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ARTICLE

The Khorana score for prediction of venous thromboembolism in cancer patients: a systematic review and meta-analysis

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ABSTRACT

We aimed to evaluate the performance of the Khorana score in predicting venous thromboembolic events in ambulatory cancer patients. Embase and MEDLINE were searched from January 2008 to June 2018 for studies which evaluated the Khorana score. Two authors independently screened studies for eligibility, extracted data, and assessed risk of bias. Additional data on the 6-month incidence of venous thromboembolism were sought by contacting corresponding authors. The incidence in each Khorana score risk group was estimated with random effects meta-analysis. A total of 45 articles and eight abstracts were included, comprising 55 cohorts enrolling 34,555 ambulatory cancer patients. For 27,849 patients (81%), 6-month follow-up data were obtained. Overall, 19% of patients had a Khorana score of 0 points, 64% a score of 1 or 2 points, and 17% a score of 3 or more points. The incidence of venous thromboembolism in the first six months was 5.0% (95%CI: 3.9-6.5) in patients with a low-risk Khorana score (0 points), 6.6% (95%CI: 5.6-7.7) in those with an intermediate-risk Khorana score (1 or 2 points), and 11.0% (95%CI: 8.8-13.8) in those with a high-risk Khorana score (3 points or higher). Of the patients with venous thromboembolism in the first six months, 23.4% (95%CI: 18.4-29.4) had been classified as high risk according to the Khorana score. In conclusion, the Khorana score can be used to select ambulatory cancer patients at high risk of venous thromboembolism for thromboprophylaxis; however, most events occur outside this high-risk group.

Introduction

Venous thromboembolism (VTE) is a burdensome and frequent complication in patients with active cancer. The estimated overall 12-month incidence is approximately 6-8% but varies widely across tumor types.[1,2] VTE is associated with substantial morbidity and mortality,[3] decreases quality of life,[4] and can lead to interruption or discontinuation of cancer treatment. Although thromboprophylaxis effectively reduces the risk of VTE,[5] current guidelines recommend against its routine use in ambulatory cancer patients, probably due to the high number that require treatment, the fear of bleeding, and the considerable burden associated with daily injections of low-molecular-weight heparins.[6]

Risk stratification tools may help to reduce the number requiring treatment by guiding selection of cancer patients at high risk of VTE. An ideal risk score would help clinicians identify both patients with a negligible risk as well as those at very high risk needing intervention. The best-known risk stratification tool is the Khorana score, which was introduced in 2008. This score assigns points to five clinical and pre-chemotherapy laboratory parameters: primary tumor site (+1 or 2

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points), platelet count of 350x10^9/L or more (+1 point), hemoglobin concentration of 100 g/L or lower or use of erythropoiesis-stimulating agents (+1 point), leukocyte count of 11x10^9/L or higher (+1 point), and a Body Mass Index of 35 kg/m^2 or higher (+1 point) (Table 1).[7] A sum score of 0 points classifies patients as being at low risk of VTE, 1 or 2 points at intermediate risk, and those with 3 or more points at high risk. The Khorana score is endorsed by the latest guideline updates of the American Society of Clinical Oncology and the National Comprehensive Cancer Network to select ambulatory cancer patients for thromboprophylaxis.[6,8]

Over 50 studies have evaluated the score since its publication, but reported results were often conflicting. A clear interpretation of these findings is further hampered by the substantial variation in study design, cancer types included, and duration of follow up, ranging from a median of 2 to 79 months.[9,10]

To obtain valid and interpretable summary estimates of the performance of the Khorana score, based on the evidence available, we performed a systematic review and meta-analysis, specifically focusing on 6-month follow-up outcomes of all published relevant studies by obtaining additional data, thereby minimizing between-study heterogeneity. Our findings provide physicians with clinically useful data on the absolute risks of VTE associated with a low-, intermediate-, and high-risk Khorana score in ambulatory patients with cancer.

Table 1. Khorana risk score.

Patients' characteristics	Risk score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecological, bladder, or testicular)	1
Prechemotherapy platelet count ≥350 x 10^9/L	1
Prechemotherapy hemoglobin level <100 g/L or use of red cell growth factors	1
Prechemotherapy leukocyte count >11 x 10^9/L	1
Body Mass Index ≥35 kg/m^2	1

Methods

This report adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance (See checklist in *Online Supplementary Table S1*).[11]

Search strategy and data collection

A comprehensive search was performed in Embase and MEDLINE from January 2008 to June 2018 to identify studies that had evaluated the Khorana score in ambulatory cancer patients. In addition, studies presented as abstracts at conferences of the American Society of Hematology (ASH) or the International Society on Thrombosis and Haemostasis (ISTH) were identified by a manual search. Two reviewers (FIM and MC) independently screened studies and assessed bias with the Quality in Prognosis Studies (QUIPS) tool.[12] The search strategy is shown in *Online Supplementary Table S2*, and a full explanation of study selection, data extraction, and bias assessment is provided in *Online Supplementary list 1*.

Additional data

Because the number of events are expected to increase with the duration of follow up, we evaluated the incidence of VTE during a pre-specified follow-up duration to minimize between-study heterogeneity in observation time. Since the majority of venous thromboembolic events occur in the first six months after start of chemotherapy,[1] this 6-month follow-up period was considered most relevant. Corresponding authors of included studies not reporting the 6-month period were contacted and invited to provide additional data for this period.

Statistical analysis

The primary outcome measure was the proportion of cancer patients who developed VTE during the first six months of study follow up in those with a low (0 points), intermediate (1-2 points), or high (3 or more points) Khorana score. VTE was defined as the composite of radiologically confirmed symptomatic or incidental distal or proximal lower-extremity deep-vein thrombosis, upper-extremity deep-vein thrombosis, or pulmonary embolism. Studies with a fixed follow-up time less than six months in their study design were not included in the analysis of the 6-month outcomes. The derivation cohort of the Khorana score was excluded from analysis.[7] As currently ongoing clinical trials (*clinicaltrials.gov identifier: 02048865 and 02555878*) select patients with a score of 2 or more for thromboprophylaxis; the primary outcome was also assessed for this alternative positivity threshold. Secondary outcome measures included the proportion of patients with VTE during overall follow up, the proportion of VTE occurring in the high-risk group, and the relative risk of VTE for patients with a high-risk score (≥3 points) *versus* those with a low-to-intermediate risk score (0-2 points) in the first six months and during complete follow up. A sensitivity analysis was performed restricted to studies not judged to be at high risk of bias in any of the domains.

A random effects model with logit transformation and inverse variance weighting was used to calculate summary estimates. Forest plots are presented with back-transformed study-specific estimates and corresponding 95% confidence and prediction intervals. Between-study heterogeneity was assessed by calculating tau-squared (τ^2) using restricted maximum likelihood estimation. Differences between subgroups were tested for significance with a χ^2 test. $P<0.05$ was considered statistically significant. Publication bias was explored with a funnel plot using the relative risk between high- and low-to-intermediate risk patients on the x-axis.[13] Analyses were performed with R computing software, version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria; *www.r-project.org*), in particular using the meta package version 4.9-0.

Results

Search results

The database and manual search yielded 1,826 unique articles and 53 abstracts, of which 1,641 were excluded on the basis of title and abstract (Figure 1). Another 50 studies were excluded after full-text assessment because the Khorana score was not reported (n=31), VTE incidence was not reported (n=6), the study population only comprised patients with VTE (n=6), the cohort was a duplicate report (n=5), or the study had a case-control design (n=2).

A total of 45 articles and eight abstracts were included in the analysis, comprising 55 cohorts and 34,555 ambulatory cancer patients, of whom 2,386 (6.9%) were diagnosed with VTE during follow up. Most studies included patients with various tumors (n=22; 42%), while others had confined recruitment to patients with gastrointestinal

Table 2. Studies with relevant characteristics.

Author (year)	Type	Study design‡	Newly diagnosed cancer only	VTE screening before study start	Cancer type	Median follow up duration (months)	Study population*	Total follow up: patients with VTE, n (%)	First 6 months: patients with VTE, n (%)
Abdel-Razeq (2017)[25]	Article	Retrospective	No	No	Various	40	1,677	96 (5.7%)	83 (4.9%)
Ades (2015)[26]	Article	Retrospective	No	No	Colorectal	27.5	151	35 (23.2%)	15 (9.9%)
Austin (2017)[27]	Abstract	Retrospective	NR	No	Various	12	740	72 (9.7%)	64 (8.6%)
Ayyappan (2016)[28]	Abstract	Retrospective	Yes	No	DLBCL	46	241	45 (18.7%)	29 (12.0%)
Bezan-Graz (2017)[10]	Article	Retrospective	NR	No	Testicular	79.2	586	30 (5.1%)	27 (4.6%)
Bezan-Zurich (2017)[10]	Article	Retrospective	NR	No	Testicular	NR	303	21 (6.9%)	21 (6.9%)
Borchmann (2016)[29]	Abstract	Retrospective	No	No	HL	12	5,409	169 (3.1%)	158 (2.9%)
Cella (2017)[30]	Article	Prospective	NR	Yes	Various	8.3	827	52 (6.3%)	38 (4.6%)
Ferroni (2015)[31]	Article	Prospective	Yes	No	Various	9.2	810	54 (6.7%)	43 (5.3%)
Ferroni (2012)[32]	Article	Retrospective	Yes	No	Lung	6.9	108	16 (14.8%)	14 (13.0%)
Fuentes (2017)[33]	Article	Retrospective	Yes	No	Gastric	21.3	108	9 (8.3%)	4 (3.7%)
George (2011)[34,35]	Article	Prospective	NR	NR	Various	6	1,553	53 (3.4%)	53 (3.4%)
Guadagni (2017)[36]	Article	Retrospective	Yes	No	Gastrointestinal	11.0	342	32 (9.4%)	24 (7.0%)
Kearney (2009)[37]	Abstract	Retrospective	NR	No	Various	NR	112	23 (20.5%)	NR
Khorana (2017)[38]	Article	Prospective	No	Yes	Various	2.8	48	10 (20.8%)	10 (20.8%)
Khorana (2014)[39]	Article	Prospective	Yes	Yes	Various	3.7	35	8 (22.9%)	8 (22.9%)
Khorana-cohort 2 (2008)[7]	Article	Prospective	No	No	Various	2.4	1,365	28 (2.1%)	NR
Kim (2012)[40]	Article	Retrospective	Yes	No	Various	18.9	90	15 (16.7%)	NR
Kruger (2017)[41]	Article	Retrospective	No	No	Pancreatic	9.2	111	16 (14.4%)	11 (9.9%)
Kuderer (2017)[42]	Article	Prospective	NR	No	Lung	6.0	1,780	111 (6.2%)	111 (6.2%)
Kuk (2017)[43]	Article	Retrospective	Yes	No	Ovarian	NR	57	5 (8.8%)	NR
Kunapareddy (2017)[44]	Abstract	Prospective	NR	No	Various	7.9	191	25 (13.1%)	25 (13.1%)
Lim (2015)[45]	Article	Retrospective	Yes	No	DLBCL	41.9	322	29 (9.0%)	25 (7.8%)
Lubberts (2016)[46]	Article	Prospective	Yes	No	Testicular	33.0	72	4 (5.6%)	3 (4.2%)
Lustig (2015)[47]	Article	Prospective	No	No	Various	3.0	580	35 (6.0%)	35 (6.0%)
Mandala (2012)[9]	Article	Prospective	No	No	Various	2.0	1,412	56 (4.0%)	NR
Mansfield (2016)[48]	Article	Retrospective	NR	No	Lung	15.2	658	79 (12.0%)	44 (6.7%)
Misch (2013)[49]	Article	Retrospective	No	No	Glioma	NR	38	4 (10.5%)	NR
Moore (2011)[50]	Article	Retrospective	NR	No	Various	NR	932	168 (18.0%)	NR
Munoz-Martin (2018)[51]	Article	Prospective	NR	No	Various	6.0	389	71 (18.3%)	71 (18.3%)
Munoz-Martin (2014)[52]	Article	Retrospective	No	No	Pancreatic	9.5	73	22 (30.1%)	14 (19.2%)
Noble (2015)[53,54]	Article	Prospective	Yes	NR	Lung	6,0	1,068	69 (6.5%)	69 (6.5%)
Panizo (2015)[55]	Article	Prospective	No	No	Various	3.0	841	43 (5.1%)	43 (5.1%)
Papaxoinis[56]	Article	Retrospective	Yes	No	Gastrointestinal	43.0	526	49 (9.3%)	49 (9.3%)
Park (2017)[57]	Article	Prospective	Yes	No	Gastric	10.8	241	23 (9.5%)	14 (5.8%)
Patel (2015)[58]	Article	Prospective	Yes	No	Prostate	24.0	948	58 (6.1%)	41 (4.3%)
Pelzer (2013)[24,59]	Article	Prospective	Yes	No	Pancreatic	12.0	144	21 (14.6%)	21 (14.6%)
Petitto (2017)[60]	Abstract	Prospective	Yes	No	Various	6.0	553	28 (5.1%)	NR
Posch (2016)[61]	Article	Prospective	No	No	Various	24.0	1,594	127 (8.0%)	91 (5.7%)
Ramos (2016)[62]	Article	Retrospective	Yes	No	Urothelial	8.6	943	89 (9.4%)	55 (5.8%)
Ruch (2012)[63]	Abstract	Retrospective	NR	No	Pancreatic	8.8	85	19 (22.4%)	NR
Rupa-Matysek (2018)[64]	Article	Retrospective	Yes	No	DLBCL	37.0	428	64 (15.0%)	35 (8.2%)
Rupa-Matysek (2018)[65]	Article	Retrospective	Yes	No	Lung	14.0	118	20 ((16.9%)	NR
Santi (2017)[66]	Article	Prospective	Yes	No	NHL	6.0	1,189	15 (1.3%)	15 (1.3%)
Sohal (2016)[67]	Abstract	Prospective	NR	No	Colorectal	6.0	1,593	86 (5.4%)	86 (5.4%)
Srikanthan cohort 1 (2015)[68]	Article	Retrospective	Yes	No	Testicular	NR	207	20 (9.7%)	20 (9.7%)
Srikanthan cohort 2 (2015)[68]	Article	Retrospective	Yes	No	Testicular	NR	105	10 (9.5%)	10 (9.5%)

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Author (year)	Type	Study design‡	Newly diagnosed cancer only	VTE screening before study start	Cancer type	Median follow up duration in months	Study population*	Total follow up: patients with VTE, n (%)	First 6 months: Patients with VTE, n (%)
Tafur (2015)[69]	Article	Prospective	Yes	No	Various	10.4	241	29 (12.0%)	24 (10.0%)
van Es (2017)[70]	Article	Prospective	No	No	Various	6.0	843	53 (6.3%)	53 (6.3%)
van Es (2017)[71]	Article	Retrospective	Yes	No	Pancreatic	7.7	147	20 (13.6%)	13 (8.8%)
Vathiotis[72]	Article	Retrospective	Yes	No	Lung	3.7	130	13 (10.0%)	7 (5.4%)
Verso (2012)[23]	Article	Prospective	No	No	Various	3.7	381	15 (3.9%)	15 (3.9%)
Wang (2017)[73]	Article	Retrospective	NR	No	Hepatocellular	11.9	270	16 (5.9%)	11 (4.1%)
Yust-Katz (2015)[74]	Article	Retrospective	Yes	No	Glioblastoma	NR	440	64 (14.5%)	NR
Zahir (2017)[75]	Article	Retrospective	No	No	Various	NR	400	42 (10.5%)	42 (10.5%)

VTE: venous thromboembolism; n: number; DLBCL: diffuse large B-cell lymphoma; NR:not reported; NHL: non-Hodgkin lymphoma.

(n=12; 23%), lung (n=6; 11%), urogenital (n=6; 11%), hematologic (n=5; 9%), or central nervous system cancer (n=2; 4%). Almost half of the studies had a prospective design (n=25; 47%); the majority also included incidentally detected VTE as outcome event (n=32; 60%). Study group size ranged from 35 to 5,409 patients. Median follow-up duration ranged from 2 to 79 months. Key study characteristics of included studies are shown in Table 2.

The 6-month follow-up data were reported in eight of the included studies. For 11 studies, no additional data were obtained after contacting the corresponding author because the authors did not reply despite reminders (n=8), were not able to retrieve the data (n=1), or where not willing to share the data (n=2). For 34 studies, additional data were obtained, yielding available 6-month data for 27,849 of the available 34,555 patients (81%).

Risk of bias

Using the pre-specified Quality in Prognosis Studies (QUIPS) criteria, 25 studies were judged to be at high risk of bias for one or more of the bias domains. All eight included abstracts and four articles were judged to be at high risk of bias because of insufficient reporting on methods. Other reasons were a high risk of bias in the applicability of the Khorana score (n=1), patient selection (n=4), outcome (n=3), study attrition (n=2), participation (n=4), prognostic factor measurement (n=3), outcome measurement (n=5), and confounding factors (n=4). *Online Supplementary Table S4* summarizes the risk of bias assessment for all studies. A funnel plot did not indicate evidence of publication bias (*Online Supplementary Figure S1*).

Risk classification by the Khorana score

Overall, 6,319 patients (19%) had a Khorana score of 0 points (low risk), 21,172 patients (64%) a score of 1 or 2 points (intermediate risk), and 5,614 patients (17%) a score of 3 or more points (high risk). The group with a Khorana score of 0 or 1 point comprised 15,107 patients (53%), and the group with a score of 2 points or higher 13,148 (47%).

Incidence of venous thromboembolism in the Khorana score risk groups

The incidence of VTE in the first 6-month period was 5.0% (95%CI: 3.9-6.5) in patients with a low-risk Khorana score (0 points), 6.6% (95%CI: 5.6-7.7) in those with an intermediate-risk Khorana score (1 or 2 points), and 11.0% (95%CI: 8.8-13.8) in those with a high-risk Khorana score (3 points or higher) (Table 3 and Figure 2A-C). The relative risk of VTE in the first six months was 1.8 (95%CI: 1.5-2.1) for patients with a score of 3 or higher compared to those with a score of 2 or lower (*Online Supplementary Figure S2*).

In the high-risk Khorana score group, the reported 6-month risk of VTE was lower in studies including patients with lung cancer (6.4%; 95%CI: 4.9-8.4) or hematologic malignancies (7.1%; 95%CI: 2.6-18.4) compared to studies with gastrointestinal (13.0%; 95%CI: 8.5-19.6), urogenital cancer (18.2%; 95%CI: 8.6-34.6), or various cancers (11.5%; 95%CI: 8.6-15.3, lung *vs.* various, *P*=0.0008; hematologic *vs.* various, *P*=0.000). The 6-month incidence in the group with a Khorana score of 1 point or lower was 5.5% (95%CI: 4.5-6.9) compared to 8.9% (95%CI: 7.3-10.8) in the group with a score of 2 or more points, corresponding to a relative risk of 1.5 (95%CI: 1.3-1.8).

During the overall study follow-up period, that ranged from a median of two to 79 months, the summary incidence of VTE was 5.7% (95%CI: 4.2-7.9) in patients with a low-risk Khorana score (0 points), 8.6% (95%CI: 7.3-10.2) in those with an intermediate-risk Khorana score (1 or 2 points), and 14.0% (95%CI:11.7-16.7) in those with a high-risk Khorana score (3 points or higher) (Table 3 and *Online Supplementary Figure S3A-C*).

Distribution of venous thromboembolic events over the Khorana score risk groups

Of all patients who developed VTE in the first six months, 23.4% (95%CI: 18.4-29.4) had been classified as high risk with the Khorana score (3 points or higher). All other thromboembolic events occurred in the intermediate- or low-risk groups (76.6%; 95%CI:70.6 -81.6). For the total follow-up duration, the proportion of events occurring in the high-risk group was 23.7% (95%CI: 18.7-29.5).

Sensitivity analyses

Results were consistent in the sensitivity analysis in which studies judged to be at high risk of bias in one or more of the bias domains were excluded (Table 3). When excluding these studies, the 6-month risks of VTE in patients with a Khorana score of 0, 1 to 2, and 3 points or higher were 4.6% (95%CI: 3.2-6.5), 6.1% ((95%CI: 5.0-7.4), and 11.1% (95%CI: 8.3-14.7), respectively. The inci-

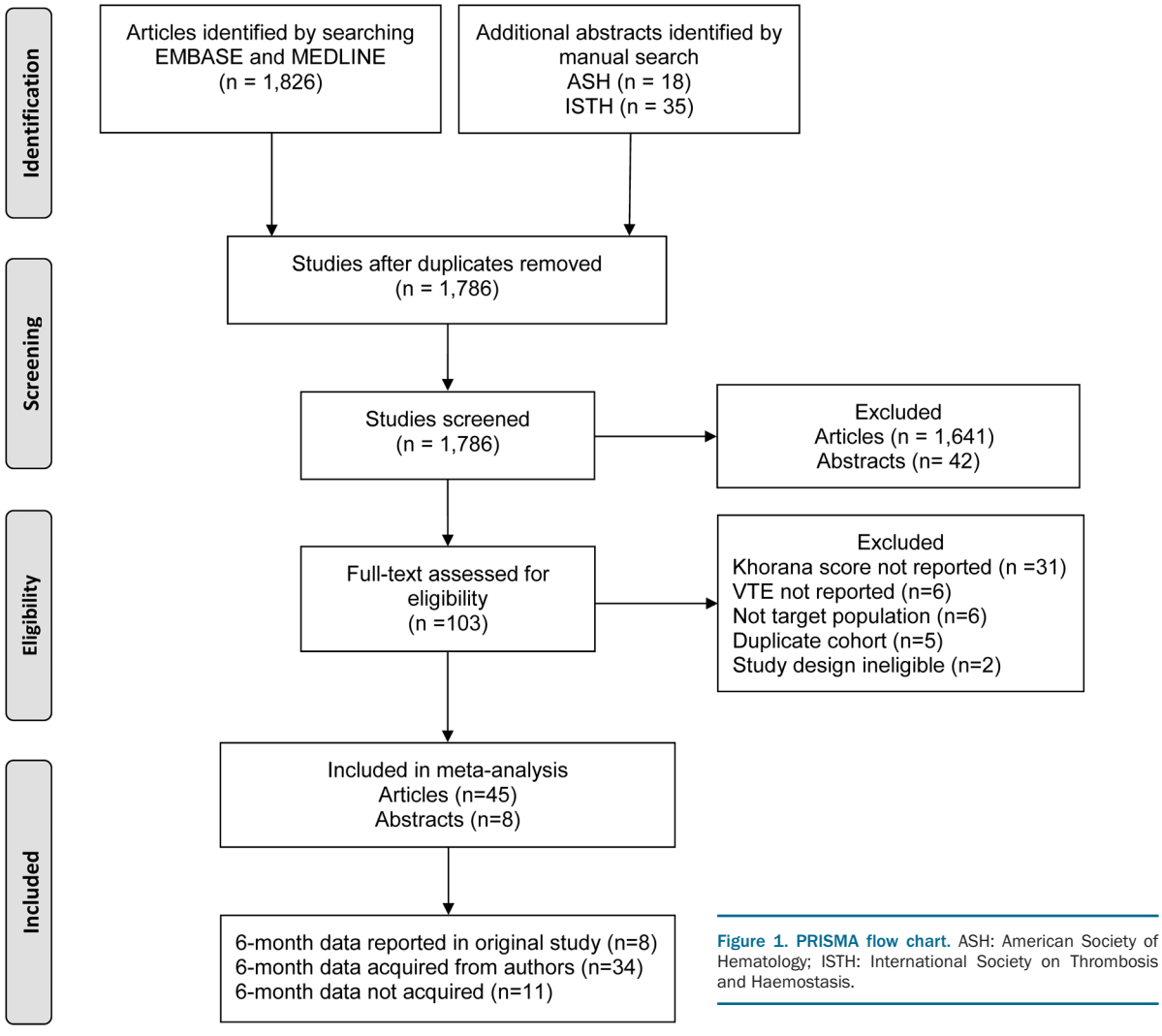


Figure 1. PRISMA flow chart. ASH: American Society of Hematology; ISTH: International Society on Thrombosis and Haemostasis.

dence in the group with a score of 2 points or higher was 8.3% (95%CI: 6.4-10.7). The relative risk of patients with a score of 3 or higher compared to those with a lower score was 1.9 (95%CI: 1.5-2.3).

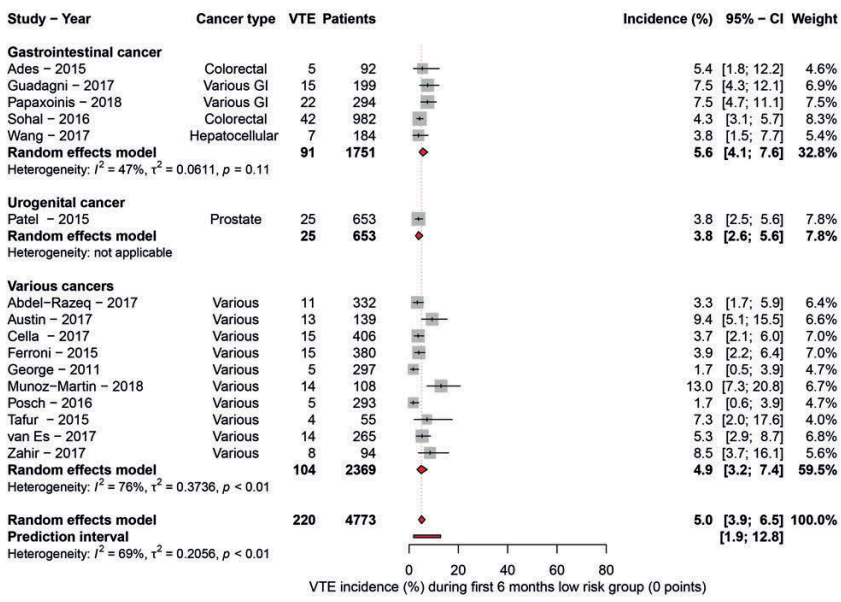
Discussion

This systematic review and meta-analysis examined the performance of the Khorana score in predicting VTE in over 34,000 patient ambulatory patients with various types of cancer. To minimize between-study heterogeneity and obtain clinically relevant estimates, the main analysis was restricted to the first six months of follow up. During this period, the summary estimate of the risk of VTE in patients with a high-risk Khorana score was 11.0%, which was significantly higher than in those with a low-risk (5.0%) or intermediate-risk (6.6%) score. These findings indicate that the Khorana score may help clinicians in selecting patients at high risk of VTE for thromboprophylaxis, which is in support of the suggestions presented in current guidelines.

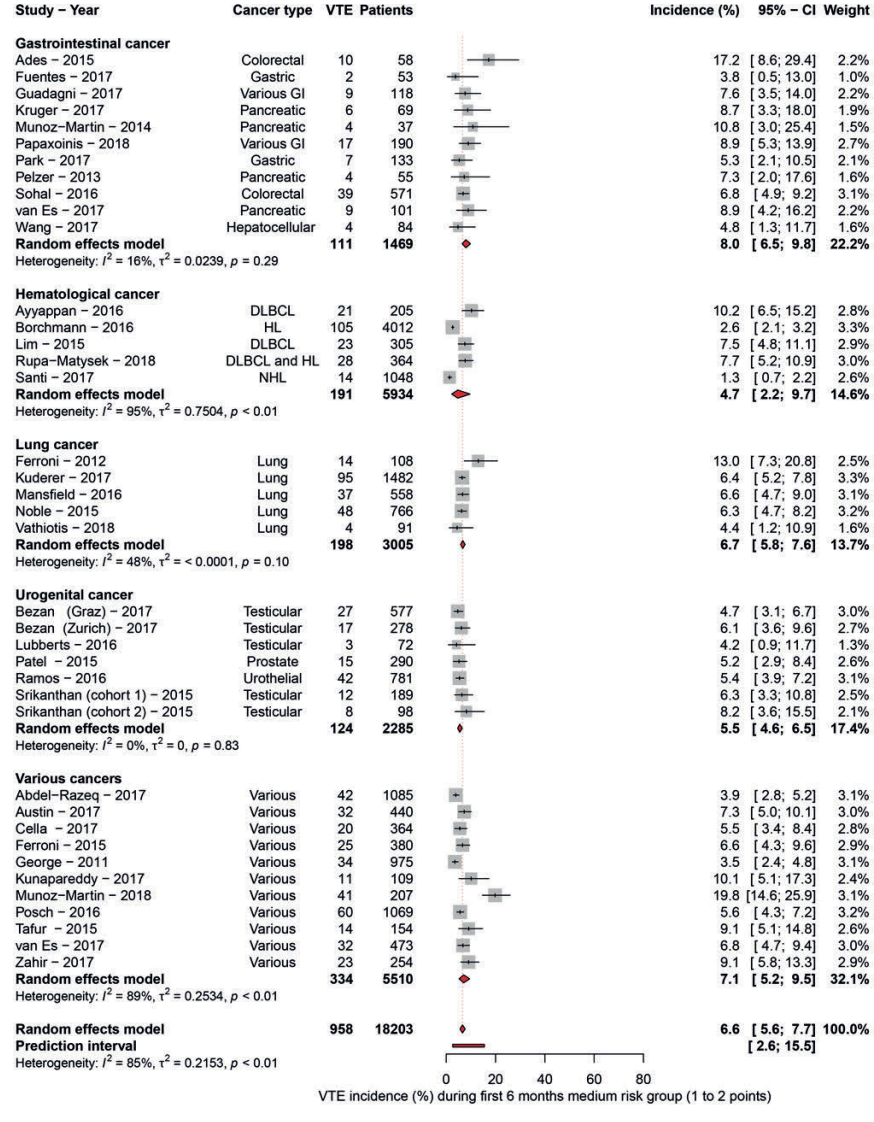
The analyses also highlight several limitations of the score. Within the high-risk group, the estimated risk of VTE was considerably lower for patients with lung cancer and hematologic malignancies than for those with other cancer types (Figure 2C). Hence, the Khorana score appears to be less informative for these two large groups of patients. Furthermore, the VTE incidence in patients with a low-to-intermediate risk score was 5-7%, which indicates that the residual risk in this group is still substantial. Therefore, the Khorana score is of limited use in ruling out a future venous thromboembolic event. Lastly, the Khorana score is designed to select patients in the high-risk group for thromboprophylaxis. However, about one in four (23.4%, 95%CI: 18.4-29.4) of the venous thromboembolic events occur in patients with a high-risk Khorana score. This means that a substantial amount of cancer patients with subsequent venous thromboembolic events will not be identified with this form of risk stratification, and will, therefore, not benefit from thromboprophylaxis.

A major strength of this study is the additional data obtained from 34 studies on the 6-month incidence of VTE after starting chemotherapy, representing 81% of cancer patients in the available relevant literature. This approach minimized between-study heterogeneity related to the broad range of reported median follow-up durations. We considered this 6-month period to be clinically

A


Study – Year | Cancer type | VTE | Patients | Incidence (%) 95% – CI | Weight
Gastrointestinal cancer
Ades – 2015 | Colorectal | 5 | 92 | 5.4 [1.8; 12.2] | 4.6%
Guadagni – 2017 | Various GI | 15 | 199 | 7.5 [4.3; 12.1] | 6.9%
Papaxoinis – 2018 | Various GI | 22 | 294 | 7.5 [4.7; 11.1] | 7.5%
Sohal – 2016 | Colorectal | 42 | 982 | 4.3 [3.1; 5.7] | 8.3%
Wang – 2017 | Hepatocellular | 7 | 184 | 3.8 [1.5; 7.7] | 5.4%
Random effects model | 91 | 1751 | 5.6 [4.1; 7.6] | 32.8%
Heterogeneity: I^2 = 47%, τ^2 = 0.0611, p = 0.11
Urogenital cancer
Patel – 2015 | Prostate | 25 | 653 | 3.8 [2.5; 5.6] | 7.8%
Random effects model | 25 | 653 | 3.8 [2.6; 5.6] | 7.8%
Heterogeneity: not applicable
Various cancers
Abdel-Razeq – 2017 | Various | 11 | 332 | 3.3 [1.7; 5.9] | 6.4%
Austin – 2017 | Various | 13 | 139 | 9.4 [5.1; 15.5] | 6.6%
Cella – 2017 | Various | 15 | 406 | 3.7 [2.1; 6.0] | 7.0%
Ferroni – 2015 | Various | 15 | 380 | 3.9 [2.2; 6.4] | 7.0%
George – 2011 | Various | 5 | 297 | 1.7 [0.5; 3.9] | 4.7%
Munoz-Martin – 2018 | Various | 14 | 108 | 13.0 [7.3; 20.8] | 6.7%
Posch – 2016 | Various | 5 | 293 | 1.7 [0.6; 3.9] | 4.7%
Tafur – 2015 | Various | 4 | 55 | 7.3 [2.0; 17.6] | 4.0%
van Es – 2017 | Various | 14 | 265 | 5.3 [2.9; 8.7] | 6.8%
Zahir – 2017 | Various | 8 | 94 | 8.5 [3.7; 16.1] | 5.6%
Random effects model | 104 | 2369 | 4.9 [3.2; 7.4] | 59.5%
Heterogeneity: I^2 = 76%, τ^2 = 0.3736, p < 0.01
Random effects model | 220 | 4773 | 5.0 [3.9; 6.5] | 100.0%
Prediction interval | [1.9; 12.8]
Heterogeneity: I^2 = 69%, τ^2 = 0.2056, p < 0.01
0 20 40 60 80
VTE incidence (%) during first 6 months low risk group (0 points)

B


Study – Year | Cancer type | VTE | Patients | Incidence (%) 95% – CI | Weight
Gastrointestinal cancer
Ades – 2015 | Colorectal | 10 | 58 | 17.2 [8.6; 29.4] | 2.2%
Fuentes – 2017 | Gastric | 2 | 53 | 3.8 [0.5; 13.0] | 1.0%
Guadagni – 2017 | Various GI | 9 | 118 | 7.6 [3.5; 14.0] | 2.2%
Kruger – 2017 | Pancreatic | 6 | 69 | 8.7 [3.3; 18.0] | 1.9%
Munoz-Martin – 2014 | Pancreatic | 4 | 37 | 10.8 [3.0; 25.4] | 1.5%
Papaxoinis – 2018 | Various GI | 17 | 190 | 8.9 [5.3; 13.9] | 2.7%
Park – 2017 | Gastric | 7 | 133 | 5.3 [2.1; 10.5] | 2.1%
Pelzer – 2013 | Pancreatic | 4 | 55 | 7.3 [2.0; 17.6] | 1.6%
Sohal – 2016 | Colorectal | 39 | 571 | 6.8 [4.9; 9.2] | 3.1%
van Es – 2017 | Pancreatic | 9 | 101 | 8.9 [4.2; 16.2] | 2.2%
Wang – 2017 | Hepatocellular | 4 | 84 | 4.8 [1.3; 11.7] | 1.6%
Random effects model | 111 | 1469 | 8.0 [6.5; 9.8] | 22.2%
Heterogeneity: I^2 = 16%, τ^2 = 0.0239, p = 0.29
Hematological cancer
Ayyappan – 2016 | DLBCL | 21 | 205 | 10.2 [6.5; 15.2] | 2.8%
Borchmann – 2016 | HL | 105 | 4012 | 2.6 [2.1; 3.2] | 3.3%
Lim – 2015 | DLBCL | 23 | 305 | 7.5 [4.8; 11.1] | 2.9%
Rupa-Matysek – 2018 | DLBCL and HL | 28 | 364 | 7.7 [5.2; 10.9] | 3.0%
Santi – 2017 | NHL | 14 | 1048 | 1.3 [0.7; 2.2] | 2.6%
Random effects model | 191 | 5934 | 4.7 [2.2; 9.7] | 14.6%
Heterogeneity: I^2 = 95%, τ^2 = 0.7504, p < 0.01
Lung cancer
Ferroni – 2012 | Lung | 14 | 108 | 13.0 [7.3; 20.8] | 2.5%
Kuderer – 2017 | Lung | 95 | 1482 | 6.4 [5.2; 7.8] | 3.3%
Mansfield – 2016 | Lung | 37 | 558 | 6.6 [4.7; 9.0] | 3.1%
Noble – 2015 | Lung | 48 | 766 | 6.3 [4.7; 8.2] | 3.2%
Vathiotis – 2018 | Lung | 4 | 91 | 4.4 [1.2; 10.9] | 1.6%
Random effects model | 198 | 3005 | 6.7 [5.8; 7.6] | 13.7%
Heterogeneity: I^2 = 48%, τ^2 = < 0.0001, p = 0.10
Urogenital cancer
Bezan (Graz) – 2017 | Testicular | 27 | 577 | 4.7 [3.1; 6.7] | 3.0%
Bezan (Zurich) – 2017 | Testicular | 17 | 278 | 6.1 [3.6; 9.6] | 2.7%
Lubberts – 2016 | Testicular | 3 | 72 | 4.2 [0.9; 11.7] | 1.3%
Patel – 2015 | Prostate | 15 | 290 | 5.2 [2.9; 8.4] | 2.6%
Ramos – 2016 | Urothelial | 42 | 781 | 5.4 [3.9; 7.2] | 3.1%
Srikanthan (cohort 1) – 2015 | Testicular | 12 | 189 | 6.3 [3.3; 10.8] | 2.5%
Srikanthan (cohort 2) – 2015 | Testicular | 8 | 98 | 8.2 [3.6; 15.5] | 2.1%
Random effects model | 124 | 2285 | 5.5 [4.6; 6.5] | 17.4%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.83
Various cancers
Abdel-Razeq – 2017 | Various | 42 | 1085 | 3.9 [2.8; 5.2] | 3.1%
Austin – 2017 | Various | 32 | 440 | 7.3 [5.0; 10.1] | 3.0%
Cella – 2017 | Various | 20 | 364 | 5.5 [3.4; 8.4] | 2.8%
Ferroni – 2015 | Various | 25 | 380 | 6.6 [4.3; 9.6] | 2.9%
George – 2011 | Various | 34 | 975 | 3.5 [2.4; 4.8] | 3.1%
Kunapareddy – 2017 | Various | 11 | 109 | 10.1 [5.1; 17.3] | 2.4%
Munoz-Martin – 2018 | Various | 41 | 207 | 19.8 [14.6; 25.9] | 3.1%
Posch – 2016 | Various | 60 | 1069 | 5.6 [4.3; 7.2] | 3.2%
Tafur – 2015 | Various | 14 | 154 | 9.1 [5.1; 14.8] | 2.6%
van Es – 2017 | Various | 32 | 473 | 6.8 [4.7; 9.4] | 3.0%
Zahir – 2017 | Various | 23 | 254 | 9.1 [5.8; 13.3] | 2.9%
Random effects model | 334 | 5510 | 7.1 [5.2; 9.5] | 32.1%
Heterogeneity: I^2 = 89%, τ^2 = 0.2534, p < 0.01
Random effects model | 958 | 18203 | 6.6 [5.6; 7.7] | 100.0%
Prediction interval | [2.6; 15.5]
Heterogeneity: I^2 = 85%, τ^2 = 0.2153, p < 0.01
0 20 40 60 80
VTE incidence (%) during first 6 months medium risk group (1 to 2 points)

C

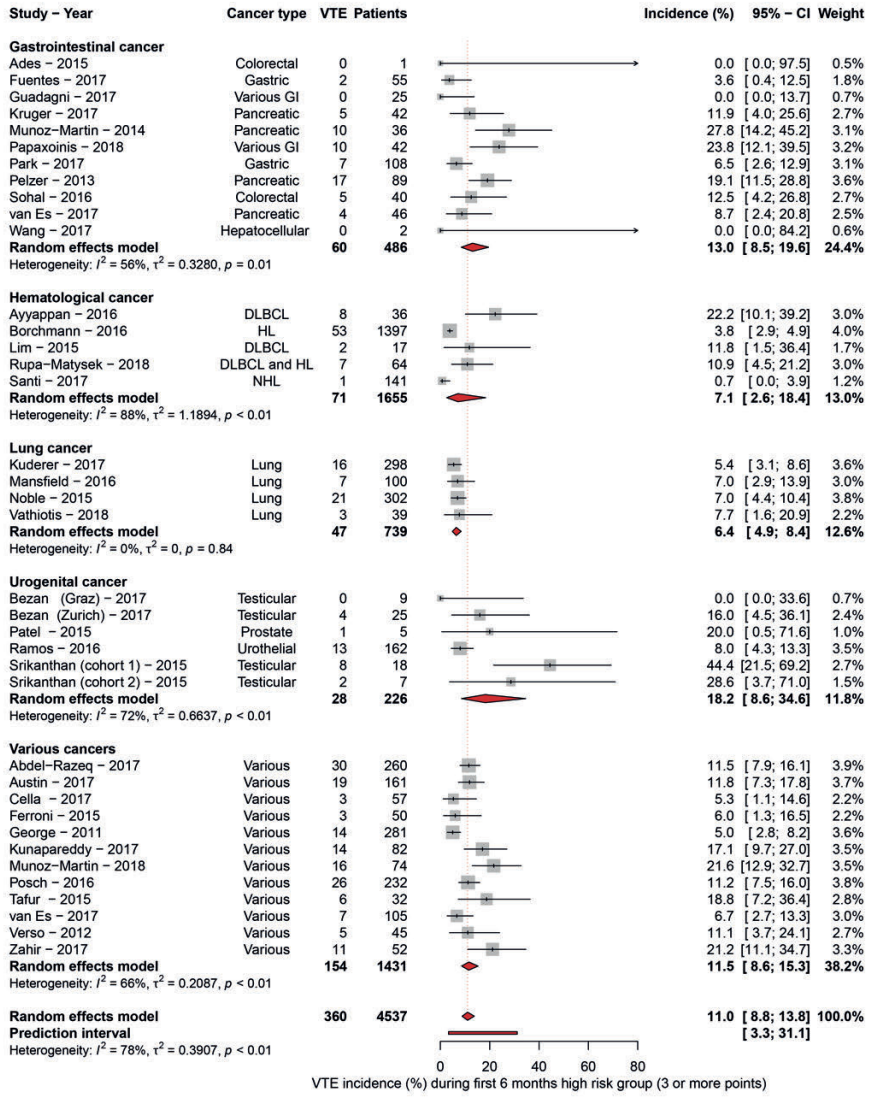


Figure 2. Venous thromboembolism incidence in the low-, intermediate-, and high-risk group over six months. Venous thromboembolism incidence in the low-risk (A), intermediate-risk (B), and high-risk (C) groups according to the Khorana score, over six months follow up.

most relevant. Prediction of VTE only for the first few months of chemotherapy may be too short, since the risk remains elevated throughout the first six months. On the other hand, the Khorana score calculated with pre-chemotherapy laboratory data likely predicts less well for longer term (>6 months) than for shorter term intervals. The inclusion of more than 50 studies enabled the meta-analysis for various subgroups of cancer patients, showing that the performance of the Khorana score varies across tumor types. A potential limitation is the substantial proportion of studies judged to be at high risk of bias (*Online Supplementary Table S4*). However, the sensitivity analyses restricted to studies at low risk of bias did not materially alter the results (Table 3). When the analysis was restricted to studies with a prospective design or to studies without systematic VTE screening preceding study, results were comparable (*data not shown*). Additional data for the first six months could not be obtained for eleven studies, possibly introducing sampling bias. We believe, however, that the magnitude of this risk of bias is at best modest since 6-month data were available in the final analyses for 81% of all patients. Some studies included more types of venous thromboembolic events than specified in our primary outcome. However, these types of venous thromboembolic events occur infrequently. A large proportion of the studies (n=32, 60%) included incidentally detected VTE, unlike the outcome in the derivation study of the Khorana score.[7] However, we believe these events should also be considered since clinical outcomes in patients with incidental VTE are similar to those with symptomatic events.[14-16] Consequently, international guidelines regard incidental VTE events as clinically relevant and recommend anticoagulant treatment, as for patients with symptomatic VTE.[6,17] Despite minimizing bias due to differ-

ences in follow up by using 6-month outcome data, considerable residual heterogeneity was observed in the analyses. This is expected in meta-analyses of predictive model performance, especially when evaluating risk assessment tools across various cancers.[18] Nonetheless, we believe the presented estimates overall and for subgroups by cancer type are the most reliable ones based on the current literature, and can help clinicians to decide whether to use the score in their practice.

Two currently ongoing randomized trials use the Khorana score to select cancer patients at high risk of VTE for thromboprophylaxis (*clinicaltrials.gov identifier: 02048865 and 02555878*). Interestingly, these studies apply a positivity threshold of 2 points rather than the conventional 3 points. Our analyses demonstrate that this approach increases the proportion of patients classified as high risk (17-47%) while in parallel decreasing the absolute risk of VTE in this group (11-9%). As a conse-

Table 3. Summary estimates for 6-month and total follow-up duration.[‡]

	Incidence of VTE					Relative risk *versus* lower risk groups		Proportion of all VTE
	Khorana score 0 % (95% CI)	Khorana score 1-2 % (95% CI)	Khorana score ≥3 % (95% CI)	Khorana score ≤1 % (95% CI)	Khorana score≥2 % (95% CI)	Khorana score ≥3 (95% CI)	Khorana score ≥2 (95% CI)	Khorana score ≥3 % (95% CI)
6 months follow-up duration	5.0 (3.9-6.5)	6.6 (5.6-7.7)	11.0 (8.8-13.8)	5.5 (4.5-6.9)	8.9 (7.3-10.8)	1.8 (1.5-2.1)	1.5 (1.3-1.8)	23.4 (18.4-29.4)
Total study follow-up duration*	5.7 (4.2-7.9)	8.6 (7.3-10.2)	14.0 (11.7-16.7)	6.8 (5.2-8.9)	11.3 (9.4-13.4)	1.7 (1.5-2.0)	1.5 (1.3-1.8)	23.7 (18.7-29.5)
Low and moderate bias studies only								
6 months follow-up duration	4.6 (3.2-6.5)	6.1 (5.0-7.4)	11.1 (8.3-14.7)	5.0 (4.0-6.3)	8.3 (6.4-10.7)	1.9 (1.5-2.3)	1.6 (1.3-2.0)	24.4 (17.8-32.5
Total study follow-up duration*	4.5 (3.0-6.7)	7.6 (6.0-9.5)	13.5 (10.7-16.8)	6.3 (4.9-8.1)	10.6 (8.4-13.2)	1.8 (1.4-2.2)	1.5 (1.2-1.9)	22.9 (17.2-29.9)

[‡]Estimates were derived from random effects meta-analysis. *Total follow-up duration varied substantially complicating interpretation of the results at total follow-up duration. CI: confidence interval; VTE: venous thromboembolism.

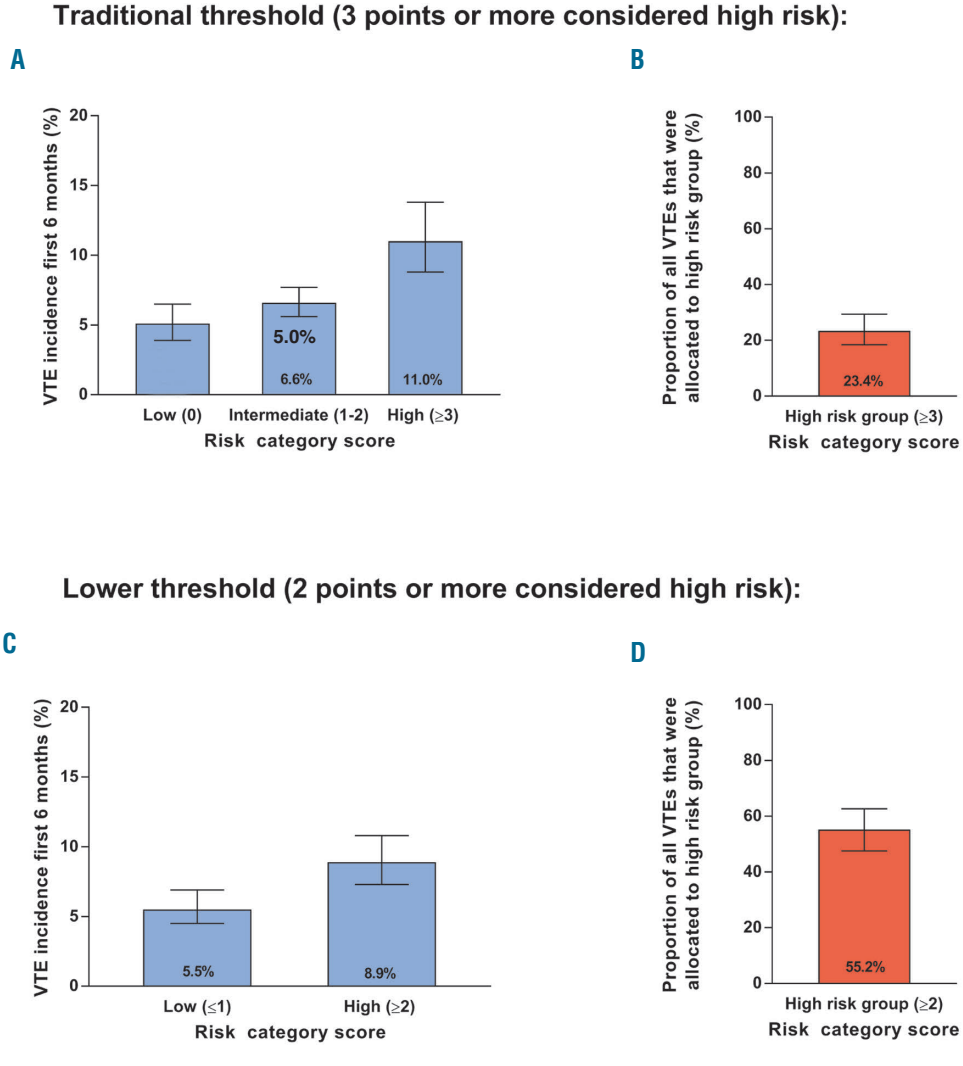


Figure 3. Estimated incidence of venous thrombosis and proportion in the high-risk group over six months. Estimated incidence of venous thrombosis (A and C) and proportion of venous thromboembolic events allocated to the high-risk group (B and D). When considering two points or more as high-risk (C and D) instead of three points or more (traditional threshold, A and B), the proportion of venous thromboembolic events allocated to the high risk groups increases, but also results in a lower incidence. VTE: venous thromboembolism.

quence, the proportion of thromboembolic events that occur in the high-risk group increases from 23% to 55% (Figure 3). It is a matter of debate whether the 9% risk of VTE during the first six months is considered high enough to justify thromboprophylaxis.

The primary aim of risk stratification with the Khorana score is to select cancer patients with a high risk of VTE suitable for long-term thromboprophylaxis. A meta-analysis of randomized trials that compared low-molecular-weight heparins in prophylactic doses in cancer patients with placebo showed an absolute risk reduction of approximately 50% during a median follow-up of ten months (RR 0.54; 95%CI: 0.38-0.75), with an increase in major bleeding events (RR 1.44; 95%CI: 0.98-2.11).[19] As the estimated 6-month incidence of VTE in cancer patients with a high Khorana score is 11.0%, thromboprophylaxis with low-molecular-weight heparins for cancer patients in this group could result in a number requiring treatment of approximately 19 when extrapolating the relative risk reduction of 0.54. When considering patients with 2 points or more as high-risk, thromboprophylaxis with low-molecular-weight heparins could result in a number requiring treatment of 24. Recent trials showed an acceptable safety profile of therapeutic doses of direct oral anticoagulants in cancer patients compared to low-molecular-weight heparins.[20,21] Since their oral administration makes these drugs more convenient, long-term thromboprophylaxis would be less burdensome and, therefore, more likely to be accepted by clinicians and patients. Whether the safety and efficacy of prophylactic doses of direct oral anticoagulants are comparable to that of low-molecular-weight heparin in cancer patients needs to be established.

The present meta-analysis shows that the Khorana score can select high-risk patients for thromboprophylaxis overall. These findings indicate that the Khorana score may help clinicians in selecting patients at high risk of VTE for thromboprophylaxis, which is in support of the suggestions presented in some guidelines and could accelerate their implementation in clinical practice. However, several limitations of the Khorana need to be taken into account, including the different in predicted performance across cancer types and the modest proportion of patients with VTE assigned to the high-risk group. Several other VTE prediction tools for cancer patients have been introduced, which may have a better performance than the Khorana score;[22-24] these scores, however, require prospective validation. Development of risk prediction models for bleeding events in patients with prophylactic anticoagulants could help to carefully weigh the benefit risk trade-off for thromboprophylaxis in cancer patients. In addition, future prediction tools should aim to address the limitations of the Khorana score, as outlined by this analysis. Novel biomarkers or genetic information from tumor biopsies could improve prediction of VTE and, therefore, merit investigation.

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