Paper IV

D-dimer measured at first venous thromboembolism is associated with future risk of cancer

Over a century has passed since a link between venous thromboembolism (VTE) and cancer was first established.[1] Since then, several studies have confirmed the two-way relationship between cancer and VTE.[2-4] The risk of cancer is highest in the first year following a VTE event, but persists for several years thereafter.[3,5] Coagulation, tumor development and progression are closely related.[2,6] Cancer cells interact with the hemostatic system, and tumor cells possess strong procoagulant properties that can induce local activation of the coagulation system.[7]

D-dimer is a fibrin degradation product, which results from the degradation of cross-linked fibrin by plasmin-induced fibrinolytic activity. Along with clinical parameters, D-dimer is a routine diagnostic tool in the initial assessment of suspected VTE, where low clinical probability and normal D-dimer levels are used to exclude VTE.[8] D-dimer levels can be elevated in malignancy, pregnancy, trauma, inflammation, heart disease or following surgery, thus making it a sensitive, yet non-specific marker of coagulation activation. Although increased D-dimer levels are independently associated with VTE and malignancy,[9] the link between markedly elevated D-dimer and the risk of subsequent cancer in patients with a first lifetime VTE has scarcely been investigated. Therefore, in a cohort of VTE patients recruited from the general population, we aimed to investigate the association between plasma D-dimer levels measured at incident VTE diagnosis and the risk of cancer within the subsequent two years.

All symptomatic VTE events (n=822) among participants of the Tromsø 1-6 surveys (source population: n=33 885) were included and followed up in the period from January 1, 1994 to December 31, 2012. A detailed description of the Tromsø study cohort has been published previously.[10] The VTE events were identified by examining the discharge registry, the autopsy registry and the radiology procedure registry at the University Hospital of North Norway, and thoroughly validated by a review of the medical records, as previously described.[11] Subjects with previous or active cancer (n=231), subjects hospitalized at the time of VTE (n=89) and subjects with missing D-dimer values (n=80) were excluded from the analysis. The study population ultimately counted 422 subjects with a first lifetime VTE event. D-dimer levels were measured as part of the diagnostic assessment of patients with suspected VTE, and a positive test was defined as a D-dimer value of >500 ng/ml fibrinogen equivalent units (FEU). All blood samples were analyzed at the Department of Clinical Chemistry at the University Hospital of North Norway, using the NycoCard D-Dimer (Nycomed Pharma, Oslo, Norway) assay from 1994-1998, and the STA®-Liatest® D-Di FM from Stago (Diagnostica Stago, Ansieres, France) from 1998-2012. Information regarding cancer diagnosis date, location and stage was obtained by linkage to the Cancer Registry of Norway.

Statistical analysis was carried out using STATA version 14.0 (Stata Corporation, College Station, TX, USA). Subjects were followed from the date of their first VTE until cancer diagnosis, death, migration, or two years after inclusion, whichever occurred first. D-dimer was analyzed as a categorical variable by dividing the study population into tertiles based on the distribution of D-dimer at the time of the VTE event (tertile 1: <2000 ng/ml, tertile 2: 2000-5000 ng/ml, tertile 3: >5000 ng/ml). Incidence rates (IRs) of cancer were calculated across the tertiles of D-dimer and expressed per 1000 person-years at risk. Cox proportional hazard regression was used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) for cancer within one and two years across the tertiles of D-dimer, using tertile 1 as the reference group. Mortality rates per 1000 person-years at one and two years following the VTE event were calculated across the D-dimer tertiles. One subject was diagnosed with cancer on the same day as the VTE event, and was included in the analysis with one day of follow-up. The Fine–Gray model was applied for sensitivity analysis to account for mortality as a competing event.[12] Competing risk regression is most often used when the occurrence of one event may alter the chance of another event occurring. Following a VTE, patients are at an increased risk of mortality, especially within the first year after diagnosis.[13] Thus, death could prevent an eventual cancer diagnosis. Traditional approaches (Cox proportional hazard regression and Kaplan-Meier) may overestimate the risk of disease, especially when considerable early mortality is present.[14]

Table 1. Characteristics at incident VTE according to tertiles of D-dimer.

	D-dimer tertiles		
	<2000 ng/mL (n=147)	2000-5000 ng/mL (n=135)	>5000 ng/mL (n=140)
Age	62.2±15.8	65.8±13.3	67.3±14.9
Sex (male)	42.2 (62)	58.5 (79)	48.6 (68)
Obesity*	19.1 (28)	19.4 (26)	14.3 (20)
Comorbidities**	17.1 (25)	17.0 (23)	21.4 (30)
Type of VTE			
DVT	57.8 (85)	58.5 (79)	53.6 (75)
PE	42.2 (62)	41.5 (56)	46.4 (65)
Provoked VTE***	34.7 (51)	41.5 (56)	42.9% (60)

*Values are numbers ±SD or percentages with numbers in parenthesis. *body mass index >30kg/m²; **comorbidities: a myocardial infarction or a stroke within 12 months preceding VTE, chronic obstructive pulmonary disease (COPD), myeloproliferative disorders, systemic lupus erythematosus (SLE), or chronic infection; ***provoking factors: recent surgery or trauma, acute medical conditions (acute myocardial infarction, ischemic stroke or major infectious disease), immobilization or any other factor described to be provoking in the medical record at the time of diagnosis. VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism.*

Of the 422 first lifetime VTE events, 239 were DVTs and 183 PEs. During a median follow-up of 4.7 years, 59 cancers were diagnosed. There were 28 cancer diagnoses within one year following a VTE diagnosis, and 34 within two years. Baseline characteristics across the tertiles of D-dimer are presented in Table 1. Subjects in the highest tertile of D-dimer were generally slightly older, less obese, and had a PE more frequently. D-dimer levels were higher in patients who developed cancer than those who did not. The curves of incidence rates of cancer separated early after the VTE diagnosis, and the two year cumulative incidence of cancer was 4.3% in tertile 1 of D-dimer, 6.9% in tertile 2 and 15.5% in tertile 3 (Figure 1). Incidence rates and hazard ratios for developing cancer within one and two years following a VTE by the tertiles of D-dimer are shown in Table 2. The one year risk of cancer was 1.6-fold (95% CI 0.5-5.0) higher in subjects in tertile 2, and 3.3-fold (95% CI 1.2-9.1) higher in subjects in tertile 3, when compared to the lowest D-dimer tertile. The risk persisted when extending the follow-up

period to two years in both tertile 2 (HR 1.6, 95% CI 0.6-4.5) and tertile 3 (HR 3.3, 95% CI 1.3-8.4). In patients who developed cancer within one year, the most common cancer sites were those of the lung (29%) and prostate (21%), and hematological cancers were (14%). The most common cancer sites diagnosed within two years of the incident VTE were the lung (27%), prostate (24%) and colorectal (15%) as well as hematological cancers (12%). Subjects in the highest D-dimer tertile who developed cancer within one year, typically had a more advanced cancer at the time of diagnosis. At the time of cancer diagnosis, 80% (8/10) of subjects in tertile 3 and 20% (1/5) in tertile 1 had some degree of metastasis (regional or distant). One and two year mortality rates were higher among subjects who had higher D-dimer levels at VTE diagnosis, in all study participants as well as in those who developed a subsequent cancer (Table 2). The risk (HR) of death during the first year after VTE with subsequent cancer development increased across the tertiles of plasma D-dimer, from 1.9-fold (95% CI 0.6-6.4) in tertile 2 to 5.7-fold (95% CI 2.0-16.5) in tertile 3 compared to tertile 1. The mortality rates (per 1000 person-years) in subjects who developed cancer were higher in tertile 3 (645, 95% CI 308-1351) than in tertile 1 (242, 95% CI 34-1721) or tertile 2 (153, 95% CI 22-1088). In patients who developed cancer within one year, the median time to death was 1020 days in tertile 1, 470 days in tertile 2 and 206 days in tertile 3. When taking the competing risk of death into account, the risk estimates for cancer remained essentially similar (Table 2).

Previous studies have reported a 2- to 4-fold higher risk of cancer within the first year after a VTE compared to the general population, and that the risk remained about 30% higher for several years following the event.[3-5] The relationship between D-dimer and occult cancer in VTE patients has not been extensively studied. Schutgens and colleagues found that high D-dimer levels at diagnosis, or during the first days of treatment for deep vein thrombosis (DVT), were associated with an increased probability of occult cancer.[15] In a retrospective study, Han and colleagues[16] investigated the role of D-dimer for the prediction of occult cancer in 169 patients with unprovoked VTE, of which 24 developed a subsequent cancer during a median of 5.3 years of follow-up. They found that D-dimer >4000 mg/ml was associated with occult cancer (HR 4.12, 95% CI 1.54-11.04). Even though the study was performed in a Korean population with a non-Western cancer site distribution, and had a strikingly low age at VTE and cancer diagnosis, the risk estimates for cancer were comparable to those in our study.

Fibrin formation is necessary for tumor growth, spread and tumor-induced angiogenesis, and fibrin degradation products possess potent angiogenic properties.[6,17] As a degradation product of cross-linked fibrin, D-dimer is a global marker of the activation of the coagulation and fibrinolytic systems. Our study showed that high D-dimer levels at incident VTE diagnosis were associated with a 3.3-fold higher risk of developing cancer.

Increased D-dimer levels are associated with mortality independent of VTE,[18] and studies have found that D-dimer is a predictor of progression and poor survival in various cancers.[9,19,20] We found that subjects in the highest D-dimer tertile had more advanced cancers at the time of diagnosis, with 80% having some degree of cancer spread of which 75% had disseminated metastases. We

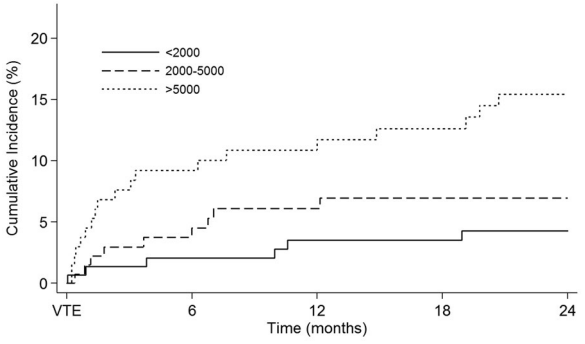

Figure 1. Cumulative incidence of cancer within two years following incident venous thromboembolism (VTE) by tertiles of D-dimer at incident VTE.

Table 2. Incidence rates (IR), hazard ratios (HR) and competing risk by death (SHR) for cancer and mortality rates (MTR) at one and two years following an incident venous thromboembolism (VTE) according to tertiles of D-dimer.

	D-dimer tertiles		
	<2000 ng/mL (n=147)	2000-5000 ng/mL (n=135)	>5000 ng/mL (n=140)
1 Year			
Events	5	8	15
IR (95% CI)	36 (15-87)	66 (33-131)	134 (81-222)
HR (95% CI)*	1.0	1.63 (0.53-5.02)	3.28 (1.18-9.12)
SHR (95% CI)*	1.0	1.62 (0.50-5.21)	3.07 (1.05-8.96)
1 year deaths (n)	4	8	23
1 year MTR (95% CI)	28 (11-76)	63 (32-127)	192 (128-290)
1 year deaths in cancer (n)	1	1	7
1 year MTR (95% CI)	242 (34-1721)	153 (22-1088)	645 (308-1351)
2 Year			
Events	6	9	19
IR (95% CI)	23 (10-50)	39 (21-76)	92 (59-145)
HR (95% CI)*	1.0	1.76 (0.58-4.47)	3.39 (1.34-8.56)
SHR (95% CI)*	1.0	1.45 (0.50-4.24)	3.15 (1.19-8.30)
2 year deaths (n)	8	13	28
2 year MTR (95% CI)	29 (15-59)	55 (32-94)	126 (87-183)
2 year deaths in cancer (n)	2	4	9
2 year MTR (95% CI)	218 (54-870)	315 (128-910)	445 (223-890)

*Incidence and mortality rates per 1000 person years, *age and sex adjusted. CI: confidence interval.*

also found that high D-dimer levels in subjects with cancer were associated with a higher risk of one year mortality. Previous studies have shown that the relative risk and cumulative incidence of VTE is overestimated in cancer patients due to a high mortality rate in these patients.[14] In the present study, however, the risk estimates were essentially unchanged when competing risk of death was taken into account. This is likely explained by the short duration of follow-up, and that both high D-dimer levels and cancer are associated with death.

The limitations of our study include the lack of statistical power to evaluate the risk of cancer by subgroups of provoked and unprovoked VTE. Moreover, two different assays were used to measure D-dimer. However, the majority of VTE events (390/422) occurred during the period that the STA®-Liatest® D-Di FM assay was used (from 1998-2012), and our risk estimates remained essentially unchanged in a sensitivity analysis restricted to these patients (*data not shown*).

In conclusion, D-dimer >5000 ng/ml at incident VTE is associated with a higher risk of subsequent cancer within one and two years. High D-dimer levels are also associated with more aggressive tumor biology and poor prognosis in these patients. As D-dimer is routinely measured in the assessment of suspected VTE, it may be a useful surrogate marker for the presence of an underlying malignancy. Our findings may suggest that high plasma D-dimer at incident VTE diagnosis should be taken into consideration when the decision to screen for underlying cancer is made.

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