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ORIGINAL ARTICLE

Evaluation of the Khorana, PROTECHT, and 5-SNP scores for prediction of venous thromboembolism in patients with cancer

Noori A. M. Guman[1,2] | Roos J. van Geffen[1] | Frits I. Mulder[1,2] | Thijs F. van Haaps[1] | Vahram Hovsepjan[1] | Mariette Labots[3] | Geert A. Cirkel[4] | Filip Y. F. L. de Vos[5] | Albert J. ten Tije[6] | Laurens V. Beerepoot[7] | Vivianne C. G. Tjan-Heijnen[8] | Hanneke W. M. van Laarhoven[3,9] | Paul Hamberg[10] | Annelie J. E. Vulink[11] | Maartje Los[12] | Aeilko H. Zwinderman[13] | Bart Ferwerda[13] | Martijn P. J. K. Lolkema[14] | Neeltje Steeghs[15] | Harry R. Büller[1] | Pieter W. Kamphuisen[1,2] | Nick van Es[1]

[1]Department of Vascular Medicine, Amsterdam Cardiovascular Science, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands

[2]Department of Internal Medicine, Tergooi Hospital, Hilversum, the Netherlands

[3]Department of Medical Oncology, Cancer Center Amsterdam, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands

[4]Department of Internal Medicine, Meander Medical Center, Amersfoort, the Netherlands

[5]Department of Medical Oncology, University Medical Center Utrecht, Utrecht, the Netherlands

[6]Department of Internal Medicine, Amphia Hospital, Breda, the Netherlands

[7]Department of Internal Medicine, Elisabeth-Tweesteden Hospital, Tilburg, the Netherlands

[8]Department of Medical Oncology, Maastricht University Medical Center, Maastricht, the Netherlands

[9]Department of Medical Oncology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands

[10]Department of Internal Medicine, Franciscus Gasthuis & Vlietland, Rotterdam-Schiedam, the Netherlands

[11]Department of Medical Oncology, Reinier de Graaf Hospital, Delft, the Netherlands

[12]Department of Internal Medicine, St Antonius Hospital, Nieuwegein, the Netherlands

[13]Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Amsterdam University Medical Center, Amsterdam, the Netherlands

[14]Department of Medical Oncology, Erasmus Medical Center, Rotterdam, the Netherlands

[15]Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, the Netherlands

Correspondence
Noori A.M. Guman, Department of Vascular Medicine, Amsterdam Cardiovascular Science, Amsterdam UMC, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands.
Email: n.a.guman@amsterdamumc.nl

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Abstract

Background: The Khorana score is a validated tool to identify cancer patients at higher risk of venous thromboembolism (VTE).

Objective: We compared its predictive performance to that of the clinical PROTECHT and the polygenic 5-SNP scores in patients who participated in the Dutch CPCT-02 study.

Patients/methods: Data on VTE and its risk factors were retrospectively collected for 2729 patients with advanced stage solid tumors planned for systemic cancer

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treatment. Patients were followed for 6 months. Overall discriminatory performance of the scores was evaluated by time-dependent c-indices. The scores were additionally evaluated dichotomously in competing risk models.

Results: A total of 160 (5.9%) patients developed VTE during follow-up. Time-dependent c-indices at 6 months for the Khorana, PROTECHT, and 5-SNP scores were 0.57 (95% confidence interval [CI]: 0.55–0.60), 0.60 (95% CI: 0.57–0.62), and 0.54 (95% CI: 0.51–0.57), respectively. The dichotomous scores classified 9.6%, 16.8%, and 9.5% as high-risk, respectively. VTE risk was about 2-fold higher among high-risk patients than low-risk patients for the Khorana (subdistribution hazard ratio [SHR] 1.9, 95% CI: 1.3–3.0), PROTECHT (SHR 2.1, 95% CI: 1.5–3.0), and 5-SNP scores (SHR 1.7, 95% CI: 1.03–2.8). The sensitivity at 6 months was 16.6% (95% CI: 10.5–22.7), 28.9% (95% CI: 21.5–36.3), and 14.9% (95% CI: 8.5-21.2), respectively.

Conclusions: Performance of the PROTECHT or 5-SNP score was not superior to that of the Khorana score. The majority of cancer patients who developed VTE during 6-month follow-up were not identified by these scores. Future directions for studies on cancer-associated VTE prediction may include combined clinical-genetic scores.

KEYWORDS
neoplasms, polymorphism, risk assessment, single nucleotide, thrombosis, venous thromboembolism

1 | INTRODUCTION

Venous thromboembolism (VTE) is a common complication in patients with cancer, associated with increased morbidity and mortality.[1,2] Compared to patients without cancer, the 12-month VTE risk is 9-fold higher in cancer patients and 20-fold higher in those receiving systemic cancer treatment.[3] Despite the considerable overall VTE risk of approximately 7% in the first 6 months after cancer diagnosis,[4] international guidelines suggest providing thromboprophylaxis for selected high-risk patients only, in whom the benefits may outweigh the bleeding risk.[5-7] The currently endorsed risk stratification tool is the Khorana score, a pan-cancer VTE risk score that assigns points to five clinical variables (Table 1), but its wide adoption in clinical practice remains limited.[8] Although discriminatory performance of the score has been confirmed in various studies, the majority of VTE events occur in cancer patients with a low Khorana score (0–1 points) due to its modest sensitivity and its inconsistent performance across cancer types.[4,9]

Consequently, other tools have been developed to improve VTE risk stratification in patients with cancer. The PROTECHT score encompasses the same risk factors of the Khorana score with the addition of gemcitabine or platinum-based chemotherapy use (Table 1). Although one previous cohort study suggested better discrimination with the PROTECHT score compared to the Khorana score (c-index 0.50 vs. 0.54), this effect was not replicated in a recent cohort study (c-index 0.61 vs. 0.60), which leaves the value of the PROTECHT score for VTE prediction in cancer patients uncertain.[10-12]

Essentials

- Various risk scores have been proposed to predict venous thromboembolism (VTE) in cancer patients.
- We evaluated the performance of the clinical Khorana and PROTECHT, and polygenic 5-SNP scores.
- Overall performance of the Khorana, PROTECHT, and 5-SNP scores was poor for predicting VTE.
- Combining genetic and clinical risk factors may possibly improve VTE prediction.

A limitation of the Khorana and PROTECHT clinical risk scores is that they consider the incorporated items as static, while laboratory parameters as well as type of chemotherapy are actually dynamic, possibly rendering a lower performance of these models over time.[13] Accumulating data suggest that the risk of cancer-associated VTE is also driven by prothrombotic single nucleotide polymorphisms (SNPs) and that these SNPs may further improve VTE risk assessment.[14,15] The 5-SNP score is a polygenic risk score including five prothrombotic mutations, which was developed to predict VTE in the general population as well as high-risk populations, including patients with cancer.[15] This score, however, lacks validation in cancer patients and its potential clinical value compared to that of the other clinical scores is unknown.

The aim of the current study was to explore whether the clinical PROTECHT score or polygenic 5-SNP score improve VTE risk stratification in cancer patients, compared to the Khorana score.

TABLE 1 Clinical and genetic risk scores for venous thromboembolism in patients with cancer

	Khorana score[8] (points)	PROTECHT score[19] (points)	5-SNP score[15] (points)
Clinical risk factors	-	-	-
Pancreatic, gastric, or primary brain cancer	2	2	-
Lung, gynecological, lymphoma, bladder, testicular, or renal	1	1	-
Prechemotherapy platelet count ≥350 x 10^9/L	1	1	-
Prechemotherapy hemoglobin level <6.2 mmol/L	1	1	-
Prechemotherapy leukocyte count >11 x 10^9/L	1	1	-
Body mass index ≥35 kg/m^2	1	1	-
Gemcitabine therapy	-	1	-
Platinum-based therapy	-	1	-
Prothrombotic SNPs	-	-	-
rs6025 (F5 gene)	-	-	N*log(3.79)
rs8176719 (ABO gene)	-	-	N*log(1.85)
rs1799963 (F2 gene)	-	-	N*log(2.78)
rs2066865 (FGG gene)	-	-	N*log(1.56)
rs2036914 (F11 gene)	-	-	N*log(1.32)

Note: Brain and renal cancer were added, respectively, to the very high- and high-risk sites, as suggested previously.[20,21]

Abbreviations: N, number of risk alleles; SNP, single nucleotide polymorphism; VTE, venous thromboembolism.

2 | METHODS

2.1 | Study design and participants

The risk scores were evaluated retrospectively using data from the Center for Personalized Cancer Treatment (CPCT-02) study, an ongoing, Dutch, multicenter prospective study in patients with histologically confirmed advanced stage solid tumors who are planned for a new line of systemic cancer treatment, including chemotherapy, targeted therapy, immunotherapy, or antihormonal therapy. The main goal of the study is to evaluate impact of the genetic tumor profile on cancer treatment efficacy. Peripheral blood samples and tumor tissue were obtained at baseline and used for whole-genome DNA sequencing using the Illumina Next Generation Sequencing platform (Illumina, v.2.17 to v.2.20). Reads were mapped to the reference genome GRCH37. Full details on CPCT-02 study methodology have been reported previously.[16]

CPCT-02 study participants from five academic and seven non-academic centers were included in the current study. Patients with ongoing therapeutic or prophylactic anticoagulant therapy (vitamin K antagonists, direct oral anticoagulants, or low molecular weight heparins) and patients with non-melanoma skin cancer only at CPCT-02 enrolment were excluded. Independent review boards of all participating hospitals approved the present study. Written informed consent for whole genome sequencing and data sharing for cancer research purposes had been obtained previously from all participants. This study adheres to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for reporting on observational studies.[17]

2.2 | Data collection and study outcomes

Clinical data on VTE and its risk factors were retrospectively collected from electronic patient charts. Whole-genome germline sequence data were obtained from the Hartwig Medical Foundation, which analyzes genetic data from the CPCT-02 study.[18] The primary outcome was VTE, defined as the composite of radiologically confirmed subsegmental or more proximal pulmonary embolism (PE), proximal and distal lower extremity deep-vein thrombosis (DVT), proximal upper-extremity DVT, splanchnic vein thrombosis, and cerebral vein thrombosis. Both symptomatic and incidental VTE were included. Incidental VTE was defined as VTE detected on imaging tests performed for other reasons than suspicion of VTE. Development of VTE was assessed by going through all radiology reports; clinical correspondence; and if possible, by searching for Dutch terms indicating VTE in electronic patient charts. All VTE events were additionally verified by two authors (F.I.M. and N.A.M.G) based on collected radiology reports and information from electronic patient charts. Patients were followed from time of

CPCT-02 study inclusion until death, loss to follow-up, VTE, or end of follow-up at 12 months.

2.3 | Risk scores

The Khorana and PROTECHT scores were calculated based on five and seven clinical items, respectively (Table 1).[8,15,19] As suggested previously,[20,21] we considered primary brain cancer as a very high-risk tumor type and renal cancer as a high-risk tumor type. Although the Khorana score traditionally assigns points to hemoglobin level <10 g/dl or use of erythropoietin stimulation agents (ESAs), the latter was not considered here, as ESAs are not prescribed to patients with cancer in Dutch practice. The 5-SNP score was calculated by assigning points to rs6025 (F5 gene), rs8176719 (ABO gene), rs1799963 (F2 gene), rs2066865 (FGG gene), and rs2036914 (F11 gene).[15] The weighted 5-SNP score was calculated by summing the number of risk alleles for each SNP multiplied by their weights. Participants could either have 0, 1, or 2 risk alleles for each SNP. As rs2036914 has been associated with reduced VTE risk, the major allele was set as risk allele. Weights were obtained by taking the natural logarithm of the odds ratios reported in the derivation study (Table S1 in supporting information).

2.4 | Statistical analysis

Standard descriptive statistics were used to summarize baseline characteristics. Overall discrimination of the scores was evaluated by calculating time-dependent c-indices with their corresponding 95% confidence intervals (CI) calculated in 250 bootstrap samples. The Khorana and PROTECHT scores were evaluated dichotomously at the positivity thresholds of 3 points, as initially proposed,[8,19] and additionally at 2 points as currently suggested in guidelines.[5,6] Because no optimal positivity threshold has been proposed for the 5-SNP score, two thresholds were selected at the points on the receiver operating curve (ROC) with at least the same specificity as the Khorana score at the positivity threshold of 2 and 3 points to compare the performance of both scores with a focus on sensitivity. The cumulative VTE incidences in patients in the high- and low-risk groups with corresponding 95% CIs were estimated using the Fine & Gray competing risk model, which considered non–VTE-related death as competing risk.[22,23] The relative risk between high- and low-risk groups was assessed by calculating subdistribution hazard ratios (SHRs) along with their 95% CI.[24] The time-dependent sensitivity and specificity were computed with their 95% CI as proposed by Blanche et al.[25] The performance of the risk scores was evaluated for VTE at 6 months follow-up in the primary analysis and at 12 months in a secondary analysis.[26-28] All patients for whom data were available to calculate at least one of the scores were included in the main analysis; a sensitivity analysis was performed restricted to patients for whom all scores could be calculated. As the Khorana score was traditionally proposed using pre-chemotherapy laboratory variables, a second subgroup analysis was performed restricted to patients with newly diagnosed cancer only, who were planned for their first line of systemic therapy. The individual components of the risk scores were assessed by estimating the SHRs with 95% CIs at 6 months in a multivariable model including all score variables. A multivariable competing risk model was used to assess the potential added value of the genetic 5-SNP score conditional on the items of the Khorana score. All statistical analyses were performed using R software (https://www.R-project.org), particularly using packages "pec," "cmprisk," and "riskRegression".

3 | RESULTS

3.1 | Baseline characteristics and incidence of VTE

A total of 3089 CPCT-02 study participants with advanced stage solid cancer were identified between July 2019 and December 2020, of whom 357 (11.6%) were using anticoagulants and 3 (0.1%) had non-melanoma skin cancer. The remaining 2729 (88.3%) patients were included in the present study. Baseline characteristics are summarized in Table 2. The median age was 63 years (interquartile range [IQR]: 55–70) and 49% of patients were female. The median time since primary cancer diagnosis was 19 months (IQR: 3–51). According to the Khorana score classification, 186 (6.8%) patients had very high-risk tumors (pancreas, stomach, and primary brain cancer), 678 (24.8%) had high-risk tumors (lung, gynecological, bladder, testicular, or renal cancer), and 1865 (68.3%) had low-risk tumors. During the first 6 months of observation, 160 (5.9%) patients developed VTE, 660 (24.2%) died, and 133 (4.9%) were lost to follow-up. The overall cumulative VTE incidence was 6.4% (95% CI: 5.5–7.4%) at 6-month follow-up. Of the 160 VTE patients, 83 (51.9%) had PE with or without DVT, 40 (25.0%) had lower-extremity DVT, and 37 (23.1%) had other types of VTE (Table S2 in supporting information). About 53% of all events were symptomatic, 41% were incidentally detected, and in 6% this was unknown. Data to calculate the Khorana and PROTECHT scores were available for 2358 (86.4%) patients, while the 5-SNP score could be calculated for 1987 (72.8%) patients. Baseline characteristics were comparable between patients with sufficient data to calculate the scores compared to those with insufficient data (Table S3 in supporting information).

3.2 | Performance of the risk scores

The time-dependent c-index at 6-month follow-up, which reflects discriminatory performance, was 0.57 (95% CI: 0.55–0.60) for the Khorana, 0.60 (95% CI: 0.57–0.62) for the PROTECHT, and 0.54 (95% CI: 0.51–0.57) for the 5-SNP scores. At the traditional positivity threshold of 3 points, the dichotomous Khorana score classified 227 (9.6%) patients as high risk and 2131 (90.4%) as low risk. The 6-month cumulative VTE incidence was 11.8% (95% CI: 7.8–16.7) among high-risk patients and 6.1% (95% CI: 5.1–7.2) among low-risk patients (SHR

TABLE 2 Baseline characteristics

	N = 2729	
Age, median (IQR)	63	(55–70)
Female sex, *n* (%)	1342	(49.2)
Primary tumor, *n* (%)	-	-
Breast	477	(17.5)
Melanoma	337	(12.3)
Colorectal	312	(11.4)
Lung	303	(11.1)
Prostate	184	(6.7)
Gynecological	136	(5.0)
Renal	122	(4.5)
Bladder/urethral	114	(4.2)
Neuroendocrine tumor	112	(4.1)
Sarcoma	108	(4.0)
Liver	75	(2.7)
Esophageal	67	(2.5)
Glioma	66	(2.4)
Cholangiocarcinoma	66	(2.4)
Gastric	60	(2.2)
Pancreas	60	(2.2)
Other	130	(4.8)
Antiplatelet therapy, *n* (%)	341	(12.5)
Smoking history, *n* (%)	-	-
Current smoker	380	(13.9)
Previous smoker	962	(35.3)
Never smoked	1141	(41.8)
Unknown	246	(9.0)
History of VTE, *n* (%)	58	(2.1)
History of ATE, *n* (%)	180	(6.6)
Performance status*, *n* (%)	-	-
ECOG < 2	2358	(86.4)
ECOG ≥ 2	175	(6.4)
Unknown	196	(7.2)
Treatment within 6 months, *n* (%)	-	-
Chemo- and/or targeted therapy	1201	(44.0)
Immunotherapy only	513	(18.8)
Antihormonal therapy only	221	(8.1)
Multiple therapies	492	(18.0)
No systemic therapy	302	(11.1)
Platinum-based therapy within 6 months, *n* (%)	541	(19.8)
Gemcitabine therapy within 6 months, *n* (%)	130	(4.8)
Body mass index ≥35 kg/m^2, *n* (%)	110	(4.0)
Hemoglobin <6.2 mmol/L, *n* (%)	208	(7.6)
Leukocyte count >11 x 10^9/L, *n* (%)	433	(15.9)
Platelet count ≥350 x 10^9/L, *n* (%)	628	(23.0)

*ECOG 2: ambulatory and capable of all self-care, but unable to carry out any work up and more than 50% of waking hours.

Abbreviations: ATE, arterial thromboembolism; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; VTE, venous thromboembolism.

1.9, 95% CI: 1.3–3.0). The sensitivity at 6 months was 16.6% (95% CI: 10.5–22.7) and specificity was 90.8% (95% CI: 89.6–92.0). When using the currently recommended positivity threshold of 2 points, 614 (26.0%) patients were classified as high risk in whom the 6-month cumulative incidence was 10.2% (95% CI: 7.9–12.9), which was 1.9-fold higher than in the low-risk group (SHR 1.9, 95% CI: 1.4–2.7). The sensitivity and specificity at this threshold were 39.2% (95% CI: 31.3–47.2) and 75.6% (95% CI: 73.7–77.6), respectively.

At the positivity threshold of 3 points, the dichotomous PROTECHT score classified 396 (16.8%) patients as high risk and 1962 (83.2%) as low risk. The 6-month cumulative incidences were 11.5% (95% CI: 8.5–15.0) and 5.6% (95% CI: 4.6–6.7), respectively (SHR 2.1, 95% CI: 1.5–3.0). The sensitivity at 6 months was 28.9% (95% CI: 21.5–36.3) and specificity was 84.2% (95% CI: 82.6–85.9). At the positivity threshold of 2 points, 809 (34.3%) patients were classified as high risk in whom the 6-month cumulative incidence was 9.6% (95% CI: 7.6–11.9), which was 2-fold higher than in the low-risk group (SHR 2.0, 95% CI: 1.4–7.2). The corresponding sensitivity and specificity were 49.6% (95% CI: 41.5–57.8) and 67.0% (95% CI: 64.9–69.1), respectively.

The dichotomous 5-SNP score was evaluated at the positivity thresholds of 1.837 and 1.391, yielding similar specificities as the Khorana score at 3 points and 2 points, respectively. At the positivity threshold of 1.837, 189 (9.5%) patients were classified as high risk and 1798 (90.5%) as low risk. The 6-month cumulative VTE incidence was 10.3% (95% CI: 6.3–15.4) among high-risk patients and 6.1% (95% CI: 5.1–7.4) among low-risk patients (SHR 1.7, 95% CI: 1.03–2.8). The sensitivity at 6 months was 14.9% (95% CI: 8.5-21.2) and specificity was 90.7% (95% CI: 89.3–92.1). At the lower positivity threshold of 1.391, 481 (24.2%) patients were classified as high risk, in whom the 6-month cumulative incidence was 7.7% (95% CI: 5.5–10.4), which was not significantly higher than in the low-risk group (SHR 1.2, 95% CI: 0.8–1.8). The sensitivity and specificity at this lower threshold were 28.2% (95% CI: 20.2–36.2) and 76.0% (95% CI: 73.9–78.1), respectively.

When evaluating the scores for prediction of events during 12-month follow-up, similar results were obtained. The cumulative incidence curves for the individual risk groups of the scores during 12 months follow-up are shown in Figure 1 parts A-F. The performance of the scores is summarized in Table 3. The sequential time-dependent c-indices of the scores during 12 months of follow-up showed that discrimination of the Khorana and PROTECHT scores decreased over time, while performance of the 5-SNP score remained relatively stable (Figure 2).

3.3 | Sensitivity analyses

In the sensitivity analysis restricted to the 1725 (63.2%) patients for whom all three scores could be calculated, results were consistent with that of the main analyses (Table S4 in supporting information). In the analyses restricted to patients with a newly diagnosed cancer, overall discrimination of all evaluated scores was poor and none of the dichotomous scores was significantly associated with increased VTE risk (Table S5 in supporting information).

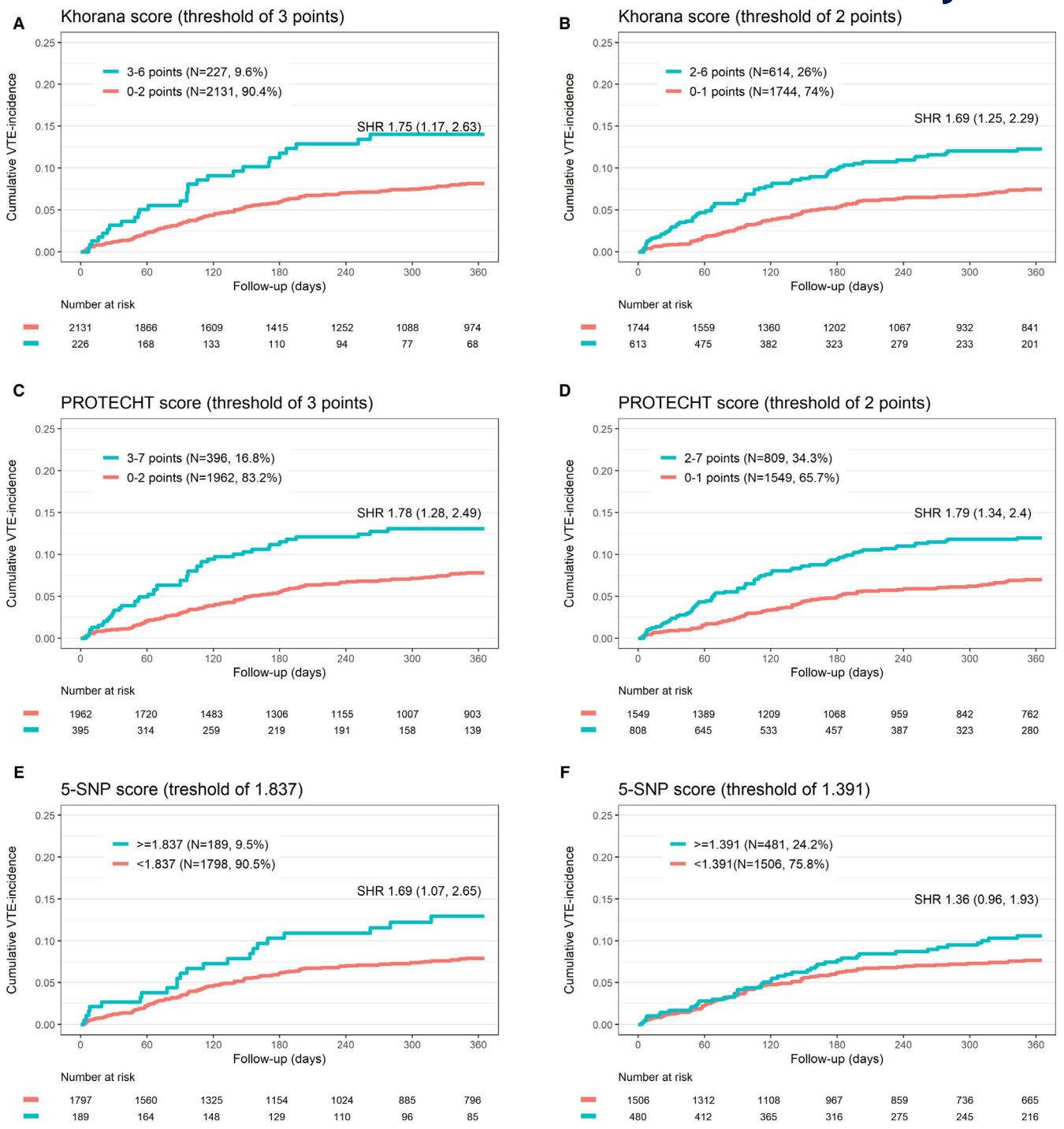

FIGURE 1 Performance of the risk scores during 12-month follow-up. Cumulative incidence of venous thromboembolism in high- and low-risk groups by the (A) Khorana score at the threshold of 3, (B) Khorana score at the threshold of 2, (C) PROTECHT score at the threshold of 3, (D) PROTECHT score at the threshold of 2, (E) 5-SNP score at the threshold of 1.837, and (F) 5-SNP score at the threshold of 1.391 points. Abbreviations: SHR, subdistribution hazard ratio; VTE, venous thromboembolism. [Color figure can be viewed at wileyonlinelibrary.com]

3.4 | Multivariable analyses

When evaluating the individual components of the Khorana and PROTECHT scores in a multivariable model, in which each variable was adjusted for the other risk items, leukocyte count >11 x 10^9/L (SHR 1.6, 95% CI: 1.1–2.4), hemoglobin level <10 g/dl (SHR 1.6, 95% CI: 1.01–2.7), and use of platinum-based chemotherapy (SHR 2.1, 95% CI 1.4–3.1) were significantly associated with the 6-month risk of VTE (Table S6 in supporting information). Of the SNPs included in the 5-SNP score, only rs6025 (factor V Leiden mutation) was significantly associated with VTE in the multivariable analyses (SHR 2.6, 95% CI: 1.4–4.7; Table S6). When adding the dichotomous 5-SNP score to Khorana risk variables in a multivariable analysis with patients for whom all data were available, none of the variables were significantly associated with VTE (Table S6).

TABLE 3 Performance of the risk scores for venous thromboembolism

	Time-dependent c-index (95% CI)	Patients in the high-risk group, n (%)	Cumulative VTE incidence, % (95% CI)		SHR high- vs. low-risk group (95% CI)	Time-dependent sensitivity, % (95% CI)	Time-dependent specificity, % (95% CI)
			Low-risk group	High-risk group			
At 6-month follow-up	-	-	-	-	-	-	-
Khorana score	0.57 (0.55–0.60)	-	-	-	-	-	-
≥3 points	-	227 (9.6)	6.1 (5.1–7.2)	11.8 (7.8–16.7)	1.9 (1.3–3.0)	16.6 (10.5–22.7)	90.8 (89.6–92.0)
≥2 points	-	614 (26.0)	5.4 (4.4–6.6)	10.2 (7.9–12.9)	1.9 (1.4–2.7)	39.2 (31.3–47.2)	75.6 (73.7–77.6)
PROTECHT score	0.60 (0.57–0.62)	-	-	-	-	-	-
≥3 points	-	396 (16.8)	5.6 (4.6–6.7)	11.5 (8.5–15.0)	2.1 (1.5–3.0)	28.9 (21.5–36.3)	84.2 (82.6–85.9)
≥2 points	-	809 (34.3)	5.0 (3.9–6.2)	9.6 (7.6–11.9)	2.0 (1.4–2.7)	49.6 (41.5–57.8)	67.0 (64.9–69.1)
5-SNP score	0.54 (0.51–0.57)	-	-	-	-	-	-
≥1.837	-	189 (9.5)	6.1 (5.1–7.4)	10.3 (6.3–15.4)	1.7 (1.03–2.8)	14.9 (8.5–21.2)	90.7 (89.3–92.1)
≥1.391	-	481 (24.2)	6.2 (5.0–7.6)	7.7 (5.5–10.4)	1.2 (0.8–1.8)	28.2 (20.2–36.2)	76.0 (73.9–78.1)
At 12-month follow-up	-	-	-	-	-	-	-
Khorana score	0.56 (0.53–0.58)	-	-	-	-	-	-
≥3 points	-	227 (9.6)	8.1 (6.9–9.4)	14.0 (9.6–19.3)	1.8 (1.2–2.6)	15.0 (9.9–20.2)	90.9 (89.6–92.0)
≥2 points	-	614 (26.0)	7.5 (6.3–8.9)	12.3 (9.7–15.2)	1.7 (1.3–2.3)	35.9 (28.9–42.9)	76.0 (73.9–78.0)
PROTECHT score	0.58 (0.56–0.60)	-	-	-	-	-	-
≥3 points	-	396 (16.8)	7.8 (6.6–9.1)	13.1 (9.8–16.8)	1.8 (1.3–2.5)	25.0 (18.8–31.2)	84.1 (82.3–85.8)
≥2 points	-	809 (34.3)	7.0 (5.7–8.4)	12.0 (9.7–14.5)	1.8 (1.3–2.4)	46.8 (39.5–54.0)	67.8 (65.6–70.1)
5-SNP score	-	-	-	-	-	-	-
≥1.837	0.55 (0.52–0.58)	189 (9.5)	7.9 (6.6–9.3)	12.9 (8.4–18.5)	1.7 (1.1–2.7)	14.8 (9.0–20.5)	90.8 (89.2–92.3)
≥1.391	-	481 (24.2)	7.7 (6.4–9.2)	10.6 (7.9–13.8)	1.4 (0.96–1.9)	30.6 (23.2–38.1)	75.9 (73.6–78.2)

Abbreviations: CI, confidence interval; c-index, concordance index; SHR, subdistribution hazard ratio; SNP, single nucleotide polymorphism; VTE, venous thromboembolism.

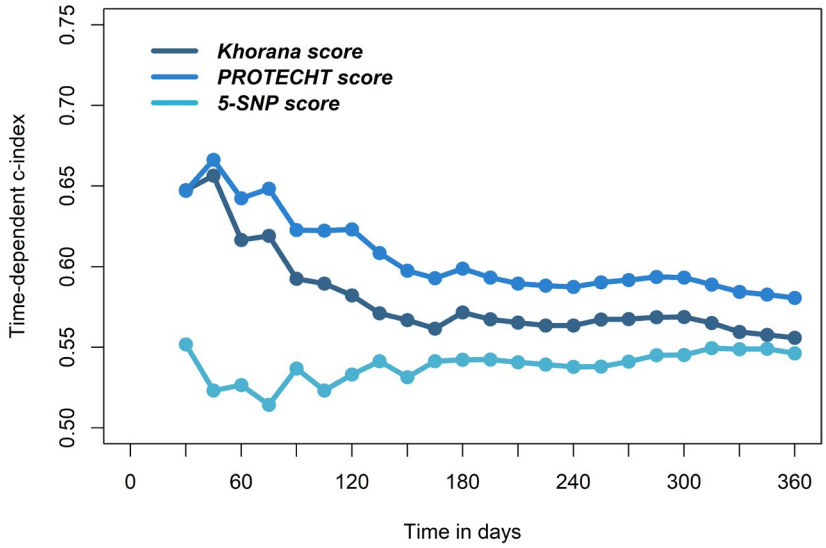

FIGURE 2 Time-dependent c-index for the Khorana, PROTECHT, and 5-SNP scores during 12-month follow-up [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

In this multicenter study of 2729 patients with locally advanced or metastatic cancer, the overall performance of the clinical Khorana and PROTECHT scores and the polygenic 5-SNP risk score was poor for predicting VTE with c-statistics ranging from 0.54 to 0.60. When used dichotomously, the Khorana and PROTECHT scores were each able to identify cancer patients with an approximately 2-fold higher risk of VTE of about 12% during 6-month follow-up, but sensitivity was generally low (16.6%–28.9%). The sensitivity of the scores increased up to 50% when applying a lower positivity threshold, indicating that half of the VTE events occurred in patients classified in the high-risk group. It should be noted that the absolute VTE risk among the high-risk patients decreased in parallel from about 12% to 10%. Furthermore, the VTE risk among low-risk patients was still considerable (about 5%–6%). Although the dichotomized 5-SNP score was associated with an increased risk of VTE, discrimination was lower than that of the clinical scores. These results indicate that the Khorana score performs suboptimally in identifying patients who may benefit from thromboprophylaxis in the present study, and that PROTECHT or 5-SNP score do not have a superior performance.

Our results also suggest that the overall performance of the clinical risk scores decreases over time, while discrimination of the 5-SNP score remains relatively stable (Figure 2). This observation may be explained by the dynamic nature of laboratory variables, body mass index (BMI), and type of chemotherapy, potentially limiting the predictive performance of clinical scores with longer follow-up durations. Evaluation of the individual components of the scores in a multivariable analysis showed that clinical as well as genetic factors (factor V Leiden mutation) were significantly associated with VTE. When evaluating the dichotomized 5-SNP score conditional on the Khorana score variables, the SHR (1.6, 95% CI: 0.9–2.8) was comparable to that of the strongest predictor in the Khorana score (SHR 1.7, 95% CI: 0.9–3.1), albeit that this finding was not statistically significant. Nonetheless, this comparable predictive strength of the genetic 5-SNP score independent of the Khorana score items suggests that genetic, static information may improve performance of clinical predictors. Although routine genetic testing for thrombophilia is unlikely to be implemented in clinical practice, the predictive performance of germline genetic mutations remains a topic of interest, as with the advent of whole-genome sequencing of tumor material, such information can become available easily for all cancer patients. A combined clinical-genetic approach has been incorporated in the TiC-Onco score, which combines a polygenic risk score, including rs6025, rs4524 (F5 gene), rs2232698 (SERPINA 10 gene), rs5985 (F13 gene), with tumor type, cancer stage, BMI, and family history of VTE.[14] Although the score was superior to the Khorana score in the derivation study (c-index 0.73 vs. 0.58), we were unable to externally validate it because the formula to calculate the score has not been published.

Our findings on the performance of the Khorana are consistent with a previous systematic review and meta-analysis including 55 studies and about 34,500 ambulatory cancer patients, which showed that the Khorana score can identify high-risk patients, but the majority of events occur among patients with a low-risk Khorana score.[4] To the best of our knowledge, only two other studies assessed the performance of the PROTECHT score.[10,11] In a prospective cohort of 876 cancer patients, the c-index was 0.59 (95% CI: 0.52–0.66) and the SHR at positivity threshold of 3 points was 2.1 (95% CI: 1.2–3.6).[10] Di Nisio et al. assessed the PROTECHT score in 776 cancer patients, and reported a c-index of 0.61 (95% CI: 0.55–0.66) and SHR of 1.8 (95% CI: 1.0–3.2) at a positivity threshold of 3 points.[11] Consistent with these studies, our results suggest only slight improvement in discrimination with the PROTECHT score compared to the Khorana score, although the sensitivity considerably increased from 39.2 for the Khorana score to 49.6% for the PROTECHT score when used dichotomously at the lower positivity threshold.

The 5-SNP score was proposed as a weighted score to account for the strength of the association with VTE for each SNP, and as a non-weighted score, which is equal to the sum of the number of risk alleles. The derivation study demonstrated an area under the ROC of 0.69 in general population, indicating moderate discrimination.

So far, the weighted score has not been assessed in cancer patients previously. In a recent case-cohort study of 1496 Norwegian cancer patients, the non-weighted 5-SNP score was significantly associated with VTE events 6 months prior to cancer diagnosis up to 2 years after (hazard ratio [HR] 1.9 for four or more risk alleles compared to zero to one risk alleles, 95% CI: 1.3–2.9).[29] When evaluating the non-weighted score in the current study, no significant association with VTE was observed (Table S7 in supporting information). Reasons for the contrast with our non-significant findings are not clear, but may relate to differences in case mix, patient selection, and follow-up duration. Because the aim is to identify cancer patients for primary thromboprophylaxis, we focused on a clinically relevant period starting from the moment of planned new cancer therapy up to 12 months after rather than including a period prior to the cancer diagnosis.

The current study is one of the largest cohort studies evaluating VTE risk assessment scores in more than 2000 patients with advanced-stage solid cancer, with a focus on comparing the performance of genetic and clinical risk scores for cancer-associated VTE. Other strengths include verification of all outcome events and performing competing risk analyses to limit overestimation. Several limitations of the study should be considered. We were unable to evaluate the CATS score, which includes D-dimer and P-selectin on top of the Khorana score, because plasma samples were not available for the included patients. Due to the retrospective design, 5% of patients were lost to follow-up and not all VTE events may have been captured. Patients lost follow-up likely had a worse prognosis than those not lost to follow-up, because they more often had very high-risk tumors (11% vs. 7%), worse performance status (Eastern Cooperative Oncology Group [ECOG] ≥ 2: 15.8% vs. 6.4%), and did not receive systemic therapy (28.6% vs. 11.1%; Table S8 in supporting information). If VTE risk among these patients was higher, we may have underestimated VTE incidence in the high-risk groups leading to a lower discriminatory performance. In addition, due to missing data, the Khorana and PROTECHT risk scores could not be calculated for 14.4% and the 5-SNP score not for 27.7%. Baseline characteristics of patients with missing data, however, were comparable to that of the main study group (Table S3). About 75% of the patients in CPCT-02 were included more than 3 months after primary cancer diagnosis, whereas most risk scores were proposed for VTE risk assessment within the first months after a new cancer diagnosis. However, the analysis restricted to the group of patients with newly diagnosed cancers only yielded similar results with a poor overall performance of all scores. In contrast with the derivation cohort of the Khorana score, this study group comprised patients receiving any type of systemic cancer therapy, including chemotherapy, targeted therapy, immunotherapy, and antihormonal therapy. Although most of these were previously associated with increased VTE risk,[3] this may have influenced the baseline VTE risk in these patients. Because not all cancer types were included in the CPCT-02 study, generalizability to specific cancer types may be limited.

In conclusion, the present findings demonstrate a poor overall discrimination of the Khorana, PROTECHT, and 5-SNP scores. When used dichotomously, the dichotomous Khorana and PROTECHT risk scores performed comparably and identified patients with 2-fold increased VTE risk. Because about 50% of cancer patients who will develop VTE in the first 6 months were not identified as high-risk patients, future studies may focus on more sensitive models or scores. More data are needed to evaluate whether genetic-clinical risk scores for VTE allow for a more accurate VTE risk assessment in cancer patients.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

F.I. Mulder, N. van Es, and H.R. Büller were responsible for conception and design of the study. N.A.M. Guman, R.J. van Geffen, T.F. van Haaps, and V. Hovsepjan collected the data. N.A.M. Guman, F.I. Mulder, and R.J. van Geffen analyzed the data, which was supported by A.H Zwinderman and B. Ferwerda. N.A.M. Guman and F.I. Mulder drafted the manuscript. All authors revised the manuscript for intellectual content, approved the final manuscript, and agreed to submission.

ORCID

Noori A. M. Guman https://orcid.org/0000-0003-1426-3170
Roos J. van Geffen https://orcid.org/0000-0003-1818-3928
Frits I. Mulder https://orcid.org/0000-0002-6902-3425
Thijs F. van Haaps https://orcid.org/0000-0002-8358-2426

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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