Risk Assessment for Thrombosis in Cancer

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Abstract

Patients with active malignancy are well-known to be at higher risk for venous thromboembolism (VTE). However, the risk of VTE varies considerably between patients and in the same patient over the natural history of their malignancy. Multiple clinical risk factors including primary site of cancer, use of systemic therapy including novel targeted agents, surgery, and hospitalization are known to increase the risk of VTE. Multiple candidate biomarkers including tissue factor, D-dimer, and soluble P-selectin have been identified. However, risk cannot be reliably predicted based on single risk factors or biomarkers. A risk assessment score has been validated in multiple populations and can identify patients at high risk for cancer-associated VTE. This review discusses the risk factors, predictive biomarkers, and new guidelines, which recommend risk assessment of VTE for all cancer patients. Potential applications of risk assessment, including targeted thromboprophylaxis, are also identified in this review.

Keywords

► venous thromboembolism
► risk score
► risk factors
► cancer

While it is a truth universally acknowledged that patients with malignancy are at substantially high risk for venous thromboembolism (VTE) as compared with the general population, the incidence of VTE varies significantly between subgroups of cancer patients, and even in the same patient over time. Broadly speaking, the risk in the general cancer population has been estimated to be 13 per 1,000 person-years (95% confidence interval [CI], 7–23) in a recent systematic review.1 This general estimate, however, does not accurately reflect the prevalence of clinical events observed in cancer patients on active treatment. For instance, in a report of 932 cancer patients receiving cisplatin-based therapy at a large cancer center, 169 (18.1%) experienced a thromboembolic event during treatment or within 4 weeks of the last dose.2 Similarly, the rate of VTE in the placebo arm of a trial of thromboprophylaxis in patients with advanced pancreas cancer was 23% over 100 days.3 Thus, the risk can be unacceptably high in certain well-defined subgroups and during certain settings. Because of this wide variation in risk, a recent update by the American Society of Clinical Oncology (ASCO) VTE Guidelines Panel recommends that patients with cancer be assessed for VTE risk at the time of chemotherapy initiation and periodically thereafter (recommendation 6.1).4 This review will discuss the known risk factors associated with VTE in malignancy, available and candidate predictive biomarkers, and the application of a risk score to assess level of risk in this setting.

Risk Factors

The risk of VTE varies depending upon individual patient-specific, disease-specific, and treatment-specific clinical risk factors (►Table 1). The patient-specific risk factors include age, race/ethnicity, presence of comorbidities, and history of VTE. Older age and African American ethnicity increase the risk of VTE in cancer patients.2 Cancer patients with a history of VTE are six to seven times more likely to develop new VTE than those without a history of VTE.5 Comorbidities such as congestive heart failure and chronic obstructive pulmonary disease may further increase the risk of VTE in cancer patients. A recent article suggests that presence of varicose veins is associated with an increased risk of cancer-associated VTE.6

Disease-specific risk factors include time after disease diagnosis, primary site, and histological type, as well as
extension of disease. The primary site of cancer appears to be the most important disease-specific risk factor. Cancer of the brain, pancreas, stomach, liver, lungs, and kidneys consistently display the highest association with VTE events (as reviewed by Khorana et al.9). In addition, emerging data suggest that VTE rates associated with hematologic malignancies, particularly myeloma, lymphomas, and leukemias appear to be similar to those seen with several solid tumors.9,10 Rates of VTE may differ even between different histological types of disease involving the same organ, with adenocarcinomas being typically associated with higher VTE risk than squamous cell carcinomas.11 The incidence of VTE in patients with non-small cell lung cancer is twice as high as that in patients with small cell lung cancer.12 Other differences in histology can also alter risk of VTE; in a recent article, patients with high-grade tumors had higher risk of VTE compared with low-grade tumors.13

The risk of VTE appears to be highest early in the course of the underlying malignant disease. A large population-based case-control study showed that the risk of VTE was highest within the first 3 months following the diagnosis of a malignancy, with an adjusted odds ratio (OR) of 53.5 (95% CI, 8.6–334.3) compared with controls without malignancy.10 The burden of malignancy is importantly associated with risk. Data from the MEGA (Multiple Environmental and Genetic Assessment) case-control study revealed that cancer patients with distant metastases had a 20- and a 58-fold increased risk of VTE compared with those with cancer without distant metastases and without malignancy, respectively.10 Even regional disease can alter risk. In a report from the Vienna group, the cumulative probability of VTE after 6 months in patients with local, regional, and distant stage cancer was 2.1, 6.5, and 6.0%, respectively (p = 0.002).14 Compared with patients with local stage disease, patients with regional and distant stage disease had a significantly higher risk of VTE in multivariable Cox-regression analysis (regional hazard ratio [HR] = 3.7; 95% CI, 1.5–9.6; distant HR = 5.4; 95% CI, 2.3–12.9). Furthermore, patients with regional or distant stage disease had significantly higher levels of D-dimer, factor VIII, and platelets, and lower hemoglobin levels than those with local stage disease.

### Treatment-associated risk factors

- Chemotherapy
- Antiangiogenic agents (bevacizumab, sorafenib, sunitinib)8
- Immunomodulatory agents (thalidomide, lenalidomide)
  - in combination regimens
- Certain hormonal therapy agents (e.g., tamoxifen)
- Erythropoiesis stimulating agents
- Transfusions
- Central venous access devices
- Inferior vena cava filters
- Radiation
- Major surgical resection

*Definitely associated with arterial thromboembolic events; unclear association with venous thromboembolism.
substantially with small alterations in treatment regimens. For instance, patients with advanced gastroesophageal cancer treated with cisplatin-based regimens have twice as high VTE rates as those treated with oxaliplatin-based regimens.\textsuperscript{20} Newer targeted agents are not exempt from thromboembolic adverse effects, particularly those that target angiogenesis. Bevacizumab-based regimens, as well as chemotherapy containing sunitinib or sorafenib, appear to increase the risk of arterial thromboembolism, but the data for risk of VTE are conflicting.\textsuperscript{21–23} In a meta-analysis, VTE occurred in 11.9% of patients treated with bevacizumab (relative risk [RR] of 1.33, 95% CI, 1.13–1.56; \( p < 0.001 \)).\textsuperscript{22} However, patients with bevacizumab stay on treatment longer because of its efficacy; in a subsequent reanalysis accounting for exposure time, the authors found no significant association with VTE when time on therapy was included as a variable (RR \( 1.10; 95\% \) CI, 0.89–1.36). Patients receiving thalidomide or lenalidomide-based combination regimens are at very high risk for VTE although, interestingly, this risk was not apparent when these drugs were initially tested as single agents.\textsuperscript{24,25} A recent article suggests that nonangiogenic targeted agents such as antipidermal growth factor antibodies, may be associated with increased risk as well.\textsuperscript{26}

In cancer patients with a first episode of VTE, predictors of recurrence while on anticoagulation include younger age, an interval of less than 3 months between VTE and cancer diagnosis, presence of metastases, leukocytosis, and an Eastern Cooperative Oncology Group (ECOG) performance status of \( 2 \).\textsuperscript{27–29} The risk of recurrent VTE is also influenced by the extent of disease, with VTE rates of 14.5, 44.1, and 54.1% reported in cancer patients with less extensive, moderately extensive, and extensive disease, respectively.\textsuperscript{30} A clinical prediction rule for recurrent VTE has recently been developed and includes four independent predictors (sex, primary tumor site, stage, and previous VTE); external validation is awaited.\textsuperscript{31}

### Biomarkers

Studies in cancer outpatients have identified several novel biomarkers as predictors of VTE events (\textit{\textbf{Table 2}}). These include baseline (prechemotherapy) elevated platelet count, elevated leukocyte count, elevated D-dimer, elevated prothrombin split products, elevated soluble P-selectin, peak thrombin generation, and elevated levels of tissue factor (TF)-bearing microparticles (TFMP) (reviewed by Pabinger et al\textsuperscript{12}). Cancer patients with any of these biomarkers have a several fold increased risk of VTE when compared with other cancer patients. It should be noted, however, that several of these studies presented the predictive potential in univariate analyses or limited multivariate analyses; in addition, several biomarkers have not undergone confirmatory reporting. Furthermore, while some of these biomarkers can be easily obtainable in daily clinical practice, others (such as soluble P-selectin and TFMP) are based on laboratory methods that are neither standardized nor available for routine clinical use. In addition, the broad applicability of some of these biomarkers has recently been questioned; for instance, the potential of TF as biomarker appears important in pancreatic cancer but not in other solid tumors.\textsuperscript{33,34} Most importantly, prospective trials that measure clinical outcome data based on specific medical interventions targeted at certain biomarkers are lacking.

#### Risk Assessment Tools

As the long list of known risk factors and biomarkers associated with VTE in malignancy indicates, the etiology of cancer-associated VTE is multifactorial. Multiple large randomized trials have attempted to identify patients at high risk for VTE based on one or two risk factors such as type of cancer and use of chemotherapy.\textsuperscript{35,36} However, event rates in such studies have been quite low indicating that a high-risk population was not selected. Based on these data, the 2013 ASCO VTE Guidelines Panel recommends against the use of single risk factors or biomarkers to identify high-risk patients.\textsuperscript{4} Rather, the panel recommends the use of a risk score that incorporates multiple variables to identify high-risk patients (\textit{\textbf{Table 3}}). The risk score for cancer-associated VTE was originally derived from a development cohort of 2,701 patients and then validated in an independent cohort of 1,365 patients from a prospective registry.\textsuperscript{37} Subsequently, the risk score was externally validated prospectively by the Vienna CATS (Cancer and Thrombosis Study) research group in 819 cancer patients.\textsuperscript{38} The 6-month cumulative probabilities of developing VTE in the Vienna cohort were 1.5% (score of 0), 3.8% (score of 1), 9.4% (score of 2), and 17.7% (score \( \geq 3 \)). Multiple other cohort studies have further validated this score, although rates vary between studies based on heterogeneous populations and follow-up periods.\textsuperscript{39} In addition to the ASCO guidelines, the risk score has also been endorsed by the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines panels.\textsuperscript{40,41}

Expansions of the risk score have been proposed but not yet validated; one such expansion by the Vienna group incorporates additional biomarkers including D-dimer and

### Table 2 Predictive biomarkers for cancer-associated thrombosis

<table>
<thead>
<tr>
<th>Currently widely available</th>
<th>Leukocyte count (( \geq 11,000/\mu L ))\textsuperscript{37}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count (( \geq 350,000/\mu L ))\textsuperscript{37}</td>
<td>Leukocyte count (( &gt; 11,000/\mu L ))\textsuperscript{37}</td>
</tr>
<tr>
<td>Hemoglobin (( &lt; 10 ) g/dL)\textsuperscript{37}</td>
<td>D-dimer\textsuperscript{46,47}</td>
</tr>
<tr>
<td>Investigational and/or not widely available</td>
<td>Tissue factor (antigen expression, circulating microparticles, antigen, or activity)\textsuperscript{49–51}</td>
</tr>
<tr>
<td>Peak thrombin generation\textsuperscript{48}</td>
<td>Soluble P-selectin (( &gt; 53.1 ) ng/mL)\textsuperscript{52}</td>
</tr>
<tr>
<td>Factor VIII\textsuperscript{53}</td>
<td>Prothrombin fragment F1 + 2 (( &gt; 358 ) pmol/L)\textsuperscript{47}</td>
</tr>
</tbody>
</table>
Table 3 Predictive risk score for cancer-associated venous thromboembolism

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Risk scorea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of cancer</td>
<td></td>
</tr>
<tr>
<td>Very high risk (stomach, pancreas)</td>
<td>2</td>
</tr>
<tr>
<td>High risk (lung, lymphoma, gynecologic, bladder, testicular)</td>
<td>1</td>
</tr>
<tr>
<td>Prechemotherapy platelet count 350,000/mm³ or more</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin level less than 10 g/dL or use of red cell growth factors</td>
<td>1</td>
</tr>
<tr>
<td>Prechemotherapy leukocyte count more than 11,000/mm³</td>
<td>1</td>
</tr>
<tr>
<td>Body mass index 35 kg/m² or more</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: According to Khorana et al.37

aHigh risk ≥ 3; intermediate risk =1–2; low risk =0.

soluble P-selectin.38 In the expanded Vienna risk model, the cumulative VTE probability after 6 months in patients with the highest score (≥5) was 35.0%, and 10.3% in those with an intermediate score (score 3) as opposed to only 1% in patients with score 0. Although promising, this expanded score requires validation; further, P-selectin is not a widely available assay and the use of the expanded risk score clinically may therefore be limited.

Patients with myeloma are at very high risk for VTE, particularly when treated with thalidomide- or lenalidomide-containing regimens. A risk assessment algorithm has been proposed by the International Myeloma Working Group.42 The algorithm is based on expert consensus and awaits validation.

Potential Applications of the Risk Score

The development of a validated formal risk assessment approach is an important advance for the field. There are at least three potential clinical applications of the risk score. First, cancer patients are woefully unaware of the risk of VTE.43 Conducting a formal risk assessment provides an opportunity to educate patients about the warning signs and symptoms of VTE. Indeed, the new ASCO guidelines recommend that oncologists educate patients regarding VTE, particularly in high-risk settings (recommendation 6.2).44 Second, one small study suggests that screening high-risk patients as identified by the risk score can lead to diagnosis of occult VTE; in this cohort, 11% of patients had undiagnosed VTE at baseline (before starting chemotherapy). These data need confirmation, however, before clinical screening can be recommended. Finally, and perhaps most promisingly, the risk score appears to be predictive of benefit from thromboprophylaxis. When risk assessment was applied to the study population of a randomized trial of outpatient prophylaxis using nadroparin, the number need to treat to prevent one thromboembolic event fell from 50 for the full population to 15 for high-risk patients (score ≥ 3).44 Similarly, when applied to the study population of a large randomized trial of semuloparin for outpatient thromboprophylaxis, risk reduction was greater in high-risk patients (5.4% in the placebo arm vs. 1.4% in the semuloparin arm, for score ≥3 [HR, 0.27] compared with 1.3 versus 1%, respectively, for score = 0 [HR, 0.71]).45 A prospective study of outpatient thromboprophylaxis in high-risk patients based on the risk score is currently ongoing.

Conclusions

The past decade has led to the identification of several novel clinical risk factors as well as biomarkers predictive of risk of cancer-associated VTE. Unfortunately, the prevalence of VTE has risen during this time as well. The development of a validated formal risk assessment score is an important step forward in the field. New guidelines recommend that clinicians conduct risk assessment in all cancer patients initiating chemotherapy and periodically thereafter. Potential applications of risk assessment include patient education, screening, and selection of patients for outpatient thromboprophylaxis. Ongoing studies are evaluating new biomarker and –omics-based approaches to risk stratification. Building on existing knowledge, these approaches will further lead to targeted thromboprophylaxis and treatment that will reduce the burden of thrombosis and its consequences for patients with malignancy.

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Conflict of Interest

Dr. Khorana has received research funding and consulting honoraria from sanofi aventis (Bridgewater, NJ), Eisai (Woodcliff Lake, NJ), and Leo Pharma (Parsippany, NJ).

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