Thrombosis Research 164 (2018) S70–S76

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Risk prediction of cancer-associated thrombosis: Appraising the first decade and developing the future

Alok A. Khorana[a,*], Charles W. Francis[b]

[a] Cleveland Clinic, Taussig Cancer Institute and Case Comprehensive Cancer Center, Cleveland, OH, USA
[b] University of Rochester Medical Center, Rochester, NY, USA

A B S T R A C T

Cancer-associated venous thromboembolism (VTE) has major consequences for patients, including morbidity and risk of mortality. However, there is substantial variation in risk depending on a multitude of clinical risk factors and many cancer patients are at low risk for VTE. This critical concept of risk variation has led to efforts to identify patients at high or low risk for developing VTE. Our research group and others have focused on understanding and predicting risk of cancer-associated VTE. This narrative review describe research efforts conducted over the past decade, beginning with the 2008 publication of the first validated risk assessment tool in this setting. We describe current applications of the "Khorana score" including identification of high- and low-risk patients, selecting and excluding patients for thromboprophylaxis and screening high-risk patients for early detection of VTE. New approaches to risk prediction including precision medicine and next-generation sequencing are discussed. Finally, we offer suggestions on improving the field of risk prediction in this setting in the near future.

1. Introduction

The association of cancer with thrombosis, including deep vein thrombosis (DVT), pulmonary embolism (PE) and visceral vein thrombi as well as arterial events such as stroke and myocardial infarction, has been well-known for over a century. A commonly accepted parlance is that "one in five" cancer patients will develop venous thromboembolism (VTE) at some point during the natural history of their illness. However, the corollary of this statement i.e., four in five patients with cancer will *never* develop VTE, is less well understood or appreciated. While it is important to understand the impact of cancer-associated thrombosis, it is equally important to understand that there is substantial variation in risk, determined by a multitude of factors including cancer type and setting, and that a majority of cancer patients are *at low or even zero risk* of ever developing VTE.

This critical concept has led to efforts to identify which patients with cancer are likely to develop thrombosis and which are not. This approach of risk stratification could, in turn, lead to appropriate surveillance and potentially thromboprophylaxis. Over the past decade and longer, our research group and others have focused on understanding and predicting the risk of cancer-associated VTE and formulating clinically applicable algorithms in an effort to better predict an individual cancer patient's risk. In 2008, our efforts culminated in the publication of a validated risk assessment tool to stratify VTE risk in cancer patients (Table 1) [1]. This narrative review will describe research efforts conducted over the past decade dedicated to applying and improving risk assessment strategies and offer suggestions on how the field can advance in the near future.

2. Initial development and validation of risk score

In the early 2000s, studies that identified patients at highest risk of VTE were scarce (reviewed at the time in Geerts et al. [2]). Historically, the risk was observed to vary by site of cancer, and was noted to be particularly high in patients with pancreas, stomach and kidney cancers, and malignant brain tumors. Emerging data at the time highlighted other tumor types with an increased risk of VTE including lymphomas and lung cancer [3]. It was further recognized that cancer treatments contributed to the risk of VTE. Cancer patients undergoing surgery were known to have at least twice the risk of postoperative DVT and more than three times the risk of fatal PE than non-cancer patients. VTE rates were 2- to 5-fold greater in women treated with tamoxifen [4]. Chemotherapy was strongly associated with an increased risk of VTE [5–8].

Despite these strong associations, little was known about specific risk factors that predisposed to VTE in patients on active systemic

* Corresponding author at: 10201 Carnegie Ave, CA60, Cleveland, OH 44106, USA.
E-mail address: Khorana@ccf.org (A.A. Khorana).

https://doi.org/10.1016/j.thromres.2018.01.036
Received 22 November 2017; Received in revised form 18 January 2018; Accepted 19 January 2018
Available online 31 January 2018
0049-3848/

Table 1
Risk Score for Prediction of Cancer-Associated VTE [1].

Patient Characteristic	Risk Score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gyn, bladder, testicular)	1
Prechemotherapy platelet count $\geq 350 \times 10^9$/L	1
Hemoglobin level < 10 g/dL or use of red cell growth factors	1
Prechemotherapy leukocyte count > 11×10^9/L	1
Body mass index ≥ 35 kg/m^2	1

High-risk score ≥ 3.
Intermediate risk score = 1 or 2.
Low-risk score = 0.

therapy. Indeed, a major methodologic issue with population-based or hospital-based studies of VTE in cancer (the primary source of data at the time) was the heterogeneity of the study populations. Such study cohorts included a mix of post-operative patients, those with major medical illnesses or poor functional status, those receiving active systemic therapy as well as those in remission or cured of their cancer. We, therefore, decided to focus on cancer patients receiving systemic outpatient chemotherapy, a population that comprised the majority of cancer patients at risk for VTE but poorly represented in existing studies. We were fortunate to have access to a large prospective cohort study led by Prof. Gary Lyman. The ANC Study Group Registry was an observational multicenter study of cancer patients initiating a new chemotherapy regimen and followed prospectively for a maximum of four cycles. This study population allowed us to study risk factors associated with the patient's cancer and cancer-related therapy. Our initial report analyzed over 3000 patients and identified multiple risk factors for development of VTE, including novel ones such as the prechemotherapy platelet count, anemia and use of growth factors [9].

This initial effort led to a greater understanding that cancer-associated VTE is truly a multifactorial disease, associated with many risk factors which may interact in the same patient. However, identification of risk factors alone was not sufficient. Rather, risk stratification would require development of a model that incorporated multiple risk factors, and their relationships. Formal risk assessment models for DVT in specific high-risk populations had been developed in other settings and were used clinically [10–15]. At the time, no such models had been developed for cancer patients on chemotherapy. In a grant application to the National Cancer Institute, we proposed utilizing the ongoing prospective observational study discussed above to develop and validate a risk model specifically for cancer patients on chemotherapy. We were fortunate to obtain funding for this grant in 2006 (K23CA120587, PI: AAK).

Aim 1 of the grant focused on development and validation of a risk model that unified the multiple risk factors associated with VTE, and could accurately and prospectively identify a subgroup of patients whose risk was high enough for VTE prophylaxis to have a favorable risk-benefit ratio. We based our definition of “high risk” upon rates of VTE in other settings where VTE prophylaxis had been shown to be effective. A population of patients with a rate of symptomatic VTE > 7% over the first 3 cycles of chemotherapy would have an exoected asymptomatic DVT rate of 10–30%, assuming a conservative ~3 fold ratio between symptomatic and asymptomatic thrombosis. This risk of VTE was similar or greater than the observed risk in hospitalized patients with an acute medical illness, or post-operative patients for whom VTE prophylaxis had been shown to be effective [16–19]. Our analyses of the ANC Study Group prospective cohort study culminated in a 2008 paper describing a split-sample validation of a risk score to predict VTE in cancer patients initiating a new chemotherapy regimen [1]. In the final multivariate analysis of the derivation cohort, variables independently associated with risk of VTE included: primary site of cancer (very high risk or high risk), pre-chemotherapy platelet count of 350×10^9/L or more, hemoglobin level < 100 g/L (10 g/dL) and/or use of red cell growth factors, leukocyte count > 11×109/L, and body mass index of 35 kg/m2 or more (Table 1). We assigned points for the risk model based on the regression coefficients obtained from the final multivariate analysis and divided the population into 3 risk categories: low (score 0), intermediate (score 1–2), and high (score ≥ 3). For high risk patients (score ≥ 3), the model had a negative predictive value (probability of no VTE in those designated low risk) of 98.5%, a positive predictive value (probability of VTE in those designated high risk) of 7.1%, a sensitivity (probability of high risk in those experiencing VTE) of 40.0%, and a specificity (probability of low risk in those not experiencing VTE) of 88% in the derivation cohort. Similar results were obtained in the validation cohort. We concluded that the risk model could be used by clinicians for assessing risk for VTE in practice, as well as to design future trials of thromboprophylaxis although we noted that it was important to further validate this model in large observational studies and that the value of the C statistic suggested that incorporating additional variables could increase the accuracy of the model.

Since the original publication, multiple research groups have applied the risk score and shown it to be predictive of risk in a variety of cancer populations (Table 2). This step of external validation is essential to determine the clinical usability of such a risk tool. The first large prospective validation was conducted by the Vienna CATS group [20]. In this cohort study of 819 patients, 61 (7.4%) experienced VTE during a median follow-up of 656 days. This follow-up was substantially longer than the 73 days in the original study, and this accounts for the higher observed rates. The cumulative VTE probability with the original risk model in the Vienna cohort after 6 months was 17.7% in patients with the highest risk score (≥3), 9.6% with score = 2, 3.8% score = 1 and 1.5% in score = 0. Multiple retrospective and prospective cohort studies have continued to confirm the validity of this risk score (Table 2) and it remains the only score currently endorsed by multiple guidelines panels [21,22]. We note here that subsequent publications have used the term ‘Khorana score’. For consistency, we will do the same although we acknowledge the efforts of many collaborators that went into the development of this score.

Two recent reports have expanded the utility of the risk score to the inpatient setting where previously no validated cancer-specific tools exist [23,24]. In a retrospective cohort study of 2780 hospitalized patients, 106 (3.8%) developed VTE during hospitalization. High risk Khorana score (≥3) was significantly associated with VTE in uni- and multivariate analyses (OR 2.5, 95% CI 1.3–4.9) [23]. Recursive partitioning analysis suggested optimal cut point for Khorana score is 2 (OR 1.82, 1.23–2.69). Similarly, in a multicenter study of 1398 hospitalized patients the incidence of VTE was 2.9% (41/1398) overall, with 5.4% (9/166) in high, 3.2% (26/817) in moderate, and 1.4% (6/415) in low Khorana score risk groups. High risk patients were significantly more likely than low risk patients to have VTE ($p = 0.016$; OR 3.9, 95% CI 1.4–11.2).

3. Modifications of the risk score and new risk tools

Several modifications of the Khorana score have been proposed. The Vienna CATS group expanded the score by adding two biomarkers: D-dimer and soluble P-selectin. Six-month VTE rates with the expanded model were 35% in patients with score ≥ 5, 10.3% in those with score 3, and only 1.0% in patients with score 0. A limitation of this modification is lack of widespread availability of P-selectin assays; further, rates of VTE are already high enough in the high-risk subgroup to warrant prophylaxis so identifying even higher-risk patients does not add to the discriminatory power. In a post hoc subgroup analysis of the PROTECHT trial of outpatient thromboprophylaxis, investigators validated the original score and proposed a modification, termed the “Protecht score” [25]. This score added exposure to specific chemotherapy agents to the variables listed in the original model [26]. The Protecht score was applied to 378 patients enrolled in the placebo arm