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The Application of Current Proposed Venous Thromboembolism Risk Assessment Model for Ambulatory Patients With Cancer

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Abstract

Venous thromboembolism (VTE) is a commonly encountered problem in patients with cancer. In recent years, cancer treatment paradigm has shifted with most therapy offered in ambulatory outpatient settings. Excess of half VTEs in patients with cancer occur in outpatient settings without prior hospitalization, where current practice guidelines do not recommend routine prophylaxis. Risk assessment models (RAMs) for VTE in such patients were recently introduced. This study aims to assess the practical application of one of these models in clinical practice. Medical records and hospital electronic database were searched for patients with cancer having VTE. Known risk factors were collected, and risk assessment was done using the Khorana RAM. Over a 10-year period, 346 patients developed VTE in ambulatory settings. Median age was 57 and 59.0% were females. Lower extremities were involved in 196 (56.6%), while 96 (27.7%) had pulmonary embolism. Most (76.6%) patients had stage IV disease, only 9.0% had stage I or II disease. Only 156 (45.1%) patients were on active chemotherapy, for whom Khorana risk assessment score was calculated. In these patients, high risk was identified in 31 (19.9%) patients, while 81 (51.9%) had intermediate risk and 44 (28.2%) had low risk. No patients were on prophylaxis prior to VTE. Most ambulatory patients with cancer who developed VTE were not on chemotherapy, and many of those who were on active treatment had low Khorana risk scores. This illustrates the need to modify the model or develop a new one that takes into consideration this group of patients.

Keywords

deep venous thrombosis, thrombosis prophylaxis, venous thromboembolism, cancer

Introduction

Venous and, to a lesser extent, arterial thrombosis are common complications encountered in patients with cancer during the course of their treatment and follow-up.[1,2] Patients with cancer are at a much higher risk of thrombosis compared to patients without a malignancy due to many factors including the biology of cancer itself, surgeries and invasive procedures, and chemotherapy and associated complications, in addition to many other patient-related factors and comorbidities.[3,4]

Venous thromboembolism (VTE) is one of the leading causes of death in patients with cancer.[5] Many studies have also shown that survival of patients with cancer having VTE is significantly lower compared to that of patients without a VTE.[6-8] Much of the emphasis of the literature has been on VTE in patients with cancer who are hospitalized for surgical interventions or acute medical illnesses[9-11]; VTE prophylaxis for such patients is strongly endorsed by many international guidelines.[12-14] Such interventions are commonly prescribed and routinely practiced.

Cancer treatments paradigm, however, has shifted with a majority of cancer therapies currently being offered in outpatient settings. Despite this "ambulatory" cancer therapy, patients continue to have many cancer-related, treatment-related, or patient-related factors that increase their risk of VTE.[15,16] Current clinical practice guidelines do not recommend routine prophylaxis for such patients, even if receiving active chemotherapy.[12-14,17]

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Table 1. Khorana Risk Assessment Model.[a]

Patient Characteristic	Risk Score
1. Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
2. Prechemotherapy platelet count 350 $\times$ 10^9/L or more	1
3. Hemoglobin level less than 100 g/L or use of red cell growth factors	1
4. Prechemotherapy leukocyte count more than 11 $\times$ 10^9/L	1
5. BMI: 35 kg/m^2 or more	1

Abbreviation: BMI, body mass index.
[a]Risk groups: low risk = 0, intermediate risk = 1-2, high risk $\geq$ 3.

Khorana et al proposed a risk assessment model (RAM) for VTE prophylaxis for ambulatory patients with cancer receiving active chemotherapy. The model was derived from a cohort of 2701 patients with cancer and validated on an independent cohort of 1365 patients.[18]

The Khorana score is calculated by assigning points for clinical parameters that are usually available for the treating physicians. Five predictive variables were identified in a multivariate analysis model: site of primary cancer, platelet count, hemoglobin level and/or use of erythropoiesis-stimulating agents, leukocyte count, and body mass index (Table 1). Patients were stratified according to the calculated score into 3 risk groups to predict the risk of developing a VTE. The cumulative incidence of VTE at 2.5 months in the derivation and validation cohorts was 0.3% to 0.8%, 1.8% to 2.0%, and 6.7% to 7.1% in the low- intermediate-, and high-risk (score $\geq$3) categories, respectively.

Our current retrospective analysis attempts to highlight the clinical features of VTE among a group of ambulatory patients with cancer who developed thrombosis during the course of their cancer treatment and follow-up. It also assesses the practical application and predictive accuracy of Khorana RAM in routine clinical practice in a tertiary care cancer center.

Patients and Methods

Medical records and electronic hospital database, including all radiology reports, were searched for patients with cancer having a diagnosis of pulmonary embolism (PE) or venous thrombosis at any site. Following the initial phase of retrospective data collection, we established a database that is updated regularly with patient-related, disease-related, and treatment-related clinical variables. This includes, but is not limited to, patients' age, gender, comorbidities, primary cancer type, stage, type of anticancer therapies (surgery, chemotherapy, hormonal therapy, and/or radiation therapy) in addition to treatment outcomes. Known risk factors for VTE were also reviewed and recorded as were data on anticoagulant therapy including type, duration, and associated complications.

Ambulatory VTE was defined as any venous thromboembolic episode that occurred beyond 30 days of prior hospitalization and includes upper and lower extremity deep vein thrombosis (DVT) and symptomatic or asymptomatic PE. The subgroup of patients who were eligible for the Khorana RAM scoring was identified, and patients who were more than 18 years of age and about to start chemotherapy were included . Patients with arterial thrombosis were excluded.

Following the identification of the target population, VTE risk assessment using the Khorana RAM (Table 1) was performed. Clinical variables needed to calculate VTE risk score were collected just before the start of chemotherapy in patients receiving chemotherapy or the same day VTE was diagnosed in patients who were not. These data included the primary tumor site, body mass index, white blood cell, hemoglobin, and platelet counts. According to these variables, patients were grouped into 3 risk categories: low risk (score 0), intermediate risk (score 1-2), and high risk (score $\geq$3).

Statistical Analysis

Descriptive statistics were performed for all variables. Results for continuous variables are expressed as median (interquartile range). Categorical variables are expressed as numbers (percentage). All statistical analyses were carried out using SAS software (version 9.4; SAS Institute Inc, Cary, North Carolina).

Results

Our current VTE database has a total of 615 patients; all were diagnosed, treated, and followed at our institution. Three-hundred forty-six patients (56.3%) developed VTE while in ambulatory settings as defined above and will be the focus of this report and all upcoming results and discussion. The median age at VTE diagnosis for this group was 57 years (range: 18-86), and 204 (59.0%) of the patients were females.

Breast, colorectal, lung, gastric, brain, and pancreas were the most common primary cancer sites encountered. Majority (239; 76.4%) of the 313 patients with stageable disease, using the Tumor size, Node, Metastasis (TNM) staging system, had stage IV disease, while only 28 (9.0%) patients had stage I or II disease. Thirty-three (9.5%) patients were unstageable using the traditional TNM staging system (leukemia, myeloma, and brain tumors; Table 2).

Venous thrombosis involved the lower extremity in 196 (56.6%) patients, upper extremity in 30 (8.7%) patients, and the pulmonary vasculature in 96 (27.7%) patients. More than one site of involvement (mostly lower limb DVT and PE) was reported in 20 (5.8%) patients. None of the patients were on any form of prophylaxis at the time of, or prior to, VTE diagnosis.

Most patients, 190 (54.9%), were not on active chemotherapy at the time of VTE diagnosis and so the Khorana RAM was not applicable to this population. One hundred fifty-six (45.1%) patients were on or planned to start active chemotherapy and so were eligible for VTE risk assessment using the Khorana model. Data needed to calculate the risk score were available for all patients. Thirty-one (19.9%) had high risk score ($\geq$3), 81 (51.9%) had intermediate risk score (1-2), and

Table 2. Patient Characteristics.

Age		
Median, years	57	
Range, years	18-86	
	Number	%
Gender		
Male	142	41.0
Female	204	59.0
Primary cancer (total: 346)		
Breast	63	18.2
Colorectal	53	15.3
Lung	45	13.0
Gastric	28	8.1
Brain	23	6.6
Lymphoma	19	5.5
Pancreatic	17	4.9
Prostate	10	2.8
Ovarian	10	2.8
Cervix	9	2.6
Endometrium	9	2.6
Bladder	9	2.6
Others	51	14.7
Stage		
I	10	3.2
II	18	5.8
III	45	14.4
IV	239	76.4
NA	33	10.5
Site of VTE		
Lower extremity	196	56.6
Upper extremity	30	8.7
Pulmonary embolism	96	127.7
Multiple sites	20	5.8
Active anticancer treatment		
Chemotherapy	156	45.1
Hormonal therapy	26	7.5
Radiation therapy	32	9.3
Recent surgery	3	1.0

Abbreviations: NA, not applicable; VTE, venous thromboembolism.

Table 3. Risk Score.

Risk Level: Score	Number (%)
High risk: $\geq$3	31 (19.9)
Intermediate risk: 1-2	81 (51.9)
Low risk: 0	44 (28.2)

44 (28.2%) had a low risk score (0; Table 3). Majority (117; 81.3%) of patients in this group had stage IV disease and 20 (13.9%) others had stage III disease. None had stage I, and only 5 (3.5%) had stage II disease.

Twenty-five (15.1%) patients were on treatment for breast cancer, 28 (17.9%) others for colorectal cancer, 19 (12.2%) for gastric cancer, and 17 (10.9%) for lung cancer. Chemotherapy regimens varied with the primary cancer and included various agents such as fluorouracil, irinotecan, platinum compounds, taxanes, cyclophosphamide, and adriamycin. Cisplatin, known for its thrombotic potential, was given to 42 (26.9%) patients who mainly had a diagnosis of lung, gastric, or bladder cancers.

Discussion

Contrary to the conventional belief, many patients with cancer develop venous thrombosis while ambulatory with no previous recent hospitalization.[19,20] More than 50% of patients included in our "cancer and thrombosis" registry developed their VTE in ambulatory settings.

Individuals with cancer may also have a higher risk of bleeding with anticoagulation, making decisions about the use of prophylactic anticoagulants more challenging.[21-23] Additionally, patients with cancer are subject to many invasive diagnostic and therapeutic interventions, adding to the complexity of using anticoagulation even at prophylactic doses. None of the existing guidelines recommend routine VTE prophylaxis for patients in the ambulatory setting.[12-14]

Multiple clinical trials have been conducted to assess the value of VTE prophylaxis in ambulatory patients with cancer. Many of these trials selected patients based on the primary cancer site and stage such as metastatic breast, pancreatic, or lung cancers or based on the presence of additional known risk factors such as the presence of indwelling intravenous catheters.[24-28] However, results have been conflicting and many have questioned the value of VTE prophylaxis in this group of patients when survival was looked at as a primary end point.[29] However, poor quality of life associated with VTE should be also taken into consideration when evaluating patient outcome and benefit; the value of VTE prophylaxis in this setting has been compared to the use of antiemetics and pain control in patients with cancer.[30]

Given the above-mentioned limitations and the results of our analysis, we believe efforts should be directed toward establishing new high risk criteria for identification of the subgroup of ambulatory patients with cancer at higher risk of VTE. Once established, testing the value of VTE prophylaxis in the high-risk group, identified based on a validated model taking into account these identified high risk variables, might be more rewarding than relying solely on disease site or stage alone.

The RAM suggested by Khorana and his team is simple, applicable, and reproducible. It depends on clinical data that are almost always readily available to the treating clinician. The model, however, is only applicable to patients with cancer on or about to start chemotherapy, a well-known factor that aggravates the risk of clot formation. Our study showed that only 45% of ambulatory patients with cancer had their clot while on or about to start a new regimen of chemotherapy. The remaining 55% developed thrombosis without being on chemotherapy. These findings highlight a limitation of the Khorana RAM and underscore the necessity to modify this model or develop a new one that addresses this group of ambulatory patients with cancer who are not on active chemotherapy.

Few other findings in our study are worth discussion. First, even among the ambulatory patients on active chemotherapy, 28% would have been classified as low risk and thus would not

be eligible for VTE prophylaxis if the Khorana RAM is utilized to stratify patients, since VTE prophylaxis would only be routinely recommended for patients with high or intermediate risk scores. Adding this low-risk group (44 patients) to the group of patients not on chemotherapy (190 patients) will bring the total to 234 (67.6%) patients who would not be eligible for risk assessment or VTE prophylaxis with the current Khorana RAM.

Second, our data and that of many others have shown that disease stage at the time of VTE diagnosis is an important factor that should be considered in stratifying patients into different risk groups.[31,32] More than 80% of TNM stageable patients on chemotherapy had stage IV disease, while none had stage I and very few (3.5%) had stage II disease. We believe that disease stage could prove to be a valuable predictive factor in an RAM if larger clinical trials are to be conducted.

Third, brain tumors were among the 5 most common tumors associated with thrombosis regardless of whether the patient was on active treatment with chemotherapy or not. Many studies have already documented the higher risk of VTE associated with brain tumors. Khorana study did not include sufficient number of patients with brain and renal cancers or multiple myeloma, all of which have been strongly associated with VTE. This issue was taken into consideration by the Vienna Cancer and Thrombosis Study Group. Their modified scoring RAM included additional high risk primary tumor types that were not included in the original Khorana RAM (brain, myeloma, and kidney) and 2 additional laboratory values (soluble P-selectin and D-dimer levels). In a retrospective analysis, the cumulative incidence rate of VTE at 6 months using this modified RAM was 1% for the lowest risk group (0 points) and 35% for the highest risk group ($\geq$5 points).[33]

The current American Society of Clinical Oncology guidelines,[12] the American College of Chest Physicians clinical practice guidelines,[13] and the National Comprehensive Cancer Network guidelines[14] do not recommend routine VTE prophylaxis in ambulatory patients with cancer, except for those with multiple myeloma receiving thalidomide or lenalidomide plus chemotherapy or dexamethasone.

Given the mentioned limitations, establishing an international VTE registry for ambulatory patients with cancer can help define the impact of risk factors that are not currently validated as directly linked to the risk of VTE. Following the identification of high risk ambulatory patients with cancer, it will then be possible to take the findings into the next phase of evaluation and to design trials that randomize patients to receive VTE prophylaxis or current standard care. When doing so, survival advantage might not be the ideal target end point. Lower VTE rates with possible associated improvement in quality of life, in addition to the safety of anticoagulation, might be sufficient and clinically meaningful end points.

Conclusion

Most of the VTE episodes encountered in patients with cancer were diagnosed in the ambulatory setting. Current Khorana RAM was designed for ambulatory patients with cancer on active chemotherapy. Our study showed that more than half of patients with cancer developed a VTE without being on active chemotherapy, and almost a third of those on chemotherapy had low risk scores, illustrating the need to modify the current model or develop a new one that takes into consideration these findings. Establishment of an international registry for VTE in ambulatory patient with cancer can help advance research in this area.

Authors' Note

This is a retrospective study, and for this type of study, formal consent is not required

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Declaration of Conflicting Interests

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