



The risk of venous thromboembolism in cancer patients receiving chemotherapy: a meta-analysis with systematic review

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Background: The Khorana score was developed to predict the risk of venous thromboembolism (VTE) in cancer patients receiving chemotherapy. However, the utility of the Khorana score remains controversial since different studies report varying results. This meta-analysis aims to analyze the incidence of VTE with different risk stratifications using the Khorana score for overall follow-up time, incidence of deep-vein thrombosis (DVT), incidence of pulmonary embolism (PE) and bleeding in cancer patients receiving chemotherapy.

Methods: A systemic search was performed using PubMed, Embase, Cochrane Library and Web of Science for studies describing VTE incidence in cancer patients undergoing chemotherapy. The incidence of VTE was calculated using R computing software.

Results: We included 13 studies in this meta-analysis, with a total of 5,852 cancer patients and 424 VTE cases. Results revealed that overall incidence of low, intermediate and high-risk groups were 2% (95% CI: 1–6%), 11% (95% CI: 6–18%) and 14% (95% CI: 9–20%), respectively. The overall incidence of DVT and PE were 6% (95% CI: 4–10%) and 4% (95% CI: 2–7%), respectively. Lastly, bleeding rate was 4% (95% CI: 2–8%).

Conclusions: According to this meta-analysis, the Khorana score is suitable for cancer patients receiving chemotherapy in a 3–6-month timeframe rather than “forever”. The incidence of PE in this population was significantly greater than what was observed for non-cancer patients. More than half of VTE events occurred within 6 months of commencing chemotherapy.

Keywords: Venous thromboembolism (VTE); cancer; chemotherapy; Khorana score; meta-analysis

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Introduction

Venous thromboembolisms (VTE), such as deep-vein thrombosis (DVT) and pulmonary embolism (PE), are major complications that lead to death in cancer patients (1). There are many factors influencing the increased risk of VTE in cancer patients, including chemotherapy. Due to direct

effects on vascular endothelium (2), there is a 6- to 7-fold risk of cancer-associated VTE observed in patients treated with chemotherapy (3). Regardless, few cancer patients receive thromboprophylaxis during chemotherapy (4). Presently, clinical guidelines do not clearly illustrate the conditions where patients should receive primary

VTE prevention during chemotherapy (5). Therefore, it is necessary to monitor for VTE in cancer patients undergoing chemotherapy.

The Khorana score, or the best validated model, has been recommended by the *National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology* to identify cancer patients at risk for VTE and those who would be eligible for thromboprophylaxis (6). By applying five risk factors, the Khorana score (Table S1) classifies cancer patients based on three risk stratifications, including low (score =0), intermediate (score =1–2) and high (score \geq 3) risk groups. However, previous studies have reported that the incidence of VTE ranges, and these rates are 0.8–13%, 1.8–15.9% and 6.7–41.4% in the low, intermediate and high-risk groups, respectively (7). Moreover, other studies have indicated no differences between intermediate and high-risk groups in relation to VTE incidence (8,9), even though there is a higher rate observed in intermediate compared to high-risk groups (10). Recently, two randomized controlled trials (RCTs) (11,12) considered cancer patients with a score of 2 points or greater at high risk for developing VTE. By pooling published data, this meta-analysis aims to investigate the incidence of VTE in cancer patients undergoing chemotherapy with different risks stratified using the Khorana score. This article is presented in accordance with the PRISMA reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-3292>).

Methods

Search strategy

Meta-analysis was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. Two researchers independently searched the literature. Databases used for eligible studies included PubMed, Embase, Cochrane Library, and Web of Science, from January 1, 2008 to May 1, 2019. Conflicts between the two researchers were resolved through discussion. To retrieve all eligible articles, search terms ((Khorana or KRS) and (neoplasms OR neoplas* OR cancer OR malign* OR tumor*)) were used. There were no limits placed on the study design or language. Studies published before 2008 were not included since the Khorana score was released in 2008. The CRD registration number is CRD42019135938.

Inclusion and exclusion criteria

Patient and study inclusion criteria included: (I) adults (>18 years old) diagnosed with a malignancy and undergoing chemotherapy; (II) no prior history of VTE and not receiving thromboprophylaxis at baseline; (III) risk stratification of VTE classified using the Khorana score, calculated on the first day of chemotherapy or the day before chemotherapy; (IV) RCTs, retrospective cohort studies or prospective cohort studies. Patient and study exclusion criteria included studies containing recurrent VTE, patients who were pregnant and individuals receiving thromboprophylaxis.

Outcomes

Outcomes included incidence of all VTE and bleeding events. VTE was defined as symptomatic or asymptomatic distal lower-extremity DVT, upper-extremity DVT, proximal lower-extremity DVT, upper-extremity DVT, superficial vein thrombosis, PE and splanchnic vein thrombosis. Bleeding events are composed of major bleeding and clinically relevant non-major bleeding. Major bleeding was defined by the International Society as Thrombosis and Hemostasis.

Data extraction

The following data were extracted: study design, publication year, study location, mean age, sex, proportion (male), chemotherapy regimen, follow-up time, risk category, outcomes, frequency of VTE and bleeding in different stratifications.

Quality assessment

In this meta-analysis, the quality of studies was assessed using a customized Newcastle-Ottawa Scale (NOS) quality assessment scale analyzing study representativeness, applicability of the Khorana score, outcome measurement, adequacy of cohort follow-up and applicability of outcomes (Table S2).

Statistical methods

All data were analyzed using R computing software, version (3.6.0) (R Foundation for Statistical Computing). The meta-analysis was analyzed using logit transformation (13). The I-squared (I^2) statistic was calculated to quantify

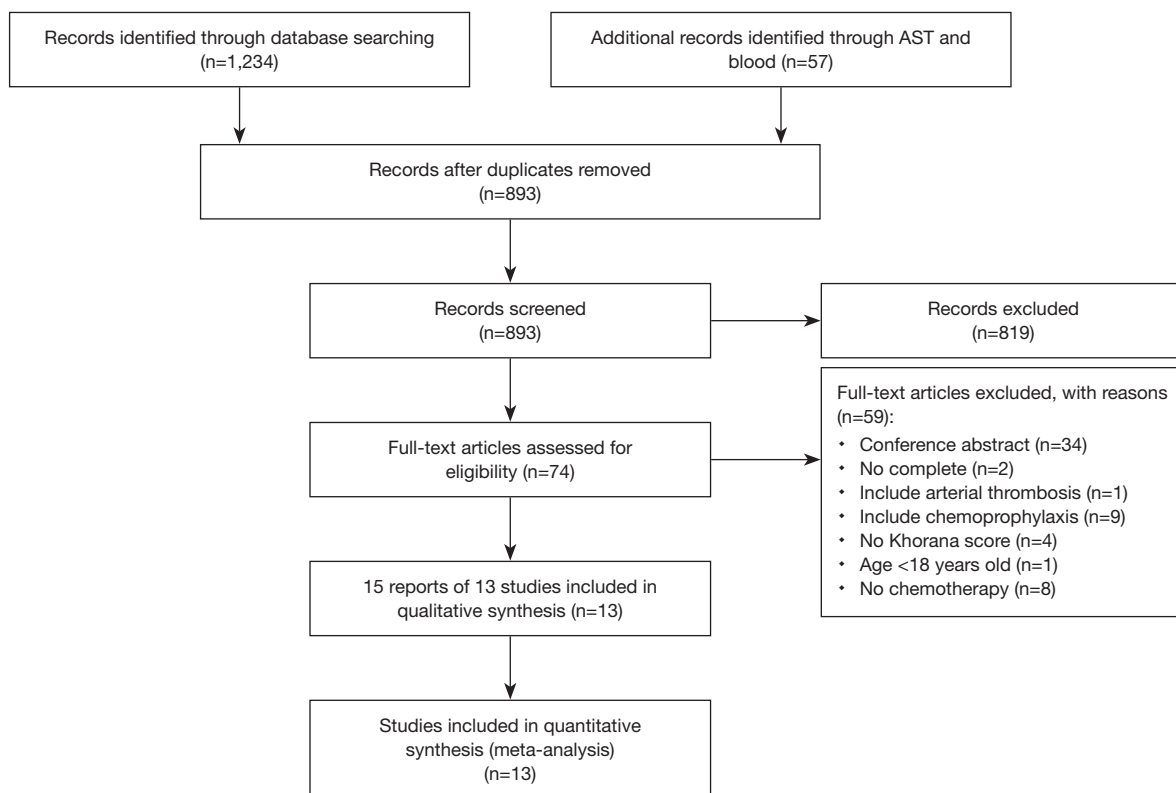


Figure 1 Flowchart illustrating the search strategy used for study inclusion.

heterogeneity among the studies. The meta-analysis was performed using a random-effects model and a $I^2 \geq 75\%$ was considered as high heterogeneity. For overall meta-analysis, data were used belonging to the median follow-up time and VTE incidence was analyzed as well as the corresponding 95% confidence interval (95% CI) for three risk stratifications. Stratified analyses were conducted based on the follow-up period. Publication bias was investigated using the Egger test (14). Sensitivity analysis was performed by excluding studies with high bias.

Results

Literature search

A total of 1,234 articles were obtained from all databases using custom searches. After deleting duplicates, 893 records were identified and 74 studies were selected for full-text review after reviewing the titles and abstracts of the records. The 59 remaining reports were excluded. There were 15 reports from the 13 studies meeting the inclusion criteria that were included in the meta-analysis (Figure 1).

Study characteristics

Characteristics of the 13 studies included in the meta-analysis are shown in Table 1. There was a total of 5,852 cancer patients and 424 diagnosed with VTE. Low-risk stratification was observed in five studies and there were a total of 1,300 cancer patients and 54 VTE cases. There were 9 studies including 3,029 cancer patients with intermediate risk and 230 patients diagnosed with VTE. There were 11 studies involving 850 cancer patients with a high risk and 104 VTE cases. This study represented all cancer types, including esophageal, gastric, pancreatic, lung, lymphoma, bladder and breast cancers. Follow-up time frames ranged from 2.5 to 24 months and the mean age ranged from 50 to 66 years. A study performed by Rupa-Matysek *et al.* (2017) (19) contained four datasets exhibiting different follow-up periods. The study performed by van Es *et al.* (2017) (9) contained three datasets. To estimate overall DVT, PE and bleeding rate, two additional reports were included (12,25). Most studies were identified as high quality and just 1 study showed high bias. The method used to analyze the included studies is shown in Table 2.

Table 1 Characteristics of the included studies

Study	Design	Location	Sex (M)	Mean age (year)	Chemotherapy regimens	Outcomes	Type of cancer	Follow-up time (median)	Participants (N)	Number of VTEs (N)
Khorana et al. (2008) (15)	P	United States	455	<65: 85, ≥65: 515	N	Symptomatic VTE	Breast, lung, ovarian, sarcoma, colon, lymphomas	2.5 months	1,365	28
Khorana et al. (2014) (16)	P	United States	19	N	Gemcitabine, cisplatin, carboplatin, erlotinib, capecitabine, etc.	Asymptomatic DVT, symptomatic VTE	All sites	16 weeks	35	8
Muñoz Martín et al. (2014) (8)	R	Spain	156	63 [38–88]	Gemcitabine based, platinum based, fluoropyrimidine based	Symptomatic or incidentally discovered VTE	Pancreatic	9 months	84	30
Ferroni et al. (2017) (17)	P	Italy	293	63±12	Platinum compounds, fluoropyrimidine, anthracycline, etc.	Symptomatic or asymptomatic VTE	All sites	10 months	605	43
Guadagni et al. (2017) (18)	P	Italy	197	65±10	N	Symptomatic or asymptomatic VTE	Gastrointestinal	11 months	342	34
Rupa-Matysek et al. (2017) (19)	R	Poland	209	50 [18–98]	N	Symptomatic VTE, PE	Lymphoma	37 months	428	64
Muñoz Martín et al. (2018) (20)	P	Spain	156	No VTE: 64.3, VTE: 64.1	N	Symptomatic or asymptomatic VTE	Colorectal, esophagogastric, lung, pancreatic	6 months	391	71
van Es et al. (2017) (9)	R	Dutch	88	62±10	Gemcitabine, FOLFIRINOX; Gemcitabine, nab-paclitaxel	Symptomatic or incidentally discovered VTE	Pancreatic cancer	24 months	178	22
Ferroni et al. (2012) (21)	R	Italy	80	66±9	Platinum-based regimen with: gemcitabine, pemetrexed, etc.	Symptomatic or asymptomatic VTE	Lung	6.9 months	108	16
Khorana et al. (2017) (22)	R-subjects group	Canada, United States	24	58±12	N	Symptomatic or incidentally discovered VTE	All sites	12 weeks	48	10
Carrier et al. (2019) (12)	R-placebo group	Canada	119	61.7±11.3	Alkylating, angiogenesis inhibitor, antimetabolite, corticosteroid, platinum, taxane	Symptomatic or incidentally discovered VTE	Gynecologic, lymphoma, pancreatic	180 days	283	28

Table 1 (continued)

Table 1 (continued)

Study	Design	Location	Sex (M)	Mean age (year)	Chemotherapy regimens	Outcomes	Type of cancer	Follow-up time (median)	Participants (N)	Number of VTEs (N)
Verso <i>et al.</i> (2012) (23)	R-placebo group	Italy	183	63.7±9.2	Pyrimidine analogs, platinum compounds, anthracyclines, etc.	Symptomatic or incidentally discovered VTE	Gastrointestinal, lung, breast, ovary, pancreas, head, neck,	120 days	381	15
George <i>et al.</i> (2011) (24)	RCT-placebo arm	United States	N	N	N	Symptomatic VTE, PE	Lung, pancreas, stomach, colon rectum, bladder, ovary	3.5 months	1,604	55

R, retrospective; P, prospective; VTE, venous thromboembolism; DVT, deep-vein thrombosis; PE, pulmonary embolism; RCT, randomized controlled trial.

Table 2 Customized Newcastle-Ottawa risk of bias scores for the studies

Study	Study representativeness	Applicability of Khorana score	Outcome measurement	Adequacy of follow up of cohorts	Applicability outcome	Total
Khorana <i>et al.</i> (2008)	1	1	0	1	0	3
Khorana <i>et al.</i> (2014)	1	1	1	1	0	4
Ferroni <i>et al.</i> (2017)	1	1	0	0	1	3
Guadagni <i>et al.</i> (2017)	1	1	0	1	0	3
Muñoz Martín <i>et al.</i> (2018)	1	1	0	1	1	4
Muñoz Martín <i>et al.</i> (2014)	0	1	0	0	0	1
Ferroni <i>et al.</i> (2012)	0	1	0	1	1	3
Rupa-Matysek <i>et al.</i> (2017)	0	1	0	1	0	2
van Es <i>et al.</i> (2017)	0	0	0	1	1	2
Verso <i>et al.</i> (2012)	1	1	1	0	0	3
George <i>et al.</i> (2011)	1	1	1	1	1	5
Carrier <i>et al.</i> (2019)	1	1	1	1	1	5
Khorana <i>et al.</i> (2017)	1	1	1	1	1	5

Studies were judged to be of low risk of bias (≥ 2 points) or high risk of bias (< 2 points).

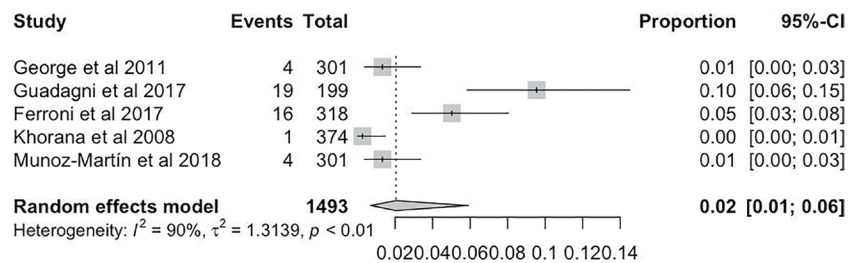


Figure 2 Forest plot of the pooled overall VTE incidence in cancer patients at low risk. VTE, venous thromboembolism.

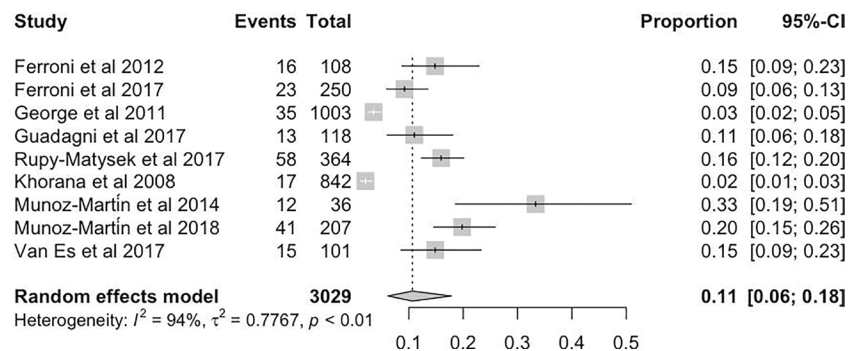


Figure 3 Forest plot of the pooled overall VTE incidence in cancer patients at intermediate risk. VTE, venous thromboembolism.

Overall VTE incidence at different risk scores

The incidence of VTE was 2% (95% CI: 1–6%, $I^2 = 90\%$, $P < 0.01$), 11% (95% CI: 6–18%, $I^2 = 94\%$, $P < 0.01$) and 14% (95% CI: 9–20%, $I^2 = 75\%$, $P < 0.01$) in cancer patients with low-risk [Khorana Risk Score (KRS) = 0] (Figure 2), intermediate-risk (KRS = 1–2) (Figure 3) and high-risk scores (KRS ≥ 3) (Figure 4), respectively. When considering two or more points as high-risk instead of three or more points, the incidence of VTE in cancer patients with high risk was 14% (95% CI: 8–23%, $I^2 = 79\%$, $P < 0.01$) (Figure 5).

VTE incidence at different follow-up times

The incidence of cancer-related VTE differed based on follow-up times (8). Khorana *et al.* (2013) (26) reported that 66–72.5% of VTE events occurred within 6 months. In this meta-analysis, the median time of the first VTE event was 1.3, 2.5, 3.2 and 4.7 months as shown by four different studies (16–19). According to the study reported by van Es *et al.* (2017) (9), there was no difference in VTE incidence between 12 and 24 months. Therefore, we classified the studies into two groups based on follow-up time for analysis. The two groups were divided into 3–6 and 7–12 months.

The incidence of VTE at 3–6 and 7–12 months was 1% (95% CI: 0–2%, $I^2 = 1\%$, $P = 0.32$) and 7% (95% CI: 4–11%, $I^2 = 48\%$, $P = 0.05$) at low risk, 7% (95% CI: 3–14%, $I^2 = 95\%$, $P < 0.01$) and 14% (95% CI: 11–19%, $I^2 = 63\%$, $P < 0.01$) at intermediate risk and 12% (95% CI: 8–17%, $I^2 = 69\%$, $P < 0.01$) and 15% (95% CI: 9–26%, $I^2 = 66\%$, $P < 0.01$) at high risk, respectively (Figure 6, Figures S1–S3).

DVT, PE and bleeding incidence rates

The incidence of DVT and PE in the cases analyzed was 6% (95% CI: 4–10%, $I^2 = 86\%$, $P < 0.01$) and 4% (95% CI: 2–7%, $I^2 = 85\%$, $P < 0.01$), respectively (Figures 7,8). Bleeding incidence was 4% (95% CI: 2–8%, $I^2 = 81\%$, $P < 0.01$) (Figure 9).

Sensitivity analysis and publication bias

There was no significant publication bias detected by Egger's test (low risk: $P = 0.0992$, intermediate risk: $P = 0.9143$, high risk: $P = 0.7999$). To assess whether high bias affected heterogeneity, the study performed by Muñoz Martín *et al.* (2014) was removed (8) and the overall incidence of VTE was 9% (95% CI: 5–15%, $I^2 = 94\%$, $P < 0.01$) and 14% (95% CI:

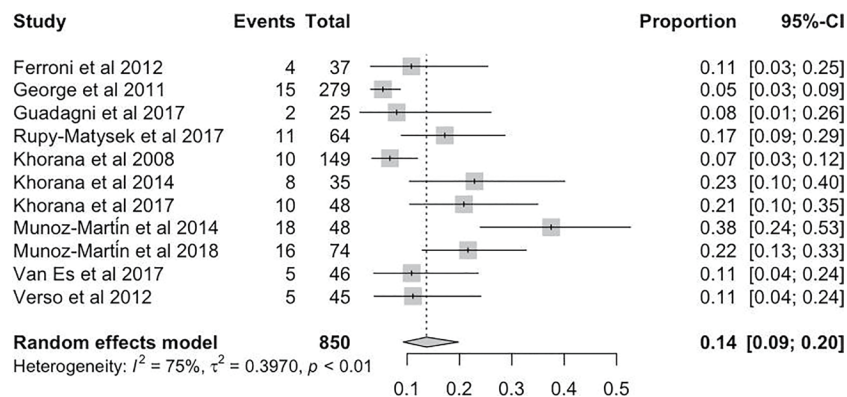


Figure 4 Forest plot of the pooled overall VTE incidence in cancer patients at high risk. VTE, venous thromboembolism.

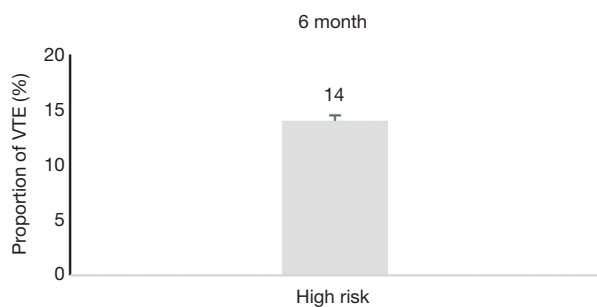


Figure 5 The VTE incidence in cancer patients when considering two points or more as high risk. VTE, venous thromboembolism.

9–20%, $I^2 = 75\%$, $P < 0.01$) at intermediate and high-risk levels, respectively. The incidence of VTE at 3–6 and 7–12 months was 7% (95% CI: 3–14%, $I^2 = 95\%$, $P < 0.01$) and 13% (95% CI: 10–16%, $I^2 = 26\%$, $P = 0.22$) at intermediate risk and 12% (95% CI: 8–17%, $I^2 = 69\%$, $P < 0.01$) and 12% (95% CI: 8–18%, $I^2 = 0\%$, $P = 0.75$) at high risk, respectively.

Discussion

Here, we systematically analyzed the incidence of VTE at different risk stratification levels using the Khorana score and overall bleeding rate in cancer patients undergoing chemotherapy. We demonstrated that the time frame Khorana score prediction was 3–6 months rather than “forever”.

According to the meta-analysis, the incidence of DVT was higher than PE, which was significantly greater than the rate in non-cancer patients (0.2%) (26). Two studies (8,26) reported that PE, which has a high fatality rate, was asymptomatic and combined with DVT in most cases.

Meanwhile, the guidelines recommend anticoagulant treatment for incidental VTE events as for cancer patients with symptomatic VTE (27).

Our analysis revealed a higher incidence of VTE than the study that developed the Khorana score since, besides one other study (19), the studies contained in our meta-analysis included both symptomatic and asymptomatic VTE as outcomes. However, the original study only included symptomatic VTE cases. Our analysis also indicated that over half of VTE events occurred in 6 months, similar to two other studies (21,26). Interestingly, although the incidence of VTE differed at 6 months for different risk stratifications based on the Khorana score, the incidence of VTE at 12 months between intermediate and high-risk groups were the same. This result is similar to meta-analysis results published by Mulder *et al.* (28) that revealed that the Khorana score had limited use in ruling out future venous thromboembolic events (>6 months) since it calculated laboratory data before chemotherapy. Recent RCTs (11,12) and Mulder *et al.* (28) considered two or more points as high risk instead of 3 or more points. Our study agrees with this view by finding that VTE incidence was similar in cancer patients undergoing chemotherapy despite considering two to three or more points as high risk.

Additionally, the meta-analysis presented here confirmed the viewpoint of Imberti and colleagues (29) who showed that the incidence rate of cancer-related VTE in the real world is greater than the incidence rate of VTE in RCTs. A study conducted by van Es *et al.* (30) reported a 6-month VTE incidence based on a 6.4% Khorana score in low-to-intermediate risk patients and a score of 9.8% in high-risk patients. However, in the study presented here, we observed higher incidence. This discrepancy may be partially

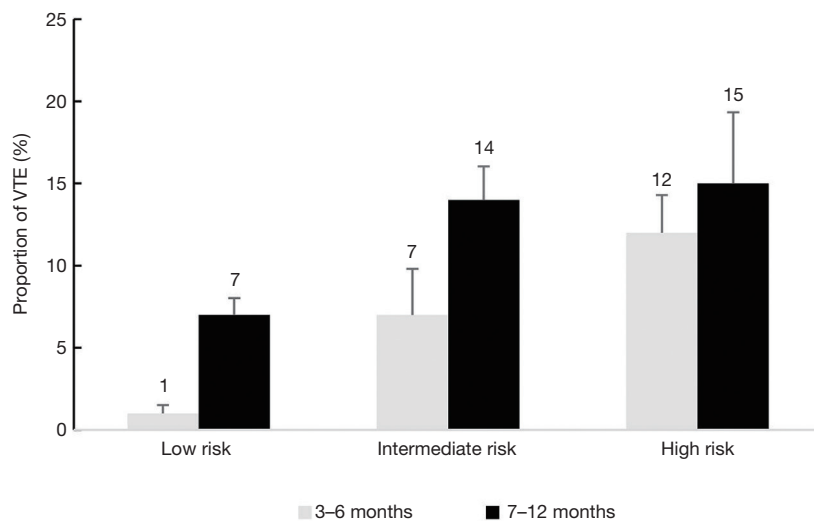


Figure 6 The incidence of different follow-up times in cancer patients at different risk levels. VTE, venous thromboembolism.

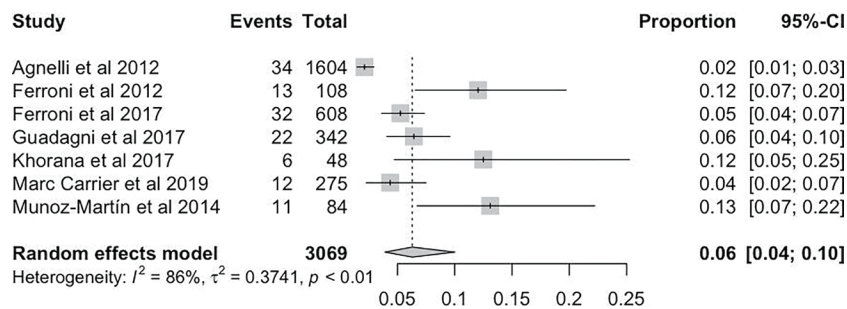


Figure 7 Forest plot of the pooled overall DVT incidence in cancer patients. DVT, deep-vein thrombosis.

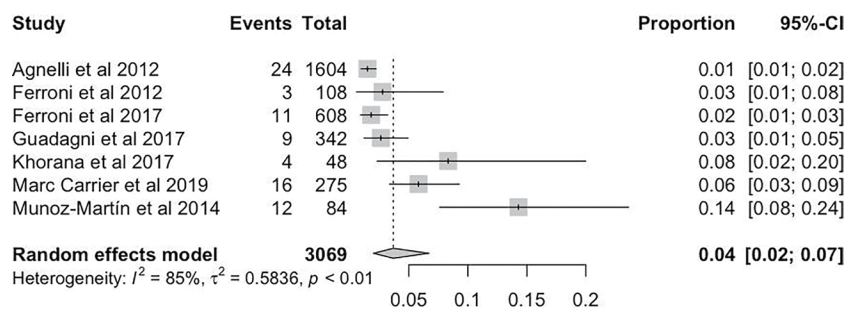


Figure 8 Forest plot of the pooled overall PE incidence in cancer patients. PE, pulmonary embolism.

explained by the fact that the study performed by van Es and colleagues only included RCTs and solid tumors (30). Meanwhile, observation cohort studies are more reliable in terms of demonstrating causality compared to other observational studies. The study performed by Mulder *et al.* (28), which included RCTs and cohort studies, showed

that the incidence of VTE ranged from 5.1–11% in the first 6 months, which was lower than what was observed in our study. This difference may be caused by different anti-cancer therapies and thromboprophylaxis that the Mulder study did not exclude, where only some cancer patients received chemotherapy or showed thromboprophylaxis at

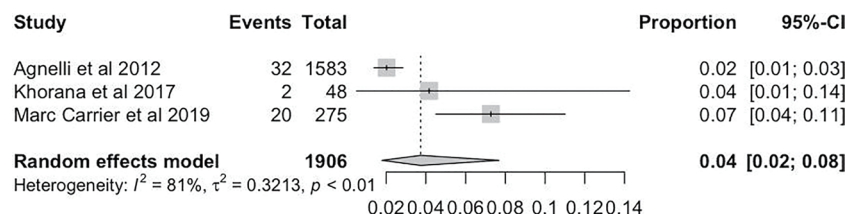


Figure 9 Forest plot of the pooled overall bleeding incidence in cancer patients.

baseline. It is worth noting that the incidence of cancer-related VTE in the real world is higher than shown in the meta-analysis results. It is difficult to estimate the “true” rate because not all studies screen at baseline, which detects asymptomatic VTE. In the eligible studies included in our analyses, only the CASSINI trial (11), study by Khorana *et al.* (2014) (16) and study by Khorana *et al.* (2017) (22) contained baseline screening and screening during trials.

Interestingly, our results were contrary to recent cohort studies reporting that the Khorana scoring system is not ideal for predicting VTE regarding three aspects. First, two cohort studies (19,31) reported that age (>60 years), tumor burden, inflammatory activity and poor performance were independent risk factors for VTE but that the Khorana score was not since body mass index (BMI) and leukocyte count (WBC) were useless for assessing lymphoma progression. Thus, the Khorana score is not suitable for all malignancy types, particularly lymphoid malignancies. Second, some studies involved patients with lung and pancreatic cancers, which have a high incidence rate of VTE and failed to show the utility of the Khorana score. A meta-analysis conducted in 2017 also found that the Khorana score poorly differentiated between individuals at high and low risk for VTE in lung cancer patients (30), even though patients with stage IV lung cancer may benefit from extended prophylaxis due to a significant reduction in VTE and no increase in bleeding events (32). An individual, patient data meta-analysis performed in 2020 indicated that the Khorana score was unable to stratify lung cancer patients based on their VTE risk (33). Third, one study (17) including all cancer types also indicated that the Khorana score was not ideal for predicting cancer-associated VTE, possibly due to different treatment regimens. These differences emphasize that although the Khorana score is able to distinguish patients with various cancers at different risk stratification levels, it may not accurately perform when it comes to predicting VTE incidence in lung, pancreatic and lymphoid cancers.

Despite our findings, the study presented here also has

some limitations. First, the study population involved patients that were heterogeneous in nature. Our meta-analysis evaluated overall VTE incidence with high heterogeneity, which was acceptable after subgroup analysis with different follow-up periods. However, there was insufficient subgroup analysis based on different cancer sites and chemotherapy regimens, which is significantly related to VTE incidence (20,34). We also analyzed VTE incidence using a retrospective cohort, prospective cohort and RCT. However, this was not able to reduce heterogeneity (data not shown). Secondly, there was considerable bias risk in the enrolled studies. For example, studies included in our analysis involved various outcomes, which may affect the results. Finally, all included studies were conducted using Western populations. As a result, the work presented here may be subject to small-study effect bias in Eastern populations.

In conclusion, the meta-analysis presented here validated the utility of the Khorana score in cancer patients receiving chemotherapy in a 3–6-month time frame and suggests this may not be sufficient to distinguish VTE incidence between intermediate and high-risk groups after 6 months. However, there were some limitations associated with the cancer site and chemotherapy regimen. The incidence of PE in cancer patients was significantly greater than what was observed in non-cancer patients and more than half of VTE events occurred in 6 months. To establish a more reliable result between Khorana score and incidence of VTE in cancer patients, additional studies need to adjust for confounding factors and focus on the cancer site and chemotherapy regimen.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at <http://dx.doi.org/10.21037/atm-20-3292>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm-20-3292>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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