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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

Link to publication in University of Groningen/UMCG research database

Comparison of risk prediction scores for venous thromboembolism in cancer patients: a prospective cohort study

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ABSTRACT

In ambulatory patients with solid cancer, routine thromboprophylaxis to prevent venous thromboembolism is not recommended. Several risk prediction scores to identify cancer patients at high risk of venous thromboembolism have been proposed, but their clinical usefulness remains a matter of debate. We evaluated and directly compared the performance of the Khorana, Vienna, PROTECHT, and CONKO scores in a multinational, prospective cohort study. Patients with advanced cancer were eligible if they were due to undergo chemotherapy or had started chemotherapy in the previous three months. The primary outcome was objectively confirmed symptomatic or incidental deep vein thrombosis or pulmonary embolism during a 6-month follow-up period. A total of 876 patients were enrolled, of whom 260 (30%) had not yet received chemotherapy. Fifty-three patients (6.1%) developed venous thromboembolism. The c-statistics of the scores ranged from 0.50 to 0.57. At the conventional positivity threshold of 3 points, the scores classified 13-34% of patients as high-risk; the 6-month incidence of venous thromboembolism in these patients ranged from 6.5% (95%CI: 2.8-12) for the Khorana score to 9.6% (95%CI: 6.6-13) for the PROTECHT score. High-risk patients had a significantly increased risk of venous thromboembolism when using the Vienna (subhazard ratio 1.7; 95%CI: 1.0-3.1) or PROTECHT (subhazard ratio 2.1; 95%CI: 1.2-3.6) scores. In conclusion, the prediction scores performed poorly in predicting venous thromboembolism in cancer patients. The Vienna CATS and PROTECHT scores appear to discriminate better between low- and high-risk patients, but further improvements are needed before they can be considered for introduction into clinical practice.

Introduction

Venous thromboembolism (VTE) complicates the clinical course in 4-5% of cancer patients[1,2] and is a major cause of morbidity and mortality.[3] The management of VTE in cancer patients is particularly challenging since both the risk of recurrent VTE and major bleeding are high during anticoagulant treatment. Current international guidelines do not recommend routine pharmacological thromboprophylaxis in ambulatory cancer patients.[4-6] Low-molecular weight heparin (LMWH) in pro-

phylactic doses halves the risk of VTE[1] and is associated with an absolute risk reduction of 2-2.5%. However, the corresponding number needed to treat (40-50) using thromboprophylaxis is considered too low to justify the potential increased risk of bleeding and the burden of daily subcutaneous injections for a prolonged period of time.[4]

Risk stratification tools have been developed to identify a subset of cancer patients in whom the risk of developing VTE is high enough to justify thromboprophylaxis. The best validated tool is a score proposed by Khorana and colleagues[7] which aims to identify cancer patients receiving chemotherapy at high risk of VTE based on the tumor type, hemoglobin concentration or use of erythropoietin stimulating agents, white blood cell count, platelet count, and Body Mass Index (BMI) (Table 1). To improve the discriminatory performance of the Khorana score, others have proposed modifications by adding biomarker measurements[8] or type of chemotherapy,[9] or by replacing BMI with performance status (Table 1).[10]

Although these scores performed well in the initial derivation studies, there have either been no subsequent external validation studies or those that have been carried out have reported conflicting results.[11-13] Yet, it is important that performance is maintained across different patient populations and settings. In addition, scores have not been directly compared in a large study of representative patients. To fill this gap, we evaluated and directly compared four clinical prediction scores for VTE in patients with advanced cancer receiving chemotherapy in a multinational cohort study.

Methods

Study design and patients

Data were collected in a multinational, prospective cohort study performed in seven hospitals in The Netherlands, Italy, France, and Mexico, designed to evaluate clinical and laboratory predictors for cancer-associated VTE. Here we report on the performance of four published clinical prediction scores for cancer-associated VTE. Outpatients with lung, esophageal, colorectal, pancreatic, breast, prostate, gastric, ovarian, or bladder cancer classified as stage III or IV according to the American Joint Committee on Cancer criteria were eligible if they were scheduled for chemotherapy within seven days or had started chemotherapy in the previous three months. Exclusion criteria included current prophylactic or therapeutic anticoagulation or adjuvant chemotherapy. None of the patients included had received routine thromboprophylaxis in accordance with current guidelines. Patients were recruited between July 2008 and February 2016. The study was approved by the institutional review boards of all participating hospitals. Patients included in the study provided written informed consent. The study was registered at *clinicaltrials.gov*
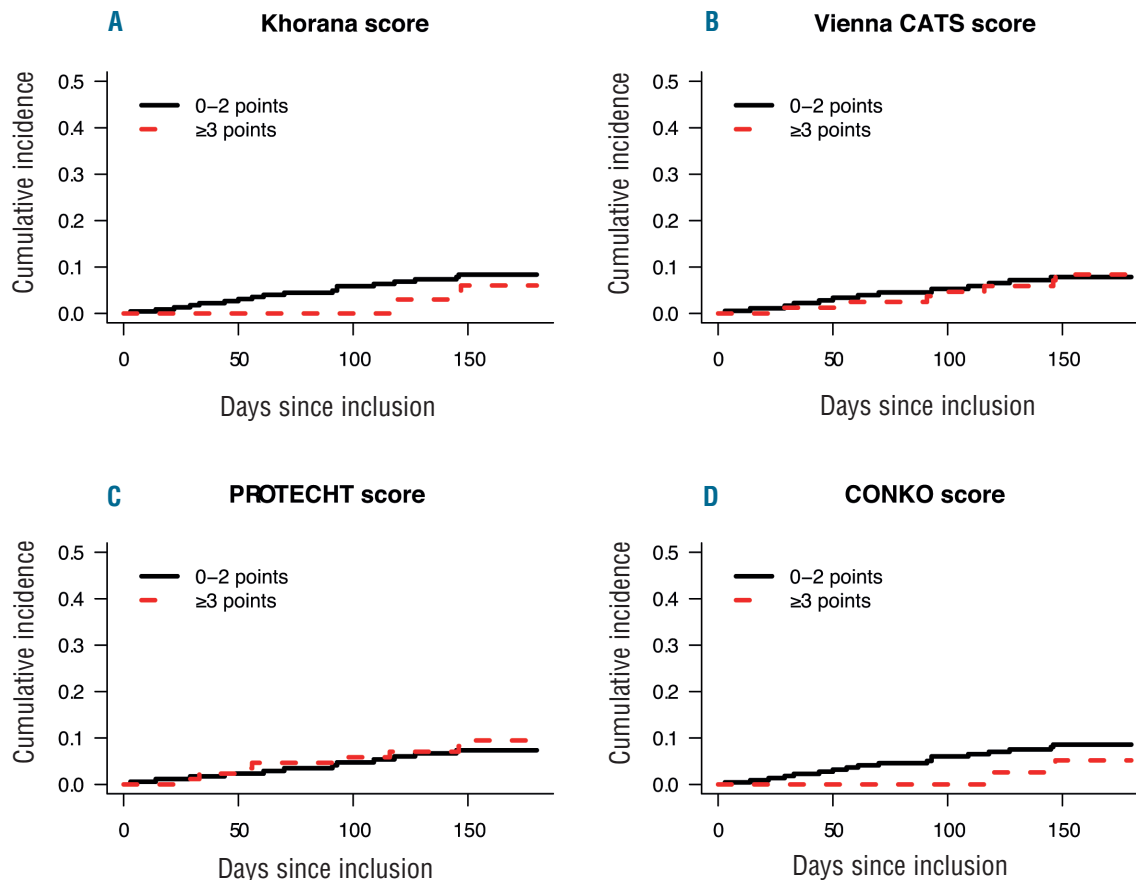

Figure 1. Cumulative incidence of venous thromboembolism in low- and high-risk patients. Cumulative incidence of venous thromboembolism in patients enrolled prior to chemotherapy (n=260) who were classified as being at low or high risk of venous thromboembolism by the (A) Khorana score, (B) Vienna CATS score, (C) PROTECHT score, and (D) CONKO score.

(*identifier: 02095925*) after the enrollment of the first patient. The present report adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.[14]

Study procedures

At baseline, healthcare professionals interviewed patients and collected baseline clinical and laboratory information from the medical charts using a standardized case report form. Patients were enrolled at oncology or vascular medicine departments. Blood was drawn in 0.109 M citrated tubes *via* antecubital venepuncture or through a peripheral catheter shortly after placement. Within one hour after blood collection, platelet poor plasma was prepared by centrifugation at 1560 g for 20 minutes and stored at -80°C after snap freezing.

A follow-up visit was scheduled at 180 days from the clinic visit by telephone and/or chart review. The primary outcome was the composite of objectively confirmed symptomatic or incidental pulmonary embolism (PE), distal or proximal leg deep vein thrombosis (DVT), or non-catheter-related upper extremity DVT (UEDVT), or symptomatic catheter-related UEDVT. VTE was considered incidental if diagnosed on imaging performed for reasons other than suspicion of VTE. Incidental events were included in the primary outcome since current guidelines suggest a treatment similar to that for symptomatic events. Patients did not undergo screening for VTE. Imaging reports of all potential outcomes were verified by 2 of the authors who were blinded to possible predictors of VTE. Deaths were not adjudicated routinely for fatal PE, but PE was considered to be fatal only if autopsy confirmed PE or in the case of an objective test positive for PE prior to death.

Evaluation of prediction scores

We evaluated the following clinical prediction scores for cancer-associated VTE: the Khorana,[7] Vienna CATS,[8] PROTECHT,[9] and CONKO scores[10] (Table 1). Characteristics of the derivation studies are provided in the *Online Supplementary Appendix text 1*. Evaluation of the Khorana score was included in the initial study protocol, while the other scores were published during the course of the study and were subsequently included in the analysis. We were unable to evaluate a recently proposed genetic risk score.[15] In order to calculate the Vienna CATS score, D-dimer (INNO-VANCE, Siemens) and soluble P-selectin (ELISA, R&D Systems, Minneapolis, MN, USA) concentrations were measured centrally in baseline samples. Analysis of samples of 98 patients from one center provided implausible results due to incorrect shipment, forcing us to omit these measurements, while the patients were retained in the dataset and among the imputed data.

For continuous scores, the overall discriminatory performance was evaluated. For dichotomized scores, we calculated the proportion of high-risk patients, the cumulative VTE incidence among high-risk patients, the cumulative VTE incidence among low-risk patients, and the difference in VTE incidence between low- and high-risk patients. Since the scores will be used in a dichotomous fashion in clinical practice by conflating the low and intermediate groups, we evaluated them at the conventional positivity threshold of 3 points, and at exploratory positivity thresholds of 2 and 4 points.

Since the derivation of the Khorana, PROTECHT, Vienna CATS, and CONKO scores was almost entirely based on symptomatic VTE, a sensitivity analysis restricted to symptomatic events was performed. Another sensitivity analysis, restricted to the first 90 days of follow up, was performed for comparison with Khorana's derivation study which had a median follow up of 2.5 months.[7]

Our study was designed to include cancer patients prior to or within three months of the start of chemotherapy. Since pre-chemotherapy blood counts are incorporated into all evaluated clinical prediction scores, we restricted the main analysis to the group of patients who had not yet received chemotherapy. The analyses were then repeated in the complete study group, calculating each score based on pre-chemotherapy blood counts, which were collected retrospectively at inclusion in patients who had already started chemotherapy. Results are thus presented for the group that mirrors cancer patients in whom the decision about thromboprophylaxis is made prior to chemotherapy and for all patients, including those for whom the question as to whether to provide thromboprophylaxis is discussed during the first months of chemotherapy.

Assuming a 6-month VTE incidence of 5-6%, the aim was to enroll approximately 800-1000 patients in order to observe about 50 events, which was considered to be sufficient for multivariable regression modeling with the five items in the Khorana score.

Table 1. Risk prediction scores for venous thromboembolism in cancer patients.

Item	Khorana score (points)	Vienna CATS score (points)	PROTECHT score (points)	CONKO score (points)
Pancreatic or gastric cancer (very high-risk tumors)	+2	+2	+2	+2
Lung, gynecological, lymphoma, bladder, or testicular (high-risk tumors)	+1	+1	+1	+1
Pre-chemotherapy hemoglobin <10 g/dL or use of erythropoietin stimulating agents	+1	+1	+1	+1
Pre-chemotherapy white blood cell count >11 x 10^9/L	+1	+1	+1	+1
Pre-chemotherapy platelet count ≥350 x 10^9/L	+1	+1	+1	+1
Body Mass Index >35 kg/m^2	+1	+1	+1	−
D-dimer >1.44 μg/L	−	+1	−	−
Soluble P-selectin >53.1 ng/L	−	+1	−	−
Gemcitabine chemotherapy	−	−	+1	−
Platinum-based chemotherapy	−	−	+1	−
WHO performance status ≥2	−	−	−	+1

WHO: World Health Organization.

Statistical analysis

The cumulative VTE incidence from enrollment to six months in low- and high-risk patients was estimated using a competing risk time-to-event analysis in which death was treated as a competing event for VTE. Unlike naïve Kaplan-Meier and Cox regression analysis, a competing risk analysis does not treat death as a censored observation, but rather takes into account that VTE cannot occur after death, thereby providing less biased estimates.[16] Time to VTE was considered censored when patients underwent cancer surgery with curative intent, started therapeutic anticoagulation for other reasons than VTE, were lost to follow up, or at the end of the 6-month follow-up period. Confidence intervals (CI) at specific time points were calculated using Choudhury's method.[17]

To evaluate the discriminatory performance of the scores, the time-dependent concordance index (c-index) was calculated while accounting for death as a competing risk.[18] The 95% confidence intervals were calculated by repeating the analyses in 250 bootstrap samples.

To assess the difference in VTE risk between low- and high-risk patients, subdistribution hazard ratios (SHR) and 95% CIs for the dichotomized scores were estimated using the competing risks regression model of Fine and Gray.[19] The predictive value of the separate items in each score was assessed by multivariable competing risks regression models. The proportionality assumption was checked by adding an interaction term between each variable and time to the model.

Multiple imputation was used to minimize the bias associated with missing data.[20] We assumed a 'missing' at random pattern in which missingness depends on other observed variables. Center, inclusion year, all baseline characteristics, and outcome data were included in the imputation model to create twenty imputed datasets. Analyses were performed separately in each imputed dataset; estimates with standard errors were combined across the datasets using Rubin's rule.[21] The complete case analyses were provided for comparison.

A significance level of 0.05 was used in statistical testing. All analyses were performed in R, v.3.3.2 (R Foundation for Statistical Computing, Vienna, Austria; *www.R-project.org*), in particular using the "mice" v.2.25 package for multiple imputation, the "cmprsk" v.2.2-7 for the competing risk analyses, and the "pec" package v.2.4.9 for the time-dependent c-indices.

Results

During the 7.5-year study period, 876 patients with stage III or IV solid cancer were enrolled, of whom 260 (30%) had not yet started chemotherapy. The mean age was 64 years; 59% of patients were male. Baseline charac-

Table 2. Baseline characteristics.

Characteristic	Prior to chemotherapy (N=260)	All patients (N=876)
Age, y, mean (SD)	63 (10)	64 (11)
Male, n (%)	156 (60)	516 (59)
Body Mass Index		
Mean (SD), kg/m^2	25 (4.3)	25 (4)
>35 kg/m^2, n (%)	7 (2.7)	27 (3.1)
WHO performance status ≥2, n (%)	25 (9.6)	79 (8)
Previous VTE, n (%)	3 (1.2)	13 (1.5)
Antiplatelet therapy, n (%)	26 (10)	109 (12)
Tumor type, n (%)		
Lung	73 (28)	224 (26)
Esophagus	47 (18)	170 (19)
Colorectal	50 (19)	158 (18)
Pancreas	36 (14)	109 (12)
Breast	18 (6.9)	82 (9.4)
Prostate	11 (4.2)	41 (4.7)
Gastric	16 (6.2)	40 (4.6)
Ovarian	7 (2.7)	39 (4.5)
Bladder	2 (0.8)	13 (1.5)
Distant metastasis, n (%)	179 (69)	581 (66)
Gemcitabine, n (%)	34 (13)	132 (15)
Platinum-based chemotherapy, n (%)	157 (60)	518 (59)
Erythropoietin stimulating agents, n (%)	21 (8.1)	58 (6.6)
Pre-chemotherapy hemoglobin <10 g/dL, n (%)	15 (5.8)	64 (7.3)
Pre-chemotherapy white blood cell count >11 x 10^9/L, n (%)	45 (17)	141 (16)
Pre-chemotherapy platelet count ≥350 x 10^9/L, n (%)	67 (26)	229 (26)
D-dimer >1.44 μg/L	76 (29)	274 (31)
Soluble P-selectin >53.1 ng/L	33 (13)	87 (9.9)

y: years; SD: Standard Deviation; VTE: venous thromboembolism; N, n: number; WHO: World Health Organization.

Table 3. Performance of different scores in patients enrolled prior to chemotherapy (n=260) and all patients (n=876).

	Khorana score	Vienna CATS score	PROTECHT score	CONKO score
Patients enrolled prior to chemotherapy (n=260)				
Time-dependent c-index at 180 days (95% CI)	0.50 (0.42-0.57)	0.57 (0.48-0.66)	0.54 (0.45-0.63)	0.50 (0.44-0.57)
High-risk patients (≥3 points), % (95% CI)	13 (9.5-18)	31 (26-37)	34 (28-40)	15 (11-20)
6-month VTE risk in low-risk patients (≤2 points), % (95% CI)	8.4 (5.1-13)	7.9 (4.4-13)	7.4 (4.0-12)	8.6 (5.3-13)
6-month VTE risk in high-risk patients (≥3 points), % (95% CI)	6.0 (1.0-18)	8.4 (3.5-16)	9.5 (4.4-17)	5.2 (0.9-16)
Subhazard ratio for high- (≥3 points) *vs.* low-risk patients (≤2 points)	0.69 (0.17-2.9)	1.1 (0.41-2.7)	1.3 (0.53-3.15)	0.58 (0.14-2.4)
All patients (n=876)				
Time-dependent c-index at 180 days (95% CI)	0.52 (0.47-0.58)	0.58 (0.51-0.66)	0.59 (0.52-0.66)	0.53 (0.47-0.59)
High-risk patients (≥3 points), % (95% CI)	13 (11-15)	27 (24-30)	35 (31-38)	15 (13-18)
6-month VTE risk in low-risk patients (≤2 points), % (95% CI)	6.5 (4.8-8.4)	5.5 (3.8-7.6)	4.7 (3.1-6.8)	6.4 (4.7-8.4)
6-month VTE risk in high-risk patients (≥3 points), % (95% CI)	6.5 (2.8-12)	9.1 (5.8-13)	9.6 (6.6-13)	7.1 (3.5-12)
SHR for high- (≥3 points) *vs.* low-risk patients (≤2 points)	1.0 (0.46-2.3)	1.7 (1.0-3.1)	2.1 (1.2-3.6)	1.1 (0.56-2.4)

CI: Confidence Interval; SHR: subdistribution Hazard Ratio; VTE: venous thromboembolism; vs.: *versus;* n: number.

teristics of the patients enrolled prior to chemotherapy and the complete study group are summarized in Table 2. No significant differences were found between patients enrolled prior to chemotherapy and those enrolled during chemotherapy, except for higher P-selectin levels in the former group. The distribution of the scores are summarized in *Online Supplementary Appendix text 2*. Multiple imputation was used to calculate the Khorana in 33 patients (4%), the Vienna CATS score in 134 patients (15%), the PROTECHT score in 38 patients (4%), and the CONKO score in 47 patients (5%), in whom data on one or more of the score items were missing.

Overall, 53 patients (6.1%) developed VTE during the 6-month follow-up period, of whom 27 only had PE (3.1%), 15 had proximal DVT (1.7%), 7 had UEDVT (0.8%), 3 had PE and DVT (0.3%), and one had isolated distal DVT (0.1%). The corresponding cumulative incidence in the competing risks analysis was 6.5% (95%CI: 4.9-8.3%) at 180 days. VTE was symptomatic in 33 cases (62%). Two events (3.8%) were fatal. The median time to VTE was 57 days (interquartile range 33-116). Ten patients (1.1%) were lost to follow up and 163 patients (19%) died.

Performance of scores

Of the 260 patients who were enrolled prior to chemotherapy, 20 (7.7%) developed VTE, including 13 symptomatic events. In this group, the area under the ROC curves for the different scores (reflecting discriminatory performance) ranged from 0.50 (95%CI: 0.44-0.57) for the CONKO score and 0.50 (95%CI: 0.42-0.57) for the

Khorana score to 0.57 (95%CI: 0.48-0.66) for the Vienna CATS score (Table 3). At the conventional positivity threshold of 3 points, the proportion of patients classified as high-risk ranged from 13% (95%CI: 9.5-18%) for the Khorana score to 34% (95%CI: 28-40%) for the PROTECHT score (Table 3). The 6-month VTE incidence in these high-risk patients ranged from 5.2% (95%CI: 0.9-16%) for the CONKO score to 9.5% (95%CI: 4.4-17%) for the PROTECHT score (Table 3; see Figure 1 for time-to-event curves). At the evaluated positivity thresholds of 2, 3, or 4 points, none of the scores was able to discriminate between low- and high-risk patients (*Online Supplementary Appendix text 3*).

The analyses were repeated in all 876 patients, including the 616 patients enrolled after the start of chemotherapy (median 28 days; interquartile range 16-56) for whom blood counts collected before chemotherapy were used to calculate the scores. Overall, results were comparable to the analyses restricted to patients enrolled prior to chemotherapy. The area under the ROC curves ranged from 0.52 (95%CI: 0.47-0.58) for the Khorana score to 0.59 (95%CI: 0.52-0.66) for the PROTECHT score (Table 3). At the conventional positivity threshold of 3 points, the Khorana score again classified 13% (95%CI: 11-15%) as high-risk, whereas the PROTECHT score classified 35% of patients (95%CI: 31-38%) as high-risk (Table 3). Among high-risk patients, the cumulative VTE incidence at six months ranged from 6.5% (95%CI: 2.8-12%) when using the Khorana score to 9.6% (95%CI: 6.6-13%) when using the PROTECHT score (Table 3). Subhazard ratios

for VTE in high- *versus* low-risk patients ranged from 1.0 (95%CI: 0.46-2.2) for the Khorana score to 1.7 (95%CI: 1.0-3.1) for the Vienna CATS score and 2.1 (95%CI: 1.2-3.7) for the PROTECHT score (Table 3; see *Online Supplementary Appendix text 4* for time-to-event curves). At positivity thresholds of 2 or 4 points, the difference in VTE risk between high- and low-risk patients was not significant for any of the scores (*Online Supplementary Appendix text 3*).

Sensitivity analyses

The sensitivity analysis restricted to symptomatic VTE in the total study group yielded comparable results (*Online Supplementary Appendix text 5*). The 6-month risk of symptomatic VTE in high-risk patients ranged from 3.7% (95%CI: 1.2-8.6%) for the Khorana score to 6.2% (95%CI: 3.8-9.4%) for the PROTECHT score.

In the sensitivity analysis restricted to the first 90 days of follow up, in which 34 of 876 patients (3.9%) developed VTE, the discriminatory performance of all scores was slightly better (*Online Supplementary Appendix text 6*). The 90-day VTE incidence in high-risk patients (≥3 points) ranged from 3.6% (95%CI: 1.2-8.4%) for the Khorana score to 6.4% (95%CI: 3.7-10%) for the Vienna CATS score and 6.4% (95%CI: 4.0-9.6%) for the PROTECHT score. The results from the complete case analysis did not substantially differ from the analysis of the imputed datasets (*Online Supplementary Appendix text 7*).

Results of the multivariable analyses are shown in *Online Supplementary Appendix text 8*. None of the Khorana score items were significantly associated with VTE in any of the scores. In the Vienna CATS score, the dichotomized D-dimer result was significantly associated with VTE (SHR 2.4; 95%CI: 1.3-4.4), while in the PROTECHT score, both gemcitabine (SHR 3.7; 95%CI: 1.8-7.6) and platinum-based chemotherapy (SHR 2.8; 95%CI: 1.4-5.6) were associated with VTE conditional on the other items.

Discussion

This multinational, prospective cohort study provides a direct comparison of the performance of four clinical and biomarker-based prediction scores for VTE in patients with advanced solid cancer receiving chemotherapy. All scores had a poor discriminatory performance, although the Vienna CATS and PROTECHT scores were able to discriminate between high- and low-risk patients when used dichotomously in the complete study group. The 6-month VTE incidence among patients classified as high-risk by these two scores was approximately 2-fold higher than in low-risk patients.

The poor overall discriminatory performance of the scores could partly be explained by the findings of the multivariable analysis. Hemoglobin levels, white blood cell counts, and platelet counts were not significantly associated with VTE. In a large prospective cohort study, Posch and colleagues also showed that the predictive performance of these items was limited,[22] thereby questioning the relevance of these items for VTE risk prediction in cancer patients. In addition, in the present study, only 3% of patients had a BMI over 35 kg/m^2, of whom none developed VTE. The low prevalence of obesity among cancer patients led Pelzer and colleagues to propose the CONKO score, in which BMI was replaced with World Health

Organization performance status.[10] However, we did not observe any significant improvement in discriminatory performance of this modified score compared to the Khorana score.

The Vienna CATS and PROTECHT score were the only two scores that could identify high-risk patients when used dichotomously. However, this significant association was observed in the complete study group, but not in patients enrolled prior to chemotherapy. Since the characteristics of patients enrolled prior to and during chemotherapy were comparable, possible explanations include differences in unobserved confounders or imprecision in the estimates. The predictive performance of the two scores in the complete study group appeared to be predominantly driven by the predictive performance of D-dimer levels in the Vienna CATS score and type of chemotherapy in the PROTECHT score, which could explain why they performed better than the Khorana and CONKO scores. Drawbacks of the Vienna CATS score include measuring D-dimer and soluble P-selectin, which may be difficult in clinical practice, while the PROTECHT score is more complex than the Khorana score because another two items are added. Moreover, the risk of VTE patients classified as low-risk by these scores was still appreciable, with 6-month rates of 5-6%, compared to 8-10% in high-risk patients.

The Khorana score has already been extensively evaluated in various studies with different patient populations and duration of follow up. In studies restricting enrollment to single tumor types, such as pancreatic[13,23] and lung cancer,[12] the Khorana score was often not able to discriminate between low- and high-risk patients, while other studies did confirm the score's predictive ability.[8,24,25] In addition, in the present study, differences in case-mix compared to the derivation study may partly explain the poor performance. For example, in the present study, the proportion of patients with esophageal cancer was higher and enrollment was restricted to patients with advanced cancer. However, evaluating clinical prediction score in other settings and populations is the very essence of external validation studies; a score should maintain its predictive performance across a broad spectrum of patients, including those more recently treated, as well as different geographical locations, before it can be adopted into clinical practice.

It has to be noted that the original Khorana score was derived in a study with a median follow up of only 2.5 months and that not all cancer types were represented. Whether results should be extrapolated to other tumor types, and whether clinical and laboratory information obtained prior to chemotherapy remains predictive beyond the initial cancer treatment period remains uncertain. This notion was supported by additional analyses, in which we observed that the area under the time-dependent ROC-curves decreased rapidly during the first weeks of follow up (*data not shown*). Similarly, in the sensitivity analysis restricted to the first three months of follow up, the discriminatory performance of the dichotomized Vienna CATS and PROTECHT scores appeared to improve somewhat compared to the complete follow-up period.

The present prospective study is one of the largest in which multiple prediction scores for cancer-associated VTE were evaluated in a representative sample of patients with various tumor types. By restricting enrollment to

patients with locally advanced or metastatic solid cancers, the majority of the patients received long-term palliative rather than short-term neoadjuvant chemotherapy, resembling the populations enrolled in trials evaluating thromboprophylaxis in ambulatory cancer patients.[26,27] Loss to follow up was minimal and outcome events were centrally verified blinded to the score results to prevent outcome bias. The multinational design of the study prevented potential single-center bias and strengthens the external validity of the findings.[28]

Our study has several limitations that merit consideration. We realize that the evaluated prediction scores all include pre-chemotherapy blood counts, while our study was designed to also include patients who had recently started chemotherapy. The main analysis was therefore restricted to 260 patients who were about to start their anticancer treatment. For patients who were receiving chemotherapy at enrollment, retrospectively collected pre-chemotherapy blood counts were used to calculate the scores to avoid potential effects of chemotherapy. The number of events observed in patients enrolled prior to chemotherapy (n=20) was sufficient to detect potential differences in VTE incidence between low- and high-risk patients, although the power may have been somewhat lower. Given the small difference in VTE risk between low- and high-risk patients, it is unlikely that a larger sample of patients enrolled prior to chemotherapy would have altered our conclusions.

Along the same line, the enrollment of patients who had already started chemotherapy may have resulted in immortal time bias. Since the risk of VTE is usually highest in the first months of chemotherapy, the estimate of the absolute VTE risk may have been conservative. In addition, if the scores were to have been truly predictive, the performance of the scores may have been underestimated. However, the findings in the complete study group were similar (and even slightly better) to those in the group enrolled prior to chemotherapy.

Sudden deaths were not routinely adjudicated for fatal PE, although PE was considered to be fatal if autopsy confirmed the diagnosis or when PE was objectively confirmed prior to death. Still, this approach may have resulted in a conservative estimate of the VTE incidence. As the proportion of such lethal events among all events is often small, relative risk estimates are unlikely to be affected.

We realize that the evaluated scores were predominantly derived from observations of symptomatic events. Since treatment recommendations are similar for incidental and for symptomatic events, thromboprophylaxis is just as important to prevent incidental VTE. These events were, therefore, included in the primary outcome. The findings of the sensitivity analysis restricted to symptomatic events was comparable to those from the overall analysis, suggesting that the examined scores have similar performance in predicting incidental events.

A different D-dimer assay was used in the present study than in the derivation study of the Vienna CATS score, which could have impacted on the discriminatory performance of the dichotomous D-dimer result. Nevertheless, D-dimer was one of the strongest predictors of VTE in the multivariable analysis, suggesting that the evaluated threshold of 1.44 mg/L may be a reasonable one, also for other assays.

What are the clinical implications of the present findings and the future steps for using prediction tools for cancer-associated VTE? A recent Cochrane systematic review demonstrated that LMWH in prophylactic doses reduces the relative risk of symptomatic VTE by 46% when compared to no thromboprophylaxis.[1] Assuming that these findings also apply to high-risk patients, the use of the Vienna CATS or PROTECHT scores to select patients for thromboprophylaxis could theoretically result in an absolute risk reduction of approximately 4-5% with a score of 20-25 needed in order to decide to start treatment. Subcutaneous injections for six months can be burdensome, perhaps even more for oncological patients with a limited life expectancy. The same Cochrane review also showed that LMWH thromboprophylaxis was associated with a non-significant 44% increase in the risk of major bleeding with a score of 125 needed before treatment is considered harmful; this should be carefully balanced against the potential benefits.

Future studies should aim to refine current risk prediction tools or develop new models in order to further improve the risk-benefit ratio of thromboprophylaxis in ambulatory cancer patients. Risk models that take into account the differences in baseline risk and prognostic factors across various types of cancer would allow personalized risks to be calculated more precisely by only using predictors that are relevant for a specific cancer type. Whether thromboprophylaxis with direct oral anticoagulants is a safe, effective, and less burdensome alternative in ambulatory cancer patients is currently being investigated in several ongoing trials that use the Khorana score for risk stratification (*e.g. clinicaltrials.gov identifiers: 02555878* and *02048865*). Interestingly, one of the trials applies the Khorana score at a lower positivity threshold of 2 points, which classifies a greater proportion of patients in the high-risk group, but in parallel may decrease the positive predictive value of the score.

The present findings do not support the use of any of the examined scores to select patients for thromboprophylaxis. The discriminatory performance of the dichotomized Vienna CATS and PROTECHT scores is somewhat encouraging, but confirmation in subsequent observational and intervention studies providing thromboprophylaxis to high-risk patients is needed before they can be used in clinical practice.

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