



Predictive factors for cancer-associated thrombosis in a large retrospective single-center study

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Abstract

Background The relationship between cancer and thrombosis has been studied for years, but reliable guidelines for thromboprophylaxis in that situation are still unclear.

Methods We retrospectively reviewed the files of 3159 consecutive patients with newly diagnosed solid tumors at Jules Bordet Institute from January 2008 to December 2011. Among them, 99 developed a symptomatic thromboembolic episode and were matched with 2 controls (nested case control). The aim was to identify risk factors of thromboembolic events and to validate in our setting the Khorana score.

Results In the cohort study, nodal status ≥ 2 , presence of metastases, and primary tumor site were found to be the most significant predictive factors of a thromboembolic event ($n = 99$; 3.1%) in the multivariate analysis. In the nested study ($n = 265$), hemoglobin < 13 g/dL or treatment with a red cell growth factor, CRP ≥ 31.6 mg/L, creatinine level > 0.96 mg/dL, chronic inflammatory disease, and personal or familial history of thromboembolic events were found to be the most significant predictive factors of a thromboembolic event in the multivariate analysis. In our population, the sensitivity, specificity, positive predictive value, and negative predictive value of the Khorana score were respectively 29%, 93%, 15%, and 96%.

Conclusion We confirm the value of the risk factors identified in the literature with the additional presence of nodal involvement, elevated CRP, and creatinine levels, which may be helpful for patient risk stratification and should be considered in future clinical trials. Our results also suggest that the Khorana score might help to identify patients who can safely be spared of thromboprophylaxis.

Keywords Venous thromboembolic events · Thromboprophylaxis · Cancer · Cohort study · Risk factors

Introduction

The relationship between cancer and thrombosis has been studied for many years [1]. Indeed, cancer is associated with a hypercoagulable state [2]. Three main mechanisms are involved, i.e., tumor production of procoagulants, tumor production of inflammatory cytokines, and the interaction between tumor cells and various blood and

endothelial cells, and enhanced by anticancer therapy [3]. As a result, studies showed an increased risk of developing a venous thromboembolic event (VTE) (e.g., deep venous thrombosis and pulmonary embolism) in cancer patients [2]. VTE is a frequent cause of death in cancer patients along with infections and is associated with significant morbidity and mortality [4, 5]. The magnitude of the risk depends on the cancer type and its extension (local disease vs metastatic disease) on the ongoing treatment (e.g., surgery, radiotherapy, chemotherapy, hormonotherapy, or targeted therapies, mainly antiangiogenic agents) [5]. The incidence of reported VTE is currently increasing probably because of improved treatment outcomes and longer patient survival, prothrombotic treatment regimens, and better diagnosis thanks to improved imaging techniques [6]. Appropriate prophylaxis of VTE is a crucial issue for both patient's safety and survival.

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Primary prophylaxis is thus not recommended routinely [7–9] but may be indicated in patients with locally advanced or metastatic solid tumor with a high TE risk [9, 10].

The Khorana predictive model to assess the risk of chemotherapy-associated VTE has been developed and validated in an ambulatory setting [11]. This model uses five simple parameters, each one accounting for 1 or 2 points: site of cancer, platelet count, hemoglobin or use of erythropoietin-stimulating agents (ESA), leukocyte count, and BMI (Table 1). A total of 3 or more points is considered to define high risk, 1 or 2 points intermediate risk, and 0 point low risk. High risk corresponds actually to 6.7% risk to develop a VTE [11]. In clinical practice, the score is helpful but it has not been validated in hospitalized cancer patients. The present study aims to validate the Khorana score in a mixed population of cancer patients (both hospitalized and ambulatory) by evaluating a retrospective cohort of patients treated at Jules Bordet Institute between 2008 and 2011 for a newly diagnosed solid tumor and identify VTE risk factors in that population. The study was approved by Jules Bordet Institute Ethics committee.

Methods

Study population

We retrospectively reviewed the files of 3159 consecutive patients with a newly diagnosed invasive solid tumor who were completely treated for the primary episode at the Jules Bordet Institute from January 2008 to December 2011 and were recorded in the hospital registry. Eligible patients needed to have been followed at least 3 years after the diagnosis of cancer. TE events were evaluated during these 3 years. Patients who died within 3 years were included in this retrospective study.

A VTE was defined as a deep venous thrombosis and/or a pulmonary embolism. Diagnostic imaging used to confirm VTE included Doppler ultrasonography, pulmonary ventilation-perfusion scan, and computed tomography (CT) angiography. Four groups were distinguished according to the associated VTE risk (Table 2): high risk (9–50%),

intermediate risk (4–6%), low risk (2–2.5%), and very low risk (<2%).

Eight items were particularly studied: TNM staging, solid tumor diagnosis and origin, presence or absence of metastases and their location, systemic therapy, age, gender, and tobacco consumption at baseline. Baseline laboratory data were also analyzed.

In a second step, a nested case control was performed; cases of VTE events were matched with 2 controls for age, gender, tumor type, and presence or absence of metastases. One control only could be found for 14 cases and no control for 6 cases, resulting in a dataset of 265 cases and controls. A list of 23 known VTE risk factors based on a literature review [8, 12] were collected for all cases and control (see Appendix Table 7). Laboratory data at the time of the VTE were also collected: hemoglobin, treatment with a red cell growth factor, platelets, leukocytes, creatinine, urea, PTT, APTT, CRP. Threshold values were selected according to the Khorana score based on the Jules Bordet Institute laboratory standards. The medical records of controls were reviewed in the same time frame compared to the initial cancer diagnosis as the matched case.

To validate the Khorana score, tumors were categorized according to their localization (Table 1) and patients' files were reviewed for information not routinely recorded in the registry: use of ESA and body mass index (BMI).

Statistics

In the first part of the study, risk factors of venous thromboembolism were first identified by univariate analysis using the chi-squared test for categorical variables and the *t* test for continuous variables. Variables significantly associated with VTE in the univariate analysis were then introduced into a stepwise logistic regression model to estimate odds ratios (OR) with a 95% confidence interval and to assess their significance.

In the nested case-control study, in order to obtain unbiased relative risk estimates from nested case-control analyses, we used the incidence density sampling program previously reported by Richardson DB and others [13]. Conditional logistic regression models were used to analyze the relationship

Table 1 Khorana's score

Characteristics	Points
Very high-risk primary cancer type: stomach, pancreas, brain	2
High-risk primary cancer type: lung, lymphoma, gynecologic, bladder, testicular, renal	1
Prechemotherapy platelet count at least 350,000/ μ L	1
Hemoglobin level less than 10 g/dL or on treatment with a red cell growth factor	1
Prechemotherapy leukocyte count greater than 11,000/ μ L	1
Body mass index ≥ 35 kg/m ²	1
High risk: score ≥ 3	

Table 2 VTE risk groups according to the tumor type

VTE risk	Primary cancer type	VTE
High risk	Pancreas, peritoneum, retroperitoneum connective tissue	9–50%
Intermediate risk	Esophagus, stomach, duodenum, colorectal, lung, gynecologic	4–6%
Low risk	Breast, head, and neck	2–2.5%
Very low risk		<2%

between potential risk factors and VTE. Findings are presented as a hazard ratio with a 95% interval confidence.

The Khorana score's predictive performances in the patients treated with chemotherapy or hormonotherapy regardless of the ambulatory or hospitalized status were assessed using classical parameters, including sensitivity (Se), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV) tabulated from a classical 2×2 table with the aim to determine the ability of the score to predict a VTE in this population.

Results

Patient's characteristics

A total of 3159 patients were included; some of their important characteristics are shown in Table 3. The most frequent primary sites were the following: breast ($n = 1119$), lung ($n = 394$), prostate ($n = 367$), colorectal ($n = 183$), and gynecologic ($n = 133$). 17.8% of the patients presented with metastases at diagnosis. Symptomatic VTE occurred in 99 patients (3.1%). Ninety-two patients died within 3 years of the diagnosis and 5 of them presented a VTE within this time frame. The characteristics of these patients at the time of the VTE are reported in Table 4. It should be pointed that in 57% of the cases, cancer

disease was metastatic at the time of the VTE and that 57% of the patients were women; the most frequent were lung and breast cancers. Seventy-one percent of the patients were hospitalized while 29% were ambulatory at the time of the VTE.

Cohort study—risk factors for VTE

In the univariate analysis, the presence of metastases at cancer diagnosis ($p < 0.0001$), T and N status ≥ 2 (0.041 and $p < 0.0001$ respectively), chemotherapy treatment ($p < 0.0001$), and the primary tumor site ($p < 0.0001$) were associated with a significant risk for TE event (Table 5).

All these factors were entered in a stepwise logistic regression analysis. N status (clinical, pathological, or yet treated) ≥ 2 , presence of metastases, and the primary tumor site (high-risk group) (Table 2) were found to be the most significant predictive factors of a VTE event in the multivariate analysis and remained in the final model (Table 5). The area under the ROC curve for this model is 0.75.

Results from the nested case-control study

In the univariate analysis, hemoglobin level < 13 g/dL or treatment with a ESA, hemoglobin level < 10 g/dL, the leukocyte count $> 11,000/\text{mm}^3$, CRP ≥ 31.6 mg/L, creatinine level > 0.96 mg/dL, blood transfusion, the presence of a central venous device, a personal or familial history of VTE, recent hospitalization, and acute disease (≤ 1 month) were associated with the occurrence of a VTE ($n = 265$) (Table 6). Seven out of 99 patients with VTE were treated with tamoxifen as compared to 428 without VTE. The difference between those 2 groups was not statistically significant (OR 0.7, $p = 0.49$).

After entering all these factors (except hemoglobin > 10 g/dL) in a logistic regression analysis, the best model was derived using an effect selection method based on the highest likelihood score (chi-square). The model identifies 5 factors in the multivariate analysis: hemoglobin level < 13 g/dL or treatment with ESA, CRP ≥ 31.6 mg/L, creatinine level > 0.96 mg/dL, chronic inflammatory disease, and personal or familial history of VTE (Table 6). All types of chronic inflammatory diseases were reviewed in this study. The most frequent reported inflammatory disease were BPCO, viral hepatitis, Behcet's disease, gout, sclerodermia, psoriasis, and rheumatoid polyarthritis.

Table 3 Patients' characteristics at the cancer diagnosis

Patients' characteristics ($n = 3159$)	<i>N</i> (%)
Primary location	
Breast	1119 (49.6)
Lung	394 (17.5)
Upper digestive tract	110 (4.9)
Colon-rectum-anus	183 (8.1)
Prostate	367 (11.6)
Gynecologic	133 (5.9)
Others	853 (27.0)
Age (years)	
≥ 65	1281 (40.6%)
< 65	1878 (59.4%)
Extension	
Synchronous metastasis	670 (21.3%)
No metastasis at the initial diagnosis	2469 (78.7%)

Table 4 Patients' characteristics at the time of the VTE ($n = 99$)

	Value	
Gender, n (%)		
Women	56 (57%)	
Men	43 (43%)	
Setting, n (%)		
Localized	43 (43%)	
Metastatic	56 (57%)	
Variables, n (%)		
Central venous catheter	45 (47%)	
Hospitalization < 4 weeks	50 (51%)	
Hypertension	35 (35%)	
Diabetes	12 (12%)	
Personal or family history of VTE	13 (13%)	
Hypercholesterolemia	20 (20%)	
Tumor type, n (%)		
Lung	24	
Breast	22	
Pancreas	10	
Colorectal	10	
Stomach, small intestine	5	
Gynecologic	7	
Others	21	
BMI (kg/m^2), n (%)		
< 18.5	13 (13%)	
≥ 30	13 (13%)	
Treatment at the time of TE, n (%)		
Chemotherapy	61 (62%)	
Hormonotherapy	11 (11%)	
Surgery	20 (20%)	
Radiotherapy	11 (11%)	
Treatment with a red cell growth factor	10 (10%)	
Transfusion	15 (15%)	
Median (standard deviation)—lab tests	Reference interval	
Platelets ($/\text{mm}^3$)	150,000–440,000	303.85 (136.2)
Hemoglobin (g/dL)	12.0–16.0	11.4 (1.8)
Leukocytes ($/\text{mm}^3$)	3500–11,000	9.00 (5.5)
APTT (s)	18.7–32.1	27.3 (6.4)
PTT (%)	70–100	83.2 (12.1)
CRP (mg/L)	< 10	56.2 (72.4)
Urea (mg/dL)	13–40	33.5 (14.4)
Creatinine (mg/dL)	0.50–0.90	0.8 (0.274)

Khorana's score

Finally, we computed the Khorana score in both hospitalized and non-hospitalized patients treated with chemotherapy or hormonotherapy to evaluate its usefulness to predict a VTE

in this population ($n = 2206$). Only 1814/2206 patients were fully assessable because of missing data. Patients with scores of 0–3 were considered to have low risk of VTE, and patients with scores > 3 were considered to have high probability of VTE. The sensitivity, specificity, positive predictive value, and negative predictive value were respectively 29.3% (95% CI 19.7–41.1), 92.8% (95% CI 91.5–94.0), 15.0% (95% CI 9.8–22.0), and 96.8% (95% CI 95.8–97.6). Contingency table is provided in Appendix Table 8.

Discussion

We identified in our study possible VTE risk factors which are important in cancer patients and the *incidence of VTE in our study population (3.1%) over a 3-year follow-up*. Our multivariate analysis identified 3 independent risk factors for VTE in the cohort study, i.e., N status ≥ 2 , the presence of metastases, and the primary tumor site (pancreas, peritoneum, retroperitoneum, connective tissue), as well as 5 independent factors in the nested study, i.e., hemoglobin level < 13 g/dL or treatment with an ESA, CRP ≥ 31.6 mg/L, creatinine level > 0.96 mg/dL, inflammatory chronic disease, and a personal or familial history of VTE. We also tried to identify which patients might possibly benefit from a primary prevention strategy using the Khorana score.

The VTE incidence in the present study is similar to what is reported in the literature; in a large unselected cohort of patients ($n = 27,479$) with cancer, the overall risk for VTE after chemotherapy initiation was 7.3% at 3.5 months and an estimated risk of 13.5% 1 year after starting chemotherapy [14]. Blom et al. reported a 3% VTE incidence in the year preceding the diagnosis of cancer or after the diagnosis of cancer among 66,329 patients [15].

Many of the risk factors identified in our analysis correspond to what is described in the literature [12, 14, 15]. Our multivariate analysis identified 3 independent risk factors of VTE: presence of metastases, high-risk primary tumor site (pancreas, peritoneum, retroperitoneum, connective tissue), and the N status ≥ 2 (based on clinical, pathological or yet treated TNM depending on the available data). The remaining missing data are due to the retrospective nature of this review.

In Blom's series, metastatic patients were also more likely to have a VTE than those with local disease [15, 16]. As far as the primary tumor site is concerned, in a large retrospective cohort of nearly 30,000 unselected cancer patients undergoing chemotherapy, Lyman et al. found that the highest VTE risk was identified in patients with pancreatic, stomach, and lung cancer [14].

To our knowledge, the nodal status has not been described previously as a risk factor for VTE; our findings suggest that the biological aggressiveness of the tumor (translated in

Table 5 Risk factors for thromboembolic event in the cohort study

Patients' characteristics	Absence of VTE (<i>n</i> = 3060)	VTE (<i>n</i> = 99)		Univariate analysis		Multivariate analysis (stepwise selection)	
		<i>n</i>	<i>N</i> (%)	%	OR (95% CI)	<i>p</i>	Adjusted OR (95% CI)
Gender							
Men	1211	43	(3.4)	1			
Women	1849	56	(2.4)	0.85 (0.57–1.28)	0.44		
Age							
< 65	1820	58	(3.1)	1			
≥ 65	1240	41	(3.2)	1.04 (0.769–1.56)	0.86		
Tobacco							
Smoker	1029	36	(3.4)	1			
Non-smoker	858	32	(3.6)	1.07 (0.66–1.73)	0.76		
Primary tumor site							
High risk	146	17	(10.4)			7.93 (3.17–19.81)	< 0.0001
Intermediate risk	774	46	(5.6)			2.54 (1.11–5.83)	
Low risk	1248	26	(2.0)			1.81 (0.80–4.09)	
Very low risk	892	10	(1.1)			1	
Metastatic disease							
Yes	614	56	(8.4)	5.1 (3.4–7.7)	< 0.0001	2.96 (1.79–4.90)	< 0.0001
No	2426	43	(1.7)			1	
Metastatic location							
Brain	112	10	(8.2)	2.96 (1.50–5.84)	0.0043		
Liver	204	26	(11.3)	4.99 (3.12–7.98)	< 0.0001		
Lung	177	17	(8.8)	3.38 (1.96–5.82)	< 0.0001		
Bone	278	15	(5.1)	1.79 (1.02–3.14)	0.041		
T status							
< 2	1118	22	(2.0)	1			
≥ 2	1415	55	53 (3.9)	1.98 (1.20–3.30)	0.0067		
Non-evaluable	527	22					
N status							
< 2	2481	55	(2.2)	1		2.79 (1.68–4.61)	< 0.0001
≥ 2	416	35	(8.4)	3.80 (2.45–5.87)	< 0.0001	1	
Non-evaluable	163	9					
Chemotherapy							
Yes	1212	15*	(1.22)				
No	1932	0					

*VTE within 1 month of a chemotherapy administration

regional positive lymph nodes) might be an important risk factor associated with development of VTE.

We did not observe an association between age and VTE in this study. However, other studies indicated that VTE, was more frequent in patients aged 65 years or above [17].

In the nested case-control study, we highlighted other risk factors in accordance with the current literature. Our multivariate analysis identified 5 independent biological and clinical risk factors: hemoglobin level < 13 g/dL or treatment with an ESA, CRP ≥ 31.6 mg/L, creatinine level > 0.96 mg/dL, inflammatory chronic disease, and a personal or familial history of VTE event. C-reactive protein is a known marker of the inflammatory status of the patient,

and it has been previously demonstrated that the presence of an inflammatory disease (e.g., cancer) significantly influenced plasma CRP [18, 19]. Exact cause-effect relationship sequence has not yet been established, and to our knowledge, CRP alone failed to demonstrate that it predicts a future VTE or is useful in the diagnosis of VTE [20]. Association of elevated CRP with other identified risk factors might be more useful for this purpose.

Previous studies reported that chronic kidney disease is associated with an increased risk of (VTE) [21, 22]. This might explain why cancer patients with increased plasma creatinine levels were at higher risk of developing a VTE in this study.

Table 6 Risk factors for thromboembolic event in the nested case-control study

Patients' characteristic nested cohort (<i>n</i> = 265)	Univariate analysis		Multivariate analysis (stepwise selection)	
	OR (95% CI)		Adjusted OR (95% CI)	
Hg < 13 g/dL or treatment with a red cell growth factor	3.43 (1.72–7.45)	0.0009	4.20 (1.48–14.51)	0.012
Hg < 13 g/dL	4.8 (2.21–12.0)	0.0002		
Hg < 10 g/dL	3.59 (1.74–7.97)	0.0009		
Leukocytes > 11,000/mm ³	2.73 (1.31–5.97)	0.0087		
CRP ≥ 31.6 mg/L	4.40 (2.30–9.11)	< 0.0001	4.61 (2.14–11.02)	0.0002
CRP ≥ 10 mg/L	3.70 (1.99–7.42)	< 0.0001		
Creatinine > 0.96 mg/dL	2.44 (1.15–5.39)	0.022	3.69 (1.35–11.14)	0.014
Urea/creatinine > 60	2.11 (0.97–4.66)	0.06		
Transfusion	4.85 (1.84–15.1)	0.0026		
Central venous device	2.13 (1.10–4.28)	0.028		
Personal or familial TE history	3.24 (1.30–8.76)	0.014	4.90 (1.28–23.84)	0.029
Recent hospitalization < 1 month	2.78 (1.61–4.97)	0.0003		
Acute disease < 1 month	3.42 (1.07–12.91)	0.047		
Chronic inflammatory disease	2.54 (1.07–7.0)	0.049	3.76 (1.22–14.21)	0.032

In the last part of the study, we applied the Khorana risk score to the 1814 evaluable patients treated with chemotherapy or hormonotherapy regardless of the ambulatory or hospitalized status with the aim to determine the ability of the score to predict a VTE in this population. In the development cohort, the model had a NPV of 96.8%, PPV of 15%, a sensitivity of 29.3%, and a specificity of 92.8%. The good NPV observed in our cohort (96.8%) was similar to the one found in the Khorana study, but PPV of 15% was disappointing [11]. In a retrospective study, performed by Mansfield et al. in 719 patients with lung cancer, the Khorana score did not predict the patients at the highest risk of VTE [23].

These results suggest that if Khorana's score might identify patients with a very low probability of VTE, its sensitivity is low as well as the PPV; thus, the Khorana score should probably not be used to select patients for primary thromboprophylaxis, but might help to identify very low-risk patients of VTE and who would safely be spared of prophylaxis. Another predictive model based on the risk factors identified in our study may be useful to complete the Khorana score for thromboprophylaxis indication. Indeed, other predictive models have been developed and validated. As an example, the retrospective study by Verso and colleagues evaluated a modified Khorana's risk assessment score, named the Protecht score, which is adding platinum- or gemcitabine-based chemotherapy to the predictive model, and in fact, it showed an improved ability to identify patients at high risk for VTE [24]. In addition, Kuderer et al. showed recently in 4405 patients that Khorana's

score was predictive of early mortality and cancer progression [25]. So, the development of VTE in patients with cancer could interfere with the patient outcome.

Conclusion

Our study confirms the value of the risk factors identified in the literature; in addition, we identified a significant risk of TE in the presence of regional nodal involvement of the primary tumors, elevated CRP, and/or creatinine levels.

Among patients with cancer, VTE risk factors should be used as predictors for thromboprophylaxis. The Khorana score is probably not optimal as a decision tool for primary prevention strategy but might help to identify the patients who can safely be spared of thromboprophylaxis. Our results may add useful information about the risk of VTE related to cancer and be helpful in clinical decision-making for specific clinical and biological conditions and patient risk stratification in future clinical trials.

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Compliance with ethical standards

The study was approved by Jules Bordet Institute Ethics Committee.

Conflict of interest The authors declare that they have no conflict of interest.

Appendix

Table 7 Known venous thromboembolism risk factors collected for the nested cohort study

Mobility
Acute disease < 1 month
BMI ≥ 25
Gender
Surgery < 1 month
Menopausal status
Hospitalization
Central venous device
Red blood cell transfusion
Erythropoietin treatment
Antiangiogenic treatment
Radiotherapy
Chemotherapy
Chronic inflammatory disease
History of TE event
Hypertension
Diabetes
Hypercholesterolemia
Recent trauma
Hormonotherapy
Postpartum
Pregnancy
Thrombophilia

For CRP, we used a cutoff corresponding to the percentile 66 of its distribution in the cohort

Table 8 Contingency table for the Khorana score

Khorana score	Thromboembolic event		Total
	Yes	No	
High risk	123	22	145
Low risk	1616	53	1669
Total	1739	75	1814

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