy.[1-5] The incidence of occult or overt malignancy in patients with thrombosis is 7-26%.[6-11] Patients with cancer are at a higher risk of developing venous thromboembolism, which has been observed especially in postoperative patients with cancer and in patients receiving chemotherapy.[12]

Although several studies have tried to define clinical conditions in which cancer is more frequent in venous thromboembolism,[3,6,10,13,14] there is still debate about routine screening for occult malignancy. It would be of interest if certain patients with thrombosis could be identified as having an increased risk of malignancy. The mechanism of the hypercoagulable state in cancer is complex and many markers of blood clotting activation are disturbed.[2,15,16] Increased concentrations of D-dimers, specific markers of fibrinolysis, can be found in patients with cancer.[19,20] In accordance with recently developed diagnostic strategies, many patients with suspected venous thromboembolism now have their D-dimer levels measured.[21-25] It would be interesting to know whether the D-dimer concentration can be used as a predictor of cancer as a cause of the venous thromboembolism in these patients. The aim of this study was to investigate whether the initial D-dimer level in patients with deep vein thrombo-

sis or early changes in D-dimer levels during treatment for deep vein thrombosis (DVT) can differentiate between patients with and without cancer.

Design and Methods

Patients were participators in a management study concerning the value of D-dimers and the clinical score in the diagnosis of deep vein thrombosis[21] and gave informed consent. The study was approved by the local medical ethical committee and was performed in accordance with the Helsinki declaration. The current study is a post hoc analysis of this diagnostic management study. Consecutive outpatients with proven deep vein thrombosis of the leg were included in this study from July 1998 to October 2001. Ineligibility criteria were the use of anticoagulants, pregnancy and not documented recanalization after a previous history of deep vein thrombosis in the ipsilateral leg. Thrombosis was diagnosed using real-time B-mode compression ultrasonography, in which lack of compressibility was the criterion for an abnormal result; a vein was considered fully compressible if no residual lumen was seen. In all patients, a D-dimer measurement was done at presentation using the Tina-quant® quantitative latex assay (Roche, Mannheim, Germany). D-dimer values above 8000 μg/L FEU (Fibrinogen Equivalent Units) were not diluted further and were reported as > 8000 μg/L FEU. Treatment for thrombosis was started immediately and was given as a once daily subcutaneous injection of a low molecular weight heparin (dalteparin; dose adjusted to weight). Oral acenocoumarol was started simultaneously. Patients were treated with dalteparin for at least 5 subsequent days until the INR was > 2·0. In all patients, a complete physical examination was performed as well as routine laboratory tests including a complete blood count, renal function and liver enzymes. If the results of these tests were abnormal, additional investigations were performed at the discretion of the physician. These investigations included X-ray of the thorax, ultrasonography of the abdomen and computed tomography.

We documented the presence of previously known malignancy (defined by ongoing treatment for cancer or recurrent or metastatic disease) and the type of malignancy that was detected at the moment of thrombosis or which developed during follow-up. Data on the follow up period were obtained by checking the medical records in our hospital from July 1998 to October 2003, by sending a questionnaire to the patient's general practitioner and by checking the national database network and registry of histo- and cytopathology. We documented age at the time of presentation with the thrombosis. A DVT was considered to be secondary if there had been preceding trauma, surgery or immobility, in the presence of malignancy (previously known or discovered at the time of presentation with the DVT) or when the patient had a thrombophilic condition (factor V Leiden, factor II mutation or protein C/S deficiency). All other DVT were considered to be idiopathic.

We had intended to measure D-dimer levels daily for a period of at least four days after the start of anticoagulation therapy. The day of presentation was considered to be day 0. This study was, however, restricted to the first 57 patients, because in 1999, we lost the opportunity for this clinical follow-up and daily D-dimer measurements as a result of the decision to treat patients with deep vein thrombosis at home.

Statistics

As D-dimer values > 8000 μg/L FEU were not diluted, no linear comparison between the groups could be made. We have made clusters of D-dimer levels, with ranges of 0-2000, 2001-4000, 4001-6000 and >6000 μg/L FEU. We used Fisher's exact method with two-tailed *p*-values for comparisons between the clusters.

Results

From July 1998 to October 2001, 218 (102 men and 116 women) consecutive outpatients with proven deep vein thrombosis of the leg were included. Of these 218 patients, 50 (23%) had or developed cancer: 28 were already known to have cancer at the moment of thrombosis, 8 had cancer discovered at presentation with thrombosis and 14 developed malignancy during the follow-up (Table 1). The median follow-up was 34 months (range 4-54 months). In the 8 patients whose cancer was discovered at presentation, all but one had metastatic disease. In the 14 patients who developed cancer during follow-up, 3 had metastatic disease. The median time to the development of cancer in the latter 14 patients was 14 months (range 3-36 months). The prevalence of cancer in patients with deep vein thrombosis who had not previously been known to have cancer was 12% (22/190). The prevalence of cancer during follow-up was 8% (14/182). D-dimer levels were measured for 4 consecutive days after the start of anticoagulation in 57 patients with proven deep vein thrombosis. There was a significant decrease in D-dimer levels over time (*data not given*). Of these 57 patients, there were 12 (21%) patients with cancer: 6 were already known to have cancer, 2 had the cancer discovered at presentation and in 4

Table 1. Prevalence of malignancy in outpatients with cancer. Of the 50 patients with cancer, 28 were previously known to have cancer, 8 had cancer discovered at presentation with deep vein thrombosis and 14 developed cancer during the follow-up.

Type of cancer	*Previously known (n)*	*At presentation (n)*	*During follow-up*	*Total (n)*
Prostate	7	1	3	11
Non-Hodgkin's lymphoma	8	–	1	9
Colorectal	3	1	4	8
Other hematologic	4	–	–	4
Lung	3	1	1	5
Stomach	1	–	1	2
Pancreas	–	2	–	2
Breast	1	1	–	2
Ovarian	–	–	2	2
Other	1	2	2	5
Total	28	8	14	50

Table 2. Prevalence of cancer that developed during follow-up according to D-dimer concentrations at presentation and age in the total group of patients with deep vein thrombosis (A) and in 57 patients with D-dimer data after 4 days of treatment (B).

A.	*D-dimer concentration (μg/L FEU) at presentation*			
	Total	*< 4000*	*> 4000*	*p value*
Total group	8 (14/182)	4 (5/112)	13 (9/70)	0.048
≥ 60 years	16 (12/75)	13 (5/38)	19 (7/37)	0.5
< 60 years	2 (2/107)	0 (0/74)	6 (2/33)	0.03

B.	*D-dimer concentration (μg/L FEU) after 4 days of treatment*			
	Total	*< 4000*	*> 4000*	*p value*
Total group	8 (4/49)	5 (2/40)	22 (2/9)	0.1
≥ 60 years	17 (4/23)	14 (2/14)	22 (2/9)	0.6
< 60 years	0 (0/26)	0 (0/26)	0 (0/0)	1.0

Values are reported as percentage (n). The p-values indicate differences between the groups according to D-dimer levels.

Table 3. Prevalence of total cancer according to D-dimer concentrations and age in the total group of patients with deep vein thrombosis (A) and in 57 patients with D-dimer data after 4 days of treatment (B).

A.	*D-dimer concentration (μg/L FEU) at presentation*			
	Total	*< 4000*	*> 4000*	*p value*
Total group	23 (50/218)	16 (21/128)	32 (29/90)	0.009
≥ 60 years	38 (39/102)	37 (19/52)	40 (20/50)	0.8
< 60 years	9 (11/116)	3 (2/76)	23 (9/40)	0.001

B.	*D-dimer concentration (μg/L FEU) after 4 days of treatment*			
	Total	*< 4000*	*> 4000*	*p value*
Total group	21 (12/57)	14 (6/44)	46 (6/13)	0.02
≥ 60 years	34 (10/29)	33 (6/18)	36 (4/11)	0.6
< 60 years	7 (2/28)	0 (0/26)	100 (2/2)	0.003

Values are reported as percentage (n). The p-values indicate differences between the groups according to D-dimer levels.

patients cancer developed during the follow-up.

The prevalences of cancer that developed during follow-up are given in Table 2. High initial D-dimer levels were associated with more cancer during follow-up than were lower D-dimer levels: 13% versus 4% (p=0.048). This was especially true for younger patients. In the 14 patients who developed cancer in the follow-up period, 64% (9/14) had D-dimer levels >4000 μg/L and 36% (5/14) had D-dimer levels <4000 μg/L (p=0.3). This percentage of patients with high D-dimer levels was significantly higher than that among the patients did not develop cancer in the follow-up period: 36% (61/168) and 64% (107/168), respectively (p=0.048). High D-dimer levels after 4 days of treatment were associated with a 15% prevalence of cancer compared with a prevalence of 5% in patients with lower D-dimer levels; this was not statistically different.

Among patients with initial D-dimer levels of 0-2000 μg/L FEU, the total prevalence of cancer (including previously known cancer, cancer discovered at presentation and cancer that developed during follow-up) in the whole group was 12% (7/59), among those with levels between 2001-4000 μg/L FEU it was 20% (14/69), at levels 4001-6000 μg/L FEU the prevalence was 33% (9/27) and at levels >6000 μg/L FEU 32% (20/63). Comparing the lowest with the highest cluster, this difference was statistically significant (p=0.009). In the total group, the total prevalence of cancer in patients with a D-dimer <4000 μg/L FEU was lower than in patients with higher D-dimer levels: 16% versus 32% (p=0.005, RR=2.0) (Table 3). In patients older than 60 years, D-dimer levels did not discriminate between patients with or without cancer whereas a significant difference was found in younger patients (3% versus 23% (p=0.001, RR=8.6) (Table 3). The total prevalences of cancer in the 57 patients with D-dimer data after 4 days of treatment are given in Table 3, showing a higher total prevalence in patients with high D-dimer levels (p=0.02, RR=3.4).

The prevalence of cancer differed according to age (Table 4). The median age of patients with cancer was higher than that of patients without cancer: 68.0 years (range 30-88) versus 55.0 years (range 18-90) (p<0.001). Of the 50 patients with thrombosis and cancer, 78% (39/50) were over 60 years old. Of the 14 patients who developed cancer in the follow-up, 86% (12/14) were older than 60 years.

Table 4. Prevalence of cancer in patients with deep vein thrombosis according to age.

			Cancer prevalence					
	Total	*p value*	*Previously known*	*p value*	*At presentation*	*p value*	*During follow-up*	*p value*
Total	23 (50/218)		13 (28/218)		4 (8/190)		(14/182)	
≥ 60 years	38 (39/102)		23 (23/102)		5 (4/79)		16 (12/75)	
		0.000001		0.00007		0.7		0.001
< 60 years	10 (11/116)		4 (5/116)		4 (4/111)		2 (2/107)	

Values are reported in percentage (n). p-values indicate differences between the two age groups. "Previously known" indicates cancer that was known to be present before the thrombosis occurred. "At presentation" indicates cancer that was discovered at the time of the thrombosis. "During follow-up" indicates cancer that developed after the thrombosis.

Prevalences of cancer in patients with idiopathic or secondary DVT are shown in Table 5. During follow-up, more patients developed cancer in the idiopathic group than did in the secondary group: 12% versus 1%, respectively (p=0.009, RR 10). Subgroup analysis showed that initial D-dimer levels could not predict the development of cancer in either the idiopathic group or in the group with secondary DVT.

Table 5. Prevalence of cancer that developed during follow-up in patients with idiopathic or secondary deep vein thrombosis (A) and according to D-dimer levels (B).

A.	*Total cancers*	*Cancer in follow-up*	*p-value*
Total	23 (50/218)	8 (14/182)	
Idiopathic	12 (13/107)	12 (13/107)	0.009
Secondary	33 (37/111)	1 (1/75)	

B.	*D-dimer level (μg/L FEU)*		
	< 4000	*> 4000*	*p-value*
Total	4 (5/112)	13 (9/70)	0.048
Idiopathic	8 (5/63)	18 (8/44)	0.1
Secondary	0 (0/49)	4 (1/26)	0.2

Values are reported as percentage (n). p-values indicate differences between idiopathic and secondary thrombosis (A) and between D-dimer levels (B).

Discussion

The total prevalence of cancer in patients with thrombosis reported in literature varies from 7 to 26%[6-11] and corresponds well with the cancer prevalence of 23% in our study. Reports on the incidence of occult cancer in patients with idiopathic deep vein thrombosis vary from 3% to 26%.[9,26-28] So far, routine screening for cancer in every patient with deep vein thrombosis has not been recommended.[13] There are reports that patients with thrombosis have an increased risk of cancer. A recent report identified the presence of bilateral deep vein thrombosis as an independent predictive factor of cancer discovery with a hazard ratio of 6.28 compared with the risk in patients with unilateral DVT.[29] The risk of developing cancer in the first year after diagnosis of thrombosis is 3 to 7 times higher in patients with idiopathic thrombosis than in patients with secondary thrombosis[11,26,28,30] and our study confirms this.

This study shows that in patients with deep vein thrombosis, high D-dimer concentrations at presentation or during the first days of treatment are indicators of an increased chance of occult forms of cancer. We found that if the initial D-dimer concentration was >4000 μg/L FEU, the prevalence of cancer during follow-up was significantly higher than if the D-dimer levels <4000 μg/L FEU (13% versus 4%). Also, if the D-dimer levels after 4 days of treatment were still >4000 μg/L FEU, the prevalence of cancer during follow-up was significantly higher than if D-dimer levels were <4000 μg/L FEU: 46% versus 14%. Furthermore, the D-dimer levels were significantly higher in patients who developed cancer in the follow-up period than in patients who did not. This implies that the D-dimer concentration at presentation and after 4 days of treatment with oral anticoagulants can select patients who are at a higher risk of having cancer. Cushman *et al*. found no association of baseline D-dimer with the occurrence of cancer-associated venous thrombosis.[31] However, that study was conducted in asymptomatic patients with a high prevalence of normal D-dimer concentrations. They used quintiles and compared the lowest quintile (D-dimer 2-69 μg/L) with the highest quintile (278-7429 μg/L). In our study, performed in symptomatic patients with proven deep vein thrombosis, the D-dimer levels were all >500 μg/L. Another difference is that the comparison of D-dimers in our study was performed at the time of the thrombosis, and not in the periods before. In a smaller recent study, Rege *et*

al.[32] investigated initial D-dimer levels and the prevalence of cancer in patients with DVT. Only 3/81 patients developed cancer during follow-up and they all had D-dimer levels >1000 ng/mL (or >2000 μg/L FEU). They concluded that a low D-dimer concentration is a strong negative predictor for associated malignancy, although the majority of the cancers were diagnosed before the DVT.

We confirm the findings of Ranft *et al.*, who found that 71% of patients with deep vein thrombosis and occult cancer were over 60 years old.[8] In our study, 80% of the patients with thrombosis and cancer were older than 60 years and of the patients who developed cancer in the follow-up, 86% were older than 60 years. Similarly, in a recent study in patients with thrombosis, 21% of the patients over 60 years old developed cancer, compared to 5% of patients younger than 60 years old.[10] This shows that the chance of patients with deep vein thrombosis having cancer increases with age and this might be a stimulus to screen for occult malignancy in patients older than 60 years. In our study, D-dimer levels had no value in defining a subgroup of elderly patients with an increased prevalence of cancer. However, in younger patients, we found a significant difference in the prevalence of cancer when comparing those with D-dimer levels above and under 4000 μg/L: 23% versus 3%, respectively, for D-dimer levels at presentation and 100% versus 0%, respectively, for D-dimers at day 4 of treatment. Therefore, especially in younger patients with deep vein thrombosis, D-dimers might be useful as indicators for underlying malignancy. A possible explanation for this age-dependency may be the fact that D-dimer concentrations will frequently be elevated in the elderly due to co-morbidity and general vessel damage.[17;33-37]

Besides defining predicting factors for developing cancer after venous thrombosis, there is no consensus on what strategy to use for screening for occult malignancy. One randomized trial used an extensive screening procedure (including physical examination, ultrasound and CT-scan of the abdomen, gastroscopy, colonoscopy, occult fecal blood test, sputum cytology, tumor markers, mammography and Pap smear) and compared this strategy with no screening in a control group.[38] Although the extensive procedure was able to detect malignancies earlier and at an earlier stage (with a sensitivity of 90%), there was (at then) no effect on the prognosis. Another report used a limited screening procedure, including physical examination, laboratory testing, chest roentgenography, ultrasound of the abdomen, tumor markers and further testing according to abnormalities found by these former investigations. The authors found a sensitivity for detecting occult malignancy of approximately 50%.[28] These studies indicate that a routine clinical evaluation at the time of the thrombosis would not be sufficient to detect patients with a malignancy, that a limited screening procedure would detect only half of the patients with occult forms of cancer and that an extensive procedure would be required. However, as future randomized trials will be very difficult to perform as they are considered to be unethical, the optimal approach remains a matter of debate.

A limitation of this study is the fact that only a small proportion of patients had occult cancer, while for clinical practice only this group is relevant. Furthermore, this study has a retrospective design. Prospective studies with a larger number of patients are warranted to confirm the possible role of D-dimer in predicting occult forms of cancer in patients with venous thrombosis.

In conclusion, we found that patients, especially those under 60 years old, with deep vein thrombosis and a D-dimer concentration > 4000 μg/L at presentation and after 4 days of treatment are at higher risk of developing cancer. Cancer-related deep vein thrombosis most frequently occurs in patients older than 60 years. Idiopathic thrombosis is associated with a higher risk of occult malignancy than is secondary thrombosis. Our results argue for a larger study investigating cost-effectiveness of screening for a malignancy in patients older than 60 years and in patients younger than 60 years with initially high and/or persistently elevated D-dimer levels.

REGS, FJLMH, DHB, MMJB: conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, provision of study materials or patients, statistical expertise. Administrative, technical, or logistic support, collection and assembly of data. The authors declare that they have no potential conflicts of interest.

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