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Long-term performance of risk scores for venous thromboembolism in ambulatory cancer patients

Running head: Prediction scores for cancer-associated thrombosis

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Abstract

The long-term performance of prediction scores for venous thromboembolism (VTE) in cancer patients has been poorly investigated. We evaluated the discriminatory performance of the Khorana, PROTECHT, CONKO, and ONKOTEV scores for the first 3-6 months and for 12 months, and re-assessed scores after 3-6 months to determine the influence of variations in patients' risk classification on performance.

Retrospective cohort of ambulatory patients with active cancer who were scheduled to receive first or new line of chemotherapy. The primary outcome was symptomatic or incidental VTE.

A total of 776 patients were included of whom 540 (70%) had distant metastases. The time-dependent c-statistics of Khorana, PROTECHT, CONKO, and ONKOTEV scores at 6 months were 0.61 (95% CI, 0.56 to 0.66), 0.61 (95% CI, 0.55 to 0.66), 0.60 (95% CI, 0.54 to 0.66), and 0.59 (0.52 to 0.66), respectively, with a tendency to decrease during follow-up. None of the scores discriminated between high and low risk patients at the conventional 3-point positivity threshold. The use of a 2-point positivity threshold improved performance of all scores and captured a higher proportion of VTE. The accuracy of risk scores re-assessed at 3-6 months was modest.

The Khorana, PROTECHT, CONKO, and ONKOTEV scores are not sufficiently accurate when used at a conventional threshold of 3 points. Performance improves at positivity threshold of 2 points, as evaluated in recent randomized studies on VTE prophylaxis. Score accuracy tends to decrease over time suggesting the need of periodic re-evaluation to estimate possible variation of risk.

Keywords: neoplasms, venous thrombosis, venous thromboembolism, predictive value of tests, biomarkers

Key points

- VTE is a frequent complication in patients with cancer, but most of these patients will not develop thrombosis during the course of their disease
- Prediction scores have been developed to identify cancer patients at higher risk of VTE in whom the benefits of thromboprophylaxis would not be offset by the risk of bleeding
- At the conventional 3-point threshold, the Khorana, PROTECHT, CONKO, and ONKOTEV scores perform poorly
- Performance improves at 2-point positivity threshold, but residual VTE risk remains substantial
- Score accuracy decreases over time suggesting the need of periodic re-evaluation

Introduction

Although venous thromboembolism (VTE) represents a frequent complication in patients with cancer undergoing chemotherapy, most of these patients will not develop thrombosis during the course of their disease [1-2]. Therefore, broad, routine use of pharmacological thromboprophylaxis would unnecessarily expose most of these patients to burdensome long-term subcutaneous heparin administration as well as to the risk of anticoagulant-related bleeding [3].

Several studies have attempted to identify cancer patients at higher risk of VTE in whom the benefits of thromboprophylaxis would not be offset by the risk of bleeding [4-5]. One of the most extensively evaluated VTE risk stratification tools for cancer patients is the score developed by Khorana and colleagues, which is calculated by assigning points to the type of tumor, low hemoglobin level or use of erythropoietic agents, high body mass index, and high platelet or white blood cell count (Supplementary Table 1) [6]. In the derivation study including over 3,000 ambulatory cancer patients, the score identified a high-risk group in whom the incidence of VTE was 7% during a mean follow-up of 3 months. These findings were replicated in a number of external cohort studies [4,7]. Similarly, two recent randomized clinical trials of pharmacological prophylaxis including cancer patients at high risk of VTE according to the Khorana score reported a VTE incidence of around 10% in patients receiving placebo, which support the use of this score to identify patients at risk of VTE [8-9]. In contrast, in a large meta-analysis of over 34,000 cancer patients, the incidence of VTE in low or intermediate risk groups according to the Khorana score was not negligible, and over half of the patients who ultimately developed cancer-associated VTE did not qualify for thromboprophylaxis based on their risk score profile [10]. Patients with a low Khorana score were not randomized nor prospectively followed in the two recent randomized studies, which leaves unclear how many eventually experienced VTE [8-9].

Efforts have been made to increase the performance of the Khorana score or derive new prediction models. For example, the Khorana score could be improved by adding measurement of D-dimer and soluble P-selectin [11], adding use of gemcitabine or platinum compounds [12], by

replacing body mass index with functional status [13], and by adding metastatic disease, vascular compression, and previous VTE to the dichotomized Khorana score (Supplementary Table 1)[14]. Nonetheless, a recent prospective validation study with 6-month follow-up found that the performance of most of these scores was still suboptimal as indicated by low c-statistics [7]. In addition, the accuracy of prediction tools for VTE in cancer patients over follow-up periods longer than 3 to 6 months has been poorly investigated. Preliminary observations suggest that performance decreases after the first weeks of follow-up [7]. Since all these scores include parameters that can vary over time, this may ultimately result in changes of patients' risk classification and score performance.

The aims of this study were to compare the discriminatory performance of the Khorana, PROTECHT, CONKO, and ONKOTEV scores for the first 3 to 6 months versus 12 months of follow-up, and to re-assess all scores after 3 to 6 months to determine variations of patients' risk classification and performance of the follow-up score compared to the score calculated at start of chemotherapy. In addition, we validated the long-term accuracy of the scores at a 2-point positivity threshold, as used in recently completed randomized studies on VTE prophylaxis in patients with cancer [8-9].

Materials and Methods

Study population

We conducted a single-center, retrospective cohort study of patients with recurrent, regionally advanced, or metastatic cancer in whom the Khorana, PROTECHT, CONKO, and ONKOTEV scores were calculated before the start of a first or new line of chemotherapy. Exclusion criteria were ongoing anticoagulant treatment for VTE diagnosed prior to start of chemotherapy or for other indications, or use of outpatient thromboprophylaxis during the study. The study was approved by the local institutional review board.

Study Outcomes

The primary outcome of the study was symptomatic or incidental VTE, defined as distal or proximal deep vein thrombosis (DVT) of the leg, upper extremity DVT, and/or pulmonary embolism (PE) [15]. Incidental VTE was defined as VTE detected by imaging tests performed for other reasons than VTE suspicion, such as assessment of response to cancer treatment, cancer re-staging or the diagnostic work-up of cancer-related complications [16].

Secondary outcomes were major bleeding, clinically relevant non-major bleeding, arterial thromboembolism, superficial vein thrombosis, and overall mortality [17-18].

Statistical considerations

Standard descriptive statistics were used to summarize patient characteristics. We calculated the Khorana, PROTECHT, CONKO, and ONKOTEV score before start of chemotherapy and after 3 to 6 months. Tumor sites were categorized into “low/intermediate”, “high”, and “very-high” risk of VTE according to the Khorana score [6]. Patients were followed for the development of VTE up to 1 year since the start of chemotherapy. The Khorana score was assessed at the conventional positivity threshold of 3 points as well as at the exploratory 2-point threshold. We also evaluated the performance of the PROTECT, CONKO, and ONKOTEV scores which are modifications of the Khorana score (Supplementary Table 1) [12-14]. We could not assess the CATS score since D-dimer and soluble P-selectin are not measured routinely [11] nor the extensive COMPASS-CAT score because data on cardiovascular risk factors were not available [19].

Overall discrimination of the scores for PE and/or DVT was assessed with a time-dependent c-statistic, while accounting for death not related to VTE as a competing risk (R package *concreg*). The 95% confidence intervals were estimated by repeating the analyses in 250 bootstrap samples. The cumulative incidence in patients with a high and low risk score was estimated using the cumulative incidence function with 95% confidence intervals calculated using Choudhury’s method, considering death not related to VTE as a competing risk. Differences between high and low risk patients were quantified by calculating subdistribution hazard ratios (SHRs) based on the competing risk regression

model of Fine & Gray (R package *cmprsk*). A multivariable Fine & Gray model was used to assess the association of the individual score items with VTE. A sensitivity analysis restricted to symptomatic events was performed. Since the proportion of patients for whom the scores could not be calculated was low (<3%), we did not use multiple imputation methods. Analyses were performed in R, version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Between January 2011 and July 2017, 887 potentially eligible cancer patients were identified of whom 111 (12.5%) were excluded because of ongoing anticoagulant treatment for VTE (N=63), atrial fibrillation (N=37), or mechanical heart valve (N=2), or because they did not attend oncological follow-up visits after the initial evaluation due to rapid cancer progression (N=48). Baseline characteristics of the remaining 776 patients are summarized in Table 1. Mean age was 65 years and 61% was male. The most frequent tumor types were non-small lung cancer (29%), colorectal cancer (29%), and gynecological cancer (11%). The distribution of the risk scores at baseline and at follow-up re-assessment is shown in Table 2.

Follow-up and outcomes

The median overall follow-up duration was 330 days (interquartile range [IQR], 159 to 365). Overall, 69 patients (8.9%) developed a thrombotic event which was DVT in 28 (3.6%), PE in 20 (2.6%), splanchnic DVT in 10 (1.3%), PE with DVT in 6 (0.8%), superficial vein thrombosis in 3 (0.4%), and arterial thrombosis in 2 (0.3%). Of the 54 PE, DVT, and PE with DVT, 27 events (50%) were symptomatic. -The 3-, 6-, and 12-month cumulative incidences of PE and/or DVT in the competing risk analysis were 2.8% (95% CI, 1.8 to 4.2), 5.6% (95% CI, 4.2 to 7.4), and 7.2% (95% CI, 5.5 to 9.2), respectively. The median time to PE and/or DVT was 104 days (95% CI, 64 to 172). During follow-up, 343 patients (44%) died and 5 (0.6%) were lost to follow-up.

Performance of baseline risk scores

The overall discriminatory performance of the baseline scores for PE and/or DVT is shown in Table 3. The time-dependent c-statistics of the Khorana, PROTECHT, CONKO, and ONKOTEV scores at 180 days were 0.61 (95% CI, 0.56 to 0.66), 0.61 (95% CI, 0.55 to 0.66), 0.60 (95% CI, 0.54 to 0.66), and 0.59 (0.52 to 0.66), respectively (Supplementary Figures 1A-D). The sensitivity analysis restricted to symptomatic events yielded comparable results (c-statistics 0.63, 0.62, 0.62, and 0.56 for the Khorana, PROTECHT, CONKO, and ONKOTEV scores, respectively).

Using the conventional positivity threshold of 3 points, the Khorana, PROTECHT, CONKO, and ONKOTEV scores classified 12%, 42%, 12%, and 2.6% of patients as high risk (Table 2). The cumulative incidence of VTE at 6 months in these high-risk patients was 3.5%, 7.6%, 4.4%, and 15% respectively, compared to 6.0%, 4.4%, 5.9%, and 5.4% in the low risk groups. The corresponding SHRs for high vs. low risk were 0.58 (95% CI, 0.18 to 0.87), 1.8 (95% CI, 0.98 to 3.3), 0.73 (95% CI, 0.26 to 2.1), and 3.0 (95% CI, 0.91 to 10) for the Khorana, PROTECHT, CONKO, and ONKOTEV scores, respectively (Figures. 1A-D). Data for the 12-month study period are presented in Table 3.

Using the alternative positivity threshold of 2 points, the Khorana, PROTECHT, CONKO, and ONKOTEV scores classified 40%, 71%, 39%, and 33% of patients as high risk (Table 2). In these high-risk groups, the cumulative incidences of PE or DVT at 6 months were 7.7%, 7.8%, 7.3%, and 7.2% compared to 4.4%, 0.5%, 4.7%, and 4.8% in patients with a low risk score, respectively. The corresponding SHRs for high vs. low risk patients were 1.8 (95% CI, 0.98 to 3.3), 17 (95% CI, 2.3 to 122), 1.6 (95% CI, 0.89 to 3.0), and 1.5 (95% CI, 0.83 to 2.8) for the Khorana, PROTECHT, CONKO, and ONKOTEV scores, respectively (Figures 2A-D).

In multivariable competing risk analyses, all score items except high platelet count had a positive association with PE and/or DVT at 6 months (Supplementary Table 2). The only items that met statistical significance were platinum-based chemotherapy in the PROTECHT score (SHR 2.5; 95% CI, 1.1 to 6.1) and previous VTE in the ONKOTEV score (SHR 17; 95% CI, 5.2 to 52).

Performance of risk scores re-assessed at 3 to 6 months

Re-assessment of the risk scores was done in 606 of 618 patients who were alive and without thrombosis (98%) at a median follow-up of 158 days (IQR, 113 to 179). From this re-assessment until the end of follow-up, 15 patients (2.5%) developed a thrombotic event of which 12 events (2.0%) were PE and/or DVT. At the conventional positivity threshold of 3 points, the re-assessed Khorana, PROTECHT, CONKO, and ONKOTEV scores re-classified 12%, 32%, 12%, and 1% of patients, respectively (Supplementary Tables 3A-D). Overall, 10%, 14%, 11%, and 3% of patients were classified as being at high risk by the re-assessed Khorana, PROTECHT, CONKO, and ONKOTEV scores. The cumulative incidence of PE or DVT at 180 days after re-assessment was 3.3%, 2.4%, 3.0%, and 5.6% in patients with a high-risk Khorana, PROTECHT, CONKO, and ONKOTEV score, respectively (Supplementary Table 4). These numbers were 1.9%, 2.0%, 1.9%, and 0.70% in those with a low risk score, corresponding to SHRs of 1.8 (95% CI, 0.38 to 8.0), 1.2% (95% CI, 0.26 to 5.5), 1.6 (95% CI, 0.34 to 7.1), and 8.1 (95% CI, 0.93 to 71), respectively.

DISCUSSION

This study confirms the poor overall discriminatory performance of the Khorana, PROTECHT, CONKO, and ONKOTEV scores for the prediction of DVT or PE in patients with cancer receiving chemotherapy. When used dichotomously, none of the scores was able to identify a group of patients with a significantly higher risk of VTE. Yet, the use of a lower positivity threshold of 2 points was associated with improved performance of all scores, but in particular the PROTECHT and CONKO scores. Time-dependent analysis suggested that scores' discrimination tends to decrease during follow-up, with limited or no value of the scores beyond the first 3 to 6 months. Re-evaluation of the four scores at 3 to 6 months changed the indication for pharmacological thromboprophylaxis in 12% up to 32% of

patients, but the use of a re-assessed score is questionable because of the low risk of DVT or PE in the following 6 months.

The Khorana score was derived in a cohort of cancer patients and subsequently externally validated [4]. In a recent large meta-analysis including more than 34,000 patients, the score was able to identify a group of patients with a higher risk of VTE (odds ratio 1.8 for high vs. lower risk); however, patients classified as being at low (0 points) or intermediate risk (1 or 2 points) had an incidence of VTE that was as high as 5.1% and 6.6%, respectively [10]. Consistently, we found an incidence of 6% in patients with a Khorana score below 3 points. Interestingly, the performance of the Khorana as well as all other scores seemed to improve substantially at a positivity threshold of 2 points as evidenced by the identification of a larger proportion of patients who eventually developed VTE and the significant difference between high and low risk patients. Although not formally derived and validated, the Khorana score at a positivity threshold of 2 points has been used by two recently completed randomized trials of primary prophylaxis to select ambulatory cancer patients at high risk of VTE [8-9]. Both studies demonstrated that 6-month prophylaxis with apixaban or rivaroxaban reduce the incidence of VTE compared with placebo, without significantly increasing the risk of major bleeding [8-9]. These trials did not include patients with a Khorana score of 1 point or less in whom the incidence of VTE was 4.4% in our study and 5.5% in the abovementioned meta-analysis. These observations suggest substantial residual VTE risk and imply that about half of patients with cancer who eventually develop VTE may not be candidate for thromboprophylaxis according to the score.

Consistent with these findings, a prospective study showed limited ability of multiple prediction scores to identify the majority of cancer patients developing VTE [7]. Failures to replicate initial findings and variations in risk score performance could stem from differences in patient populations, clinical settings, or time periods [10]. In addition, in a pooled analysis of two large cohorts, only tumor type was predictive of VTE, while all other components of the Khorana score were not associated with the development of VTE [20]. In the current study, multivariable analysis confirmed that tumor type is the only predictor of VTE in the Khorana score, though this association

did not reach statistical significance. This finding likely depends on the relatively low number of patients with high-risk tumor as well as the inclusion of tumor types that were infrequent in the derivation study, though shown to be associated with a higher risk of VTE in subsequent analyses [7,20]. Taken together, current evidence from cohort studies, a subsequent large meta-analysis, as well as two recently published randomized clinical trials support the use of a risk stratification strategy to select cancer patients for thromboprophylaxis. However, future studies should evaluate ways to improve efficiency of risk stratification to reduce the proportion of patients with VTE who are erroneously classified as at low risk.

Preliminary observations suggest that the accuracy of most scores for VTE prediction in cancer patients decreases during the first weeks of follow-up [7]. In time-dependent analysis, the modest scores' performance tended to decrease further beyond the initial 3 to 6 months, which could partly depend on VTE risk factors not present at baseline yet emerging during the dynamic cancer journey. In addition, most components of the risk scores including body weight, performance status, and blood counts often fluctuate during the course of cancer disease because of cancer treatment, co-morbidities, or cancer progression. As a result, the importance of these variables is highly contingent to the time they are evaluated and may change over time potentially affecting risk stratification and long-term predictive value of the score. Therefore, in the present study, all scores were re-calculated after the first 3 months to assess the impact of these changes between the follow-up score relative to baseline. While the discriminatory performance of the score calculated at follow-up remained poor, the relatively low number of events beyond 3 to 6 months hampers firm conclusions.

The present retrospective study including various tumor types and using laboratory data collected before start of chemotherapy is one of the largest comparisons of multiple prediction scores for cancer-associated VTE. There are some limitations that need to be acknowledged. The collection of data at pre-specified time points for evaluation of the re-assessed scores was limited. However, the proportion of patients in whom the scores could not be calculated at follow-up was

lower than 2%. Second, the single-center design of the study may limit the external validity of the findings. Third, we could not evaluate the CATS score, since D-dimer and soluble P-selectin levels are not available in routine clinical practice, nor the extensive COMPASS-CAT score, because data on cardiovascular risk factors were not available. Fourth, the number of events may not have provided enough power to detect significant differences, especially in the multivariable analyses and analyses of the re-assessed scores.

In summary, the current study confirms that the Khorana, PROTECHT, CONKO, and ONKOTEV scores do not own sufficient accuracy to select patients for pharmacological thromboprophylaxis when used at a conventional positivity threshold of 3 points. Although performance of all scores was improved with the use of a positivity threshold of 2 points, incidence of VTE in patients classified as at low risk of VTE is not negligible. Score accuracy tends to decrease over time suggesting the need of periodic re-evaluation to estimate changes in patient's risk.

Addendum

Concept and design: MDN, EP. Interpretation of data, critical writing or revising the intellectual content, and final approval of the version to be published: MDN, NvE, LR, NA, LF, MDT, CN, NT, IC, EV, MC, AWSR, EP.

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Declarations of interest

None of the authors have potential conflicts of interest to declare in relation to the current work.

References

1. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. (2013) Epidemiology of cancer-associated venous thrombosis. Blood 122:1712-23.
2. Khorana AA, Francis CW, Culakova E, Lyman GH. (2005) Risk factors for chemotherapy-associated venous thromboembolism in a prospective observational study. Cancer 104:2822–2829.
3. Di Nisio M, Porreca E, Candeloro M, De Tursi M, Russi I, Rutjes AW. (2016) Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. Cochrane Database Syst Rev. 12:CD008500.
4. Khorana AA, Francis CW. (2018) Risk prediction of cancer-associated thrombosis: Appraising the first decade and developing the future. Thromb Res 164 Suppl 1:S70-S76.
5. Pabinger I, Thaler J, Ay C. (2013) Biomarkers for prediction of venous thromboembolism in cancer. Blood 122:2011-8.
6. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. (2008) Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 111:4902-4907.
7. van Es N, Di Nisio M, Cesarman G, Kleinjan A, Otten HM, Mahé I, Wilts IT, Twint DC, Porreca E, Arrieta O, Stépanian A, Smit K, De Tursi M, Bleker SM, Bossuyt PM, Nieuwland R, Kamphuisen PW, Büller HR. (2017) Comparison of risk prediction scores for venous thromboembolism in cancer patients: a prospective cohort study. Haematologica 102:1494-1501.
8. Carrier M, Abou-Nassar K, Mallick R, Tagalakis V, Shivakumar S, Schattner A, Kuruvilla P, Hill D, Spadafora S, Marquis K, Trinkaus M, Tomiak A, Lee AYY, Gross PL, Lazo-Langner A, El-Maraghi R, Goss G, Le Gal G, Stewart D, Ramsay T, Rodger M, Witham D, Wells PS; AVERT

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Investigators. (2019~~8~~) Apixaban to prevent venous thromboembolism in patients with cancer. N Engl J Med 380:711-719~~2018. doi: 10.1056/NEJMoa1814468~~.

9. Khorana AA, Soff GA, Kakkar AK, Vadhan-Raj S, Riess H, Wun T, Streiff MB, Garcia DA, Liebman HA, Belani C, O'Reilly EM, Patel JN, Yimer HA, Wildgoose P, Burton P, Vijapurkar U, Kaul S, Eikelboom J, McBane RD, Bauer KA, Kuderer NM, Lyman GH, CASSINI Investigators. (2019~~8~~) Rivaroxaban thromboprophylaxis in high-risk ambulatory cancer patients receiving systemic therapy: results of a randomized clinical trial ~~(CASSINI)~~. ~~ASH meeting 2018; San Diego: BA 1~~N Engl J Med 380:720-728.
10. Mulder FI, Candeloro M, van Es N, Di Nisio M, Buller HR, Kamphuisen PW. (2019) Can we use the Khorana risk score to predict venous thromboembolism in patients with cancer? A systematic review and meta-analysis. Haematologica. doi: 10.3324/haematol.2018.209114
11. Ay C, Dunkler D, Marosi C, Chiriac AL, Vormittag R, Simanek R, Quehenberger P, Zielinski C, Pabinger I. (2010) Prediction of venous thromboembolism in cancer patients. Blood 116:5377-5382.
12. Verso M, Agnelli G, Barni S, Gasparini G, LaBianca R. (2012) A modified Khorana risk assessment score for venous thromboembolism in cancer patients receiving chemotherapy: the Protecht score. Intern Emerg Med 7:291–292.
13. Pelzer U, Opitz B, Deutschinoff G, Stauch M, Reitzig PC, Hahnfeld S, Müller L, Grunewald M, Stieler JM, Sinn M, Denecke T, Bischoff S, Oettle H, Dörken B, Riess H. (2015) Efficacy of Prophylactic low–molecular weight heparin for ambulatory patients with advanced pancreatic cancer: outcomes from the CONKO-004 Trial. J Clin Oncol 33:2028-34.
14. Cella CA, Di Minno G, Carlomagno C, Arcopinto M, Cerbone AM, Matano E, Tufano A, Lordick F, De Simone B, Muehlberg KS, Bruzzese D, Attademo L, Arturo C, Sodano M, Moretto R, La Fata E, De Placido S. (2017) Preventing venous thromboembolism in ambulatory cancer patients: the ONKOTEV study, Oncologist 22:601–608.

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15. Di Nisio M, van Es N, Büller HR. (2016) Deep vein thrombosis and pulmonary embolism. Lancet 388(10063):3060-3073.
16. Khorana AA, O'Connell C, Agnelli G, Liebman HA, Lee AYY, On Behalf of the Subcommittee on Hemostasis and Malignancy of the SSC of the ISTH. (2012) Incidental venous thromboembolism in oncology patients. J Thromb Haemost 10: 2602–4.
17. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. (2005) Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 3:692-694.
18. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S, Subcommittee on Control of Anticoagulation. (2015) Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost 13:2119-2126.
19. Gerotziafas GT, Taher A, Abdel-Razeq H, AboElnazar E, Spyropoulos AC, El Shemmari S, Larsen AK, Elalamy I; COMPASS–CAT Working Group. (2017) A predictive score for thrombosis associated with breast, colorectal, lung, or ovarian cancer: the prospective COMPASS-cancer-associated thrombosis study. Oncologist 22:1222–1231.
20. Pabinger I, van Es N, Heinze G, Posch F, Riedl J, Reitter EM, Di Nisio M, Cesarman-Maus G, Kraaijpoel N, Zielinski CC, Büller HR, Ay C. (2018) A clinical prediction model for cancer-associated venous thromboembolism: a development and validation study in two independent prospective cohorts. Lancet Haematol 5:e289-e298.

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Table 1. Patient characteristics

	N=776
Age, y, mean (SD)	65 (11)
Male sex, n (%)	471 (61)
Body mass index, kg/m^2	
Mean (SD)	26 (4.6)
≥35 kg/m^2, n (%)	35 (4.5)
Tumor type, n (%)	
Lung cancer	277 (36)
Colorectal	224 (29)
Gynecological	88 (11)
Pancreatic	71 (9.1)
Stomach	58 (7.5)
Urogenital	37 (4.8)
Hepatobiliary	21 (2.7)
Distant metastasis, n (%)	540 (70)
WHO performance status, n (%)	
0	510 (66)
1	226 (29)
≥2	37 (4.8)
Missing	3 (0.4)
Vascular compression or infiltration, n (%)	47 (6.1)
Chemotherapy, n (%)	
Platinum-based	413 (53)
Gemcitabin	105 (14)
Other	153 (20)
Missing	7 (0.9)
Central venous catheter, n (%)	51 (6.6)
Surgery in previous 4 weeks, n (%)	137 (18)
Previous venous thromboembolism, n (%)	6 (0.8)
Erythropoietin stimulating agents, n (%)	20 (2.6)
Hemoglobin, g/dL	
Median (IQR)	13 (11-14)
<10 g/dL, n (%)	48 (6.2)
White blood cell count, x 10^9/L	
Median (IQR)	7.0 (5.5-9.2)
>11 x 10^9/L, n (%)	104 (13)
Platelet count, x 10^9/L	
Median (IQR)	258 (198-332)
≥350 x 10^9/L, n (%)	162 (21)

Abbreviations: IQR, interquartile range; SD, standard deviation.

Table 2. Distribution of risk scores

	Baseline scores (N=776)				Re-assessed scores (N=606)			
	Khorana	**PROTECHT**	**CONKO**	**ONKOTEV**	**Khorana**	**PROTECHT**	**CONKO**	**ONKOTEV**
Points, n (%)								
0	172 (22)	65 (8.4)	174 (22)	150 (19)	168 (28)	149 (25)	166 (27)	99 (16)
1	287 (37)	145 (19)	285 (37)	355 (46)	213 (35)	217 (36)	222 (37)	304 (50)
2	218 (28)	228 (29)	211 (27)	235 (30)	155 (26)	146 (24)	144 (24)	172 (28)
3	76 (9.8)	211 (27)	80 (10)	20 (2.6)	51 (8.4)	64 (11)	54 (8.9)	18 (3.0)
4	13 (1.7)	87 (11)	14 (1.8)	0	9 (1.5)	18 (3.0)	9 (1.5)	0
5	1 (0.1)	21 (2.7)	1 (0.1)	-	1 (0.2)	2 (0.3)	2 (0.3)	-
6	0	3 (0.4)	0	-	0	1 (0.2)	0	-
Missing	9 (1.2)	16 (2.1)	11 (1.4)	16 (2.1)	9 (1.5)	9 (1.5)	9 (1.5)	13 (2.1)
Positivity threshold 3 points, n (%)								
Low risk (≤2 points)	678 (87)	438 (56)	670 (86)	740 (95)	536 (88)	512 (85)	532 (88)	575 (95)
High risk (≥3 points)	89 (12)	322 (42)	95 (12)	20 (2.6)	61 (10)	85 (14)	65 (11)	18 (3.0)
Positivity threshold 2 points, n (%)								
Low risk (≤1 points)	460 (59)	210 (27)	459 (59)	505 (65)	381 (63)	366 (60)	388 (64)	403 (67)
High risk (≥2 points)	307 (40)	550 (71)	306 (39)	255 (33)	216 (36)	231 (38)	209 (35)	190 (31)

Table 3. Performance of the risk scores for deep vein thrombosis or pulmonary embolism at the positivity threshold of 3 and 2 points

	Khorana score		PROTECHT score		CONKO score		ONKOTEV score	
Time-dependent c-index (95% CI)								
At 90 days	0.63 (0.55-0.71)		0.63 (0.55-0.72)		0.61 (0.54-0.69)		0.62 (0.51-0.74)	
At 180 days	0.61 (0.56-0.66)		0.61 (0.55-0.66)		0.60 (0.54-0.66)		0.59 (0.52-0.66)	
At 365 days	0.59 (0.54-0.65)		0.57 (0.51-0.63)		0.59 (0.53-0.65)		0.57 (0.50-0.64)	
	3-point threshold	**2-point threshold**	**3-point threshold**	**2-points threshold**	**3-point threshold**	**2-points threshold**	**3-point threshold**	**2-points threshold**
6-month follow-up								
VTE risk in low risk patients, % (95% CI)	6.0 (4.4-8.0)	4.4 (2.8-6.6)	4.4 (2.8-6.7)	0.50 (0.04-2.5)	5.9 (4.3-7.9)	4.7 (3.0-6.9)	5.4 (3.9-7.2)	4.8 (3.2-7.0)
VTE risk in high risk patients, % (95% CI)	3.5 (0.9-9.1)	7.7 (5.0-11)	7.6 (5.0-11)	7.8 (5.7-10)	4.4 (1.4-10)	7.3 (4.7-11)	15 (3.5-34)	7.2 (4.4-11)
SHR for high vs low risk patients	0.58 (0.18-0.87)	1.8 (0.98-3.3)	1.8 (0.97-3.2)	17 (2.3-122)	0.73 (0.26-2.1)	1.6 (0.89-3.0)	3.0 (0.91-10)	1.5 (0.83-2.8)
12-month follow-up								
VTE risk in low risk patients, % (95% CI)	7.6 (5.7-9.8)	5.9 (3.9-8.3)	6.2 (4.2-8.8)	2.1 (0.68-4.9)	7.6 (5.7-9.8)	6.1 (4.1-8.6)	6.9 (5.2-8.9)	6.6 (4.6-9.1)
VTE risk in high risk patients, % (95% CI)	4.8 (1.5-11)	9.4 (6.4-13)	8.6 (5.8-12)	9.2 (6.9-12)	5.5 (2.0-12)	9.1 (6.2-13)	20 (5.9-40)	8.5 (5.4-12)
SHR for high vs low risk patients	0.62 (0.22-1.7)	1.74 (0.99-2.9)	4.5 (0.85-2.5)	4.9 (1.8-14)	0.73 (0.29-1.8)	1.6 (0.91-2.6)	3.2 (1.2-9.1)	1.3 (0.77-2.3)

Abbreviations: VTE, venous thromboembolism; SHR, subdistribution hazard.

Long-term performance of risk scores for venous thromboembolism in ambulatory cancer patients

Running head: Prediction scores for cancer-associated thrombosis

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Abstract

The long-term performance of prediction scores for venous thromboembolism (VTE) in cancer patients has been poorly investigated. We evaluated the discriminatory performance of the Khorana, PROTECHT, CONKO, and ONKOTEV scores for the first 3-6 months and for 12 months, and re-assessed scores after 3-6 months to determine the influence of variations in patients' risk classification on performance.

Retrospective cohort of ambulatory patients with active cancer who were scheduled to receive first or new line of chemotherapy. The primary outcome was symptomatic or incidental VTE.

A total of 776 patients were included of whom 540 (70%) had distant metastases. The time-dependent c-statistics of Khorana, PROTECHT, CONKO, and ONKOTEV scores at 6 months were 0.61 (95% CI, 0.56 to 0.66), 0.61 (95% CI, 0.55 to 0.66), 0.60 (95% CI, 0.54 to 0.66), and 0.59 (0.52 to 0.66), respectively, with a tendency to decrease during follow-up. None of the scores discriminated between high and low risk patients at the conventional 3-point positivity threshold. The use of a 2-point positivity threshold improved performance of all scores and captured a higher proportion of VTE. The accuracy of risk scores re-assessed at 3-6 months was modest.

The Khorana, PROTECHT, CONKO, and ONKOTEV scores are not sufficiently accurate when used at a conventional threshold of 3 points. Performance improves at positivity threshold of 2 points, as evaluated in recent randomized studies on VTE prophylaxis. Score accuracy tends to decrease over time suggesting the need of periodic re-evaluation to estimate possible variation of risk.

Keywords: neoplasms, venous thrombosis, venous thromboembolism, predictive value of tests, biomarkers

Key points

- VTE is a frequent complication in patients with cancer, but most of these patients will not develop thrombosis during the course of their disease
- Prediction scores have been developed to identify cancer patients at higher risk of VTE in whom the benefits of thromboprophylaxis would not be offset by the risk of bleeding
- At the conventional 3-point threshold, the Khorana, PROTECHT, CONKO, and ONKOTEV scores perform poorly
- Performance improves at 2-point positivity threshold, but residual VTE risk remains substantial
- Score accuracy decreases over time suggesting the need of periodic re-evaluation

Introduction

Although venous thromboembolism (VTE) represents a frequent complication in patients with cancer undergoing chemotherapy, most of these patients will not develop thrombosis during the course of their disease [1-2]. Therefore, broad, routine use of pharmacological thromboprophylaxis would unnecessarily expose most of these patients to burdensome long-term subcutaneous heparin administration as well as to the risk of anticoagulant-related bleeding [3].

Several studies have attempted to identify cancer patients at higher risk of VTE in whom the benefits of thromboprophylaxis would not be offset by the risk of bleeding [4-5]. One of the most extensively evaluated VTE risk stratification tools for cancer patients is the score developed by Khorana and colleagues, which is calculated by assigning points to the type of tumor, low hemoglobin level or use of erythropoietic agents, high body mass index, and high platelet or white blood cell count (Supplementary Table 1) [6]. In the derivation study including over 3,000 ambulatory cancer patients, the score identified a high-risk group in whom the incidence of VTE was 7% during a mean follow-up of 3 months. These findings were replicated in a number of external cohort studies [4,7]. Similarly, two recent randomized clinical trials of pharmacological prophylaxis including cancer patients at high risk of VTE according to the Khorana score reported a VTE incidence of around 10% in patients receiving placebo, which support the use of this score to identify patients at risk of VTE [8-9]. In contrast, in a large meta-analysis of over 34,000 cancer patients, the incidence of VTE in low or intermediate risk groups according to the Khorana score was not negligible, and over half of the patients who ultimately developed cancer-associated VTE did not qualify for thromboprophylaxis based on their risk score profile [10]. Patients with a low Khorana score were not randomized nor prospectively followed in the two recent randomized studies, which leaves unclear how many eventually experienced VTE [8-9].

Efforts have been made to increase the performance of the Khorana score or derive new prediction models. For example, the Khorana score could be improved by adding measurement of D-dimer and soluble P-selectin [11], adding use of gemcitabine or platinum compounds [12], by

replacing body mass index with functional status [13], and by adding metastatic disease, vascular compression, and previous VTE to the dichotomized Khorana score (Supplementary Table 1)[14]. Nonetheless, a recent prospective validation study with 6-month follow-up found that the performance of most of these scores was still suboptimal as indicated by low c-statistics [7]. In addition, the accuracy of prediction tools for VTE in cancer patients over follow-up periods longer than 3 to 6 months has been poorly investigated. Preliminary observations suggest that performance decreases after the first weeks of follow-up [7]. Since all these scores include parameters that can vary over time, this may ultimately result in changes of patients' risk classification and score performance.

The aims of this study were to compare the discriminatory performance of the Khorana, PROTECHT, CONKO, and ONKOTEV scores for the first 3 to 6 months versus 12 months of follow-up, and to re-assess all scores after 3 to 6 months to determine variations of patients' risk classification and performance of the follow-up score compared to the score calculated at start of chemotherapy. In addition, we validated the long-term accuracy of the scores at a 2-point positivity threshold, as used in recently completed randomized studies on VTE prophylaxis in patients with cancer [8-9].

Materials and Methods

Study population

We conducted a single-center, retrospective cohort study of patients with recurrent, regionally advanced, or metastatic cancer in whom the Khorana, PROTECHT, CONKO, and ONKOTEV scores were calculated before the start of a first or new line of chemotherapy. Exclusion criteria were ongoing anticoagulant treatment for VTE diagnosed prior to start of chemotherapy or for other indications, or use of outpatient thromboprophylaxis during the study. The study was approved by the local institutional review board.

Study Outcomes

The primary outcome of the study was symptomatic or incidental VTE, defined as distal or proximal deep vein thrombosis (DVT) of the leg, upper extremity DVT, and/or pulmonary embolism (PE) [15]. Incidental VTE was defined as VTE detected by imaging tests performed for other reasons than VTE suspicion, such as assessment of response to cancer treatment, cancer re-staging or the diagnostic work-up of cancer-related complications [16].

Secondary outcomes were major bleeding, clinically relevant non-major bleeding, arterial thromboembolism, superficial vein thrombosis, and overall mortality [17-18].

Statistical considerations

Standard descriptive statistics were used to summarize patient characteristics. We calculated the Khorana, PROTECHT, CONKO, and ONKOTEV score before start of chemotherapy and after 3 to 6 months. Tumor sites were categorized into “low/intermediate”, “high”, and “very-high” risk of VTE according to the Khorana score [6]. Patients were followed for the development of VTE up to 1 year since the start of chemotherapy. The Khorana score was assessed at the conventional positivity threshold of 3 points as well as at the exploratory 2-point threshold. We also evaluated the performance of the PROTECT, CONKO, and ONKOTEV scores which are modifications of the Khorana score (Supplementary Table 1) [12-14]. We could not assess the CATS score since D-dimer and soluble P-selectin are not measured routinely [11] nor the extensive COMPASS-CAT score because data on cardiovascular risk factors were not available [19].

Overall discrimination of the scores for PE and/or DVT was assessed with a time-dependent c-statistic, while accounting for death not related to VTE as a competing risk (R package *concreg*). The 95% confidence intervals were estimated by repeating the analyses in 250 bootstrap samples. The cumulative incidence in patients with a high and low risk score was estimated using the cumulative incidence function with 95% confidence intervals calculated using Choudhury’s method, considering death not related to VTE as a competing risk. Differences between high and low risk patients were quantified by calculating subdistribution hazard ratios (SHRs) based on the competing risk regression

model of Fine & Gray (R package *cmprsk*). A multivariable Fine & Gray model was used to assess the association of the individual score items with VTE. A sensitivity analysis restricted to symptomatic events was performed. Since the proportion of patients for whom the scores could not be calculated was low (<3%), we did not use multiple imputation methods. Analyses were performed in R, version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Between January 2011 and July 2017, 887 potentially eligible cancer patients were identified of whom 111 (12.5%) were excluded because of ongoing anticoagulant treatment for VTE (N=63), atrial fibrillation (N=37), or mechanical heart valve (N=2), or because they did not attend oncological follow-up visits after the initial evaluation due to rapid cancer progression (N=48). Baseline characteristics of the remaining 776 patients are summarized in Table 1. Mean age was 65 years and 61% was male. The most frequent tumor types were non-small lung cancer (29%), colorectal cancer (29%), and gynecological cancer (11%). The distribution of the risk scores at baseline and at follow-up re-assessment is shown in Table 2.

Follow-up and outcomes

The median overall follow-up duration was 330 days (interquartile range [IQR], 159 to 365). Overall, 69 patients (8.9%) developed a thrombotic event which was DVT in 28 (3.6%), PE in 20 (2.6%), splanchnic DVT in 10 (1.3%), PE with DVT in 6 (0.8%), superficial vein thrombosis in 3 (0.4%), and arterial thrombosis in 2 (0.3%). Of the 54 PE, DVT, and PE with DVT, 27 events (50%) were symptomatic. The 3-, 6-, and 12-month cumulative incidences of PE and/or DVT in the competing risk analysis were 2.8% (95% CI, 1.8 to 4.2), 5.6% (95% CI, 4.2 to 7.4), and 7.2% (95% CI, 5.5 to 9.2), respectively. The median time to PE and/or DVT was 104 days (95% CI, 64 to 172). During follow-up, 343 patients (44%) died and 5 (0.6%) were lost to follow-up.

Performance of baseline risk scores

The overall discriminatory performance of the baseline scores for PE and/or DVT is shown in Table 3. The time-dependent c-statistics of the Khorana, PROTECHT, CONKO, and ONKOTEV scores at 180 days were 0.61 (95% CI, 0.56 to 0.66), 0.61 (95% CI, 0.55 to 0.66), 0.60 (95% CI, 0.54 to 0.66), and 0.59 (0.52 to 0.66), respectively (Supplementary Figures 1A-D). The sensitivity analysis restricted to symptomatic events yielded comparable results (c-statistics 0.63, 0.62, 0.62, and 0.56 for the Khorana, PROTECHT, CONKO, and ONKOTEV scores, respectively).

Using the conventional positivity threshold of 3 points, the Khorana, PROTECHT, CONKO, and ONKOTEV scores classified 12%, 42%, 12%, and 2.6% of patients as high risk (Table 2). The cumulative incidence of VTE at 6 months in these high-risk patients was 3.5%, 7.6%, 4.4%, and 15% respectively, compared to 6.0%, 4.4%, 5.9%, and 5.4% in the low risk groups. The corresponding SHRs for high vs. low risk were 0.58 (95% CI, 0.18 to 0.87), 1.8 (95% CI, 0.98 to 3.3), 0.73 (95% CI, 0.26 to 2.1), and 3.0 (95% CI, 0.91 to 10) for the Khorana, PROTECHT, CONKO, and ONKOTEV scores, respectively (Figures. 1A-D). Data for the 12-month study period are presented in Table 3.

Using the alternative positivity threshold of 2 points, the Khorana, PROTECHT, CONKO, and ONKOTEV scores classified 40%, 71%, 39%, and 33% of patients as high risk (Table 2). In these high-risk groups, the cumulative incidences of PE or DVT at 6 months were 7.7%, 7.8%, 7.3%, and 7.2% compared to 4.4%, 0.5%, 4.7%, and 4.8% in patients with a low risk score, respectively. The corresponding SHRs for high vs. low risk patients were 1.8 (95% CI, 0.98 to 3.3), 17 (95% CI, 2.3 to 122), 1.6 (95% CI, 0.89 to 3.0), and 1.5 (95% CI, 0.83 to 2.8) for the Khorana, PROTECHT, CONKO, and ONKOTEV scores, respectively (Figures 2A-D).

In multivariable competing risk analyses, all score items except high platelet count had a positive association with PE and/or DVT at 6 months (Supplementary Table 2). The only items that met statistical significance were platinum-based chemotherapy in the PROTECHT score (SHR 2.5; 95% CI, 1.1 to 6.1) and previous VTE in the ONKOTEV score (SHR 17; 95% CI, 5.2 to 52).

Performance of risk scores re-assessed at 3 to 6 months

Re-assessment of the risk scores was done in 606 of 618 patients who were alive and without thrombosis (98%) at a median follow-up of 158 days (IQR, 113 to 179). From this re-assessment until the end of follow-up, 15 patients (2.5%) developed a thrombotic event of which 12 events (2.0%) were PE and/or DVT. At the conventional positivity threshold of 3 points, the re-assessed Khorana, PROTECHT, CONKO, and ONKOTEV scores re-classified 12%, 32%, 12%, and 1% of patients, respectively (Supplementary Tables 3A-D). Overall, 10%, 14%, 11%, and 3% of patients were classified as being at high risk by the re-assessed Khorana, PROTECHT, CONKO, and ONKOTEV scores. The cumulative incidence of PE or DVT at 180 days after re-assessment was 3.3%, 2.4%, 3.0%, and 5.6% in patients with a high-risk Khorana, PROTECHT, CONKO, and ONKOTEV score, respectively (Supplementary Table 4). These numbers were 1.9%, 2.0%, 1.9%, and 0.70% in those with a low risk score, corresponding to SHRs of 1.8 (95% CI, 0.38 to 8.0), 1.2% (95% CI, 0.26 to 5.5), 1.6 (95% CI, 0.34 to 7.1), and 8.1 (95% CI, 0.93 to 71), respectively.

DISCUSSION

This study confirms the poor overall discriminatory performance of the Khorana, PROTECHT, CONKO, and ONKOTEV scores for the prediction of DVT or PE in patients with cancer receiving chemotherapy. When used dichotomously, none of the scores was able to identify a group of patients with a significantly higher risk of VTE. Yet, the use of a lower positivity threshold of 2 points was associated with improved performance of all scores, but in particular the PROTECHT and CONKO scores. Time-dependent analysis suggested that scores' discrimination tends to decrease during follow-up, with limited or no value of the scores beyond the first 3 to 6 months. Re-evaluation of the four scores at 3 to 6 months changed the indication for pharmacological thromboprophylaxis in 12% up to 32% of

patients, but the use of a re-assessed score is questionable because of the low risk of DVT or PE in the following 6 months.

The Khorana score was derived in a cohort of cancer patients and subsequently externally validated [4]. In a recent large meta-analysis including more than 34,000 patients, the score was able to identify a group of patients with a higher risk of VTE (odds ratio 1.8 for high vs. lower risk); however, patients classified as being at low (0 points) or intermediate risk (1 or 2 points) had an incidence of VTE that was as high as 5.1% and 6.6%, respectively [10]. Consistently, we found an incidence of 6% in patients with a Khorana score below 3 points. Interestingly, the performance of the Khorana as well as all other scores seemed to improve substantially at a positivity threshold of 2 points as evidenced by the identification of a larger proportion of patients who eventually developed VTE and the significant difference between high and low risk patients. Although not formally derived and validated, the Khorana score at a positivity threshold of 2 points has been used by two recently completed randomized trials of primary prophylaxis to select ambulatory cancer patients at high risk of VTE [8-9]. Both studies demonstrated that 6-month prophylaxis with apixaban or rivaroxaban reduce the incidence of VTE compared with placebo, without significantly increasing the risk of major bleeding [8-9]. These trials did not include patients with a Khorana score of 1 point or less in whom the incidence of VTE was 4.4% in our study and 5.5% in the abovementioned meta-analysis. These observations suggest substantial residual VTE risk and imply that about half of patients with cancer who eventually develop VTE may not be candidate for thromboprophylaxis according to the score.

Consistent with these findings, a prospective study showed limited ability of multiple prediction scores to identify the majority of cancer patients developing VTE [7]. Failures to replicate initial findings and variations in risk score performance could stem from differences in patient populations, clinical settings, or time periods [10]. In addition, in a pooled analysis of two large cohorts, only tumor type was predictive of VTE, while all other components of the Khorana score were not associated with the development of VTE [20]. In the current study, multivariable analysis confirmed that tumor type is the only predictor of VTE in the Khorana score, though this association

did not reach statistical significance. This finding likely depends on the relatively low number of patients with high-risk tumor as well as the inclusion of tumor types that were infrequent in the derivation study, though shown to be associated with a higher risk of VTE in subsequent analyses [7,20]. Taken together, current evidence from cohort studies, a subsequent large meta-analysis, as well as two recently published randomized clinical trials support the use of a risk stratification strategy to select cancer patients for thromboprophylaxis. However, future studies should evaluate ways to improve efficiency of risk stratification to reduce the proportion of patients with VTE who are erroneously classified as at low risk.

Preliminary observations suggest that the accuracy of most scores for VTE prediction in cancer patients decreases during the first weeks of follow-up [7]. In time-dependent analysis, the modest scores' performance tended to decrease further beyond the initial 3 to 6 months, which could partly depend on VTE risk factors not present at baseline yet emerging during the dynamic cancer journey. In addition, most components of the risk scores including body weight, performance status, and blood counts often fluctuate during the course of cancer disease because of cancer treatment, co-morbidities, or cancer progression. As a result, the importance of these variables is highly contingent to the time they are evaluated and may change over time potentially affecting risk stratification and long-term predictive value of the score. Therefore, in the present study, all scores were re-calculated after the first 3 months to assess the impact of these changes between the follow-up score relative to baseline. While the discriminatory performance of the score calculated at follow-up remained poor, the relatively low number of events beyond 3 to 6 months hampers firm conclusions.

The present retrospective study including various tumor types and using laboratory data collected before start of chemotherapy is one of the largest comparisons of multiple prediction scores for cancer-associated VTE. There are some limitations that need to be acknowledged. The collection of data at pre-specified time points for evaluation of the re-assessed scores was limited. However, the proportion of patients in whom the scores could not be calculated at follow-up was

lower than 2%. Second, the single-center design of the study may limit the external validity of the findings. Third, we could not evaluate the CATS score, since D-dimer and soluble P-selectin levels are not available in routine clinical practice, nor the extensive COMPASS-CAT score, because data on cardiovascular risk factors were not available. Fourth, the number of events may not have provided enough power to detect significant differences, especially in the multivariable analyses and analyses of the re-assessed scores.

In summary, the current study confirms that the Khorana, PROTECHT, CONKO, and ONKOTEV scores do not own sufficient accuracy to select patients for pharmacological thromboprophylaxis when used at a conventional positivity threshold of 3 points. Although performance of all scores was improved with the use of a positivity threshold of 2 points, incidence of VTE in patients classified as at low risk of VTE is not negligible. Score accuracy tends to decrease over time suggesting the need of periodic re-evaluation to estimate changes in patient's risk.

Addendum

Concept and design: MDN, EP. Interpretation of data, critical writing or revising the intellectual content, and final approval of the version to be published: MDN, NvE, LR, NA, LF, MDT, CN, NT, IC, EV, MC, AWSR, EP.

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Declarations of interest

None of the authors have potential conflicts of interest to declare in relation to the current work.

References

1. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. (2013) Epidemiology of cancer-associated venous thrombosis. Blood 122:1712-23.
2. Khorana AA, Francis CW, Culakova E, Lyman GH. (2005) Risk factors for chemotherapy-associated venous thromboembolism in a prospective observational study. Cancer 104:2822–2829.
3. Di Nisio M, Porreca E, Candeloro M, De Tursi M, Russi I, Rutjes AW. (2016) Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. Cochrane Database Syst Rev. 12:CD008500.
4. Khorana AA, Francis CW. (2018) Risk prediction of cancer-associated thrombosis: Appraising the first decade and developing the future. Thromb Res 164 Suppl 1:S70-S76.
5. Pabinger I, Thaler J, Ay C. (2013) Biomarkers for prediction of venous thromboembolism in cancer. Blood 122:2011-8.
6. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. (2008) Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 111:4902-4907.
7. van Es N, Di Nisio M, Cesarman G, Kleinjan A, Otten HM, Mahé I, Wilts IT, Twint DC, Porreca E, Arrieta O, Stépanian A, Smit K, De Tursi M, Bleker SM, Bossuyt PM, Nieuwland R, Kamphuisen PW, Büller HR. (2017) Comparison of risk prediction scores for venous thromboembolism in cancer patients: a prospective cohort study. Haematologica 102:1494-1501.
8. Carrier M, Abou-Nassar K, Mallick R, Tagalakis V, Shivakumar S, Schattner A, Kuruvilla P, Hill D, Spadafora S, Marquis K, Trinkaus M, Tomiak A, Lee AYY, Gross PL, Lazo-Langner A, El-Maraghi R, Goss G, Le Gal G, Stewart D, Ramsay T, Rodger M, Witham D, Wells PS; AVERT Investigators. (2019) Apixaban to prevent venous thromboembolism in patients with cancer. N Engl J Med 380:711-719.

9. Khorana AA, Soff GA, Kakkar AK, Vadhan-Raj S, Riess H, Wun T, Streiff MB, Garcia DA, Liebman HA, Belani C, O'Reilly EM, Patel JN, Yimer HA, Wildgoose P, Burton P, Vijapurkar U, Kaul S, Eikelboom J, McBane RD, Bauer KA, Kuderer NM, Lyman GH, CASSINI Investigators. (2019) Rivaroxaban thromboprophylaxis in high-risk ambulatory cancer patients receiving systemic therapy: results of a randomized clinical trial. N Engl J Med 380:720-728.
10. Mulder FI, Candeloro M, van Es N, Di Nisio M, Buller HR, Kamphuisen PW. (2019) Can we use the Khorana risk score to predict venous thromboembolism in patients with cancer? A systematic review and meta-analysis. Haematologica. doi: 10.3324/haematol.2018.209114
11. Ay C, Dunkler D, Marosi C, Chiriac AL, Vormittag R, Simanek R, Quehenberger P, Zielinski C, Pabinger I. (2010) Prediction of venous thromboembolism in cancer patients. Blood 116:5377-5382.
12. Verso M, Agnelli G, Barni S, Gasparini G, LaBianca R. (2012) A modified Khorana risk assessment score for venous thromboembolism in cancer patients receiving chemotherapy: the Protecht score. Intern Emerg Med 7:291–292.
13. Pelzer U, Opitz B, Deutschinoff G, Stauch M, Reitzig PC, Hahnfeld S, Müller L, Grunewald M, Stieler JM, Sinn M, Denecke T, Bischoff S, Oettle H, Dörken B, Riess H. (2015) Efficacy of Prophylactic low–molecular weight heparin for ambulatory patients with advanced pancreatic cancer: outcomes from the CONKO-004 Trial. J Clin Oncol 33:2028-34.
14. Cella CA, Di Minno G, Carlomagno C, Arcopinto M, Cerbone AM, Matano E, Tufano A, Lordick F, De Simone B, Muehlberg KS, Bruzzese D, Attademo L, Arturo C, Sodano M, Moretto R, La Fata E, De Placido S. (2017) Preventing venous thromboembolism in ambulatory cancer patients: the ONKOTEV study, Oncologist 22:601–608.
15. Di Nisio M, van Es N, Büller HR. (2016) Deep vein thrombosis and pulmonary embolism. Lancet 388(10063):3060-3073.

16. Khorana AA, O'Connell C, Agnelli G, Liebman HA, Lee AYY, On Behalf of the Subcommittee on Hemostasis and Malignancy of the SSC of the ISTH. (2012) Incidental venous thromboembolism in oncology patients. J Thromb Haemost 10: 2602–4.
17. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. (2005) Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 3:692-694.
18. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S, Subcommittee on Control of Anticoagulation. (2015) Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost 13:2119-2126.
19. Gerotziafas GT, Taher A, Abdel-Razeq H, AboElnazar E, Spyropoulos AC, El Shemmari S, Larsen AK, Elalamy I; COMPASS–CAT Working Group. (2017) A predictive score for thrombosis associated with breast, colorectal, lung, or ovarian cancer: the prospective COMPASS-cancer-associated thrombosis study. Oncologist 22:1222–1231.
20. Pabinger I, van Es N, Heinze G, Posch F, Riedl J, Reitter EM, Di Nisio M, Cesarman-Maus G, Kraaijpoel N, Zielinski CC, Büller HR, Ay C. (2018) A clinical prediction model for cancer-associated venous thromboembolism: a development and validation study in two independent prospective cohorts. Lancet Haematol 5:e289-e298.

Table 1. Patient characteristics

	N=776
Age, y, mean (SD)	65 (11)

Male sex, n (%)	471 (61)
Body mass index, kg/m^2	
Mean (SD)	26 (4.6)
≥35 kg/m^2, n (%)	35 (4.5)
Tumor type, n (%)	
Lung cancer	277 (36)
Colorectal	224 (29)
Gynecological	88 (11)
Pancreatic	71 (9.1)
Stomach	58 (7.5)
Urogenital	37 (4.8)
Hepatobiliary	21 (2.7)
Distant metastasis, n (%)	540 (70)
WHO performance status, n (%)	
0	510 (66)
1	226 (29)
≥2	37 (4.8)
Missing	3 (0.4)
Vascular compression or infiltration, n (%)	47 (6.1)
Chemotherapy, n (%)	
Platinum-based	413 (53)
Gemcitabin	105 (14)
Other	153 (20)
Missing	7 (0.9)
Central venous catheter, n (%)	51 (6.6)
Surgery in previous 4 weeks, n (%)	137 (18)
Previous venous thromboembolism, n (%)	6 (0.8)
Erythropoietin stimulating agents, n (%)	20 (2.6)
Hemoglobin, g/dL	
Median (IQR)	13 (11-14)
<10 g/dL, n (%)	48 (6.2)
White blood cell count, x 10^9/L	
Median (IQR)	7.0 (5.5-9.2)
>11 x 10^9/L, n (%)	104 (13)
Platelet count, x 10^9/L	
Median (IQR)	258 (198-332)
≥350 x 10^9/L, n (%)	162 (21)

Abbreviations: IQR, interquartile range; SD, standard deviation.

Table 2. Distribution of risk scores

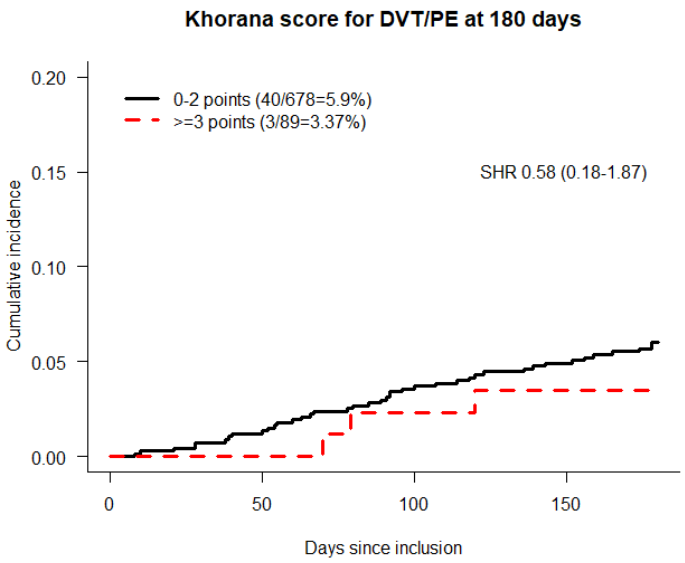
	Baseline scores (N=776)				Re-assessed scores (N=606)			
	Khorana	**PROTECHT**	**CONKO**	**ONKOTEV**	**Khorana**	**PROTECHT**	**CONKO**	**ONKOTEV**
Points, n (%)								
0	172 (22)	65 (8.4)	174 (22)	150 (19)	168 (28)	149 (25)	166 (27)	99 (16)
1	287 (37)	145 (19)	285 (37)	355 (46)	213 (35)	217 (36)	222 (37)	304 (50)
2	218 (28)	228 (29)	211 (27)	235 (30)	155 (26)	146 (24)	144 (24)	172 (28)
3	76 (9.8)	211 (27)	80 (10)	20 (2.6)	51 (8.4)	64 (11)	54 (8.9)	18 (3.0)
4	13 (1.7)	87 (11)	14 (1.8)	0	9 (1.5)	18 (3.0)	9 (1.5)	0
5	1 (0.1)	21 (2.7)	1 (0.1)	-	1 (0.2)	2 (0.3)	2 (0.3)	-
6	0	3 (0.4)	0	-	0	1 (0.2)	0	-
Missing	9 (1.2)	16 (2.1)	11 (1.4)	16 (2.1)	9 (1.5)	9 (1.5)	9 (1.5)	13 (2.1)
Positivity threshold 3 points, n (%)								
Low risk (≤2 points)	678 (87)	438 (56)	670 (86)	740 (95)	536 (88)	512 (85)	532 (88)	575 (95)
High risk (≥3 points)	89 (12)	322 (42)	95 (12)	20 (2.6)	61 (10)	85 (14)	65 (11)	18 (3.0)
Positivity threshold 2 points, n (%)								
Low risk (≤1 points)	460 (59)	210 (27)	459 (59)	505 (65)	381 (63)	366 (60)	388 (64)	403 (67)
High risk (≥2 points)	307 (40)	550 (71)	306 (39)	255 (33)	216 (36)	231 (38)	209 (35)	190 (31)

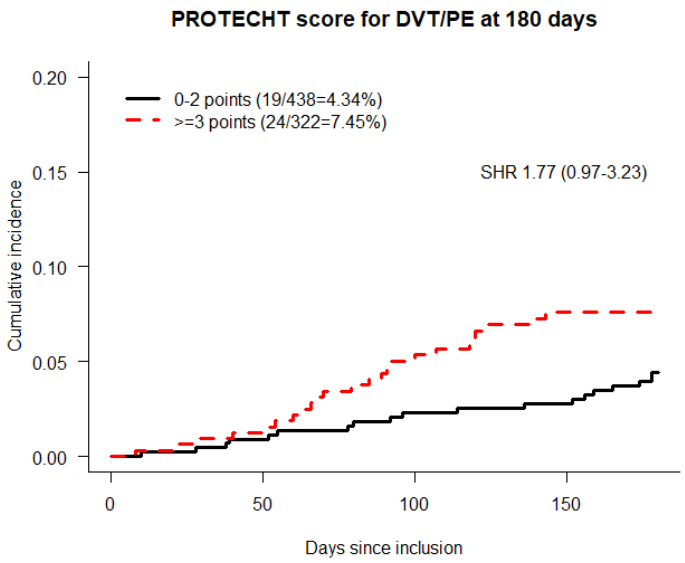
Table 3. Performance of the risk scores for deep vein thrombosis or pulmonary embolism at the positivity threshold of 3 and 2 points

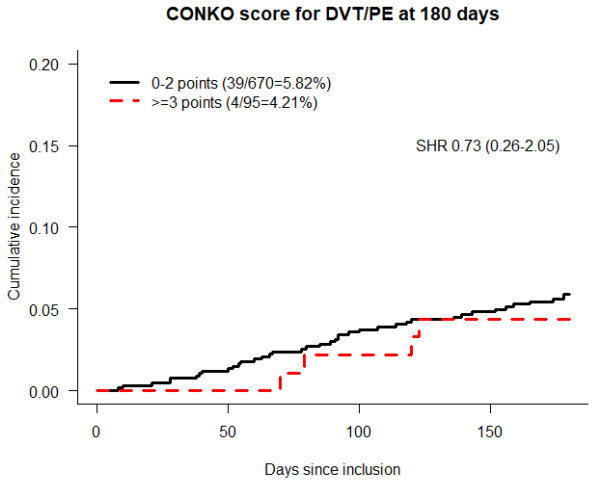
	Khorana score		PROTECHT score		CONKO score		ONKOTEV score	
Time-dependent c-index (95% CI)								
At 90 days	0.63 (0.55-0.71)		0.63 (0.55-0.72)		0.61 (0.54-0.69)		0.62 (0.51-0.74)	
At 180 days	0.61 (0.56-0.66)		0.61 (0.55-0.66)		0.60 (0.54-0.66)		0.59 (0.52-0.66)	
At 365 days	0.59 (0.54-0.65)		0.57 (0.51-0.63)		0.59 (0.53-0.65)		0.57 (0.50-0.64)	
	3-point threshold	**2-point threshold**	**3-point threshold**	**2-points threshold**	**3-point threshold**	**2-points threshold**	**3-point threshold**	**2-points threshold**
6-month follow-up								
VTE risk in low risk patients, % (95% CI)	6.0 (4.4-8.0)	4.4 (2.8-6.6)	4.4 (2.8-6.7)	0.50 (0.04-2.5)	5.9 (4.3-7.9)	4.7 (3.0-6.9)	5.4 (3.9-7.2)	4.8 (3.2-7.0)
VTE risk in high risk patients, % (95% CI)	3.5 (0.9-9.1)	7.7 (5.0-11)	7.6 (5.0-11)	7.8 (5.7-10)	4.4 (1.4-10)	7.3 (4.7-11)	15 (3.5-34)	7.2 (4.4-11)
SHR for high vs low risk patients	0.58 (0.18-0.87)	1.8 (0.98-3.3)	1.8 (0.97-3.2)	17 (2.3-122)	0.73 (0.26-2.1)	1.6 (0.89-3.0)	3.0 (0.91-10)	1.5 (0.83-2.8)
12-month follow-up								
VTE risk in low risk patients, % (95% CI)	7.6 (5.7-9.8)	5.9 (3.9-8.3)	6.2 (4.2-8.8)	2.1 (0.68-4.9)	7.6 (5.7-9.8)	6.1 (4.1-8.6)	6.9 (5.2-8.9)	6.6 (4.6-9.1)
VTE risk in high risk patients, % (95% CI)	4.8 (1.5-11)	9.4 (6.4-13)	8.6 (5.8-12)	9.2 (6.9-12)	5.5 (2.0-12)	9.1 (6.2-13)	20 (5.9-40)	8.5 (5.4-12)
SHR for high vs low risk patients	0.62 (0.22-1.7)	1.74 (0.99-2.9)	4.5 (0.85-2.5)	4.9 (1.8-14)	0.73 (0.29-1.8)	1.6 (0.91-2.6)	3.2 (1.2-9.1)	1.3 (0.77-2.3)

Abbreviations: VTE, venous thromboembolism; SHR, subdistribution hazard.

Figure 1 - A-D. Discrimination of dichotomized risk scores at 3-point positivity threshold







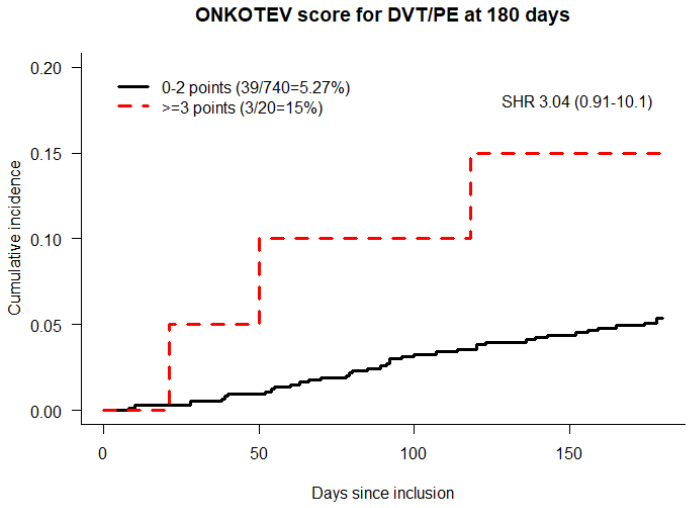


Figure 2 - A-D. Discrimination of dichotomized risk scores at 2-point positivity threshold