SUPPLEMENTARY APPENDIX

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

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Supplementary Table 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	27
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5-8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9

Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9-11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2

Supplementary Table 2. Search strategy on MEDLINE and EMBASE, 7 June 2018

MEDLINE	
1.	neoplasms[mesh] OR neoplas*[tiab] OR cancer*[tiab] OR malign*[tiab] OR tumor*[tiab] OR tumour*[tiab] (*N*=3833328)
2.	"Venous Thromboembolism"[Mesh] OR “venous thromboembolism”[All fields] OR "Venous Thrombosis"[Mesh] OR “venous thrombosis”[All fields] OR “deep vein thrombosis”[All fields] OR "Pulmonary Embolism"[Mesh] OR “pulmonary embolism”[All fields] (*N*=111493)
3.	Khorana[All Fields] OR scor*[tiab] OR stratif*[tiab] OR predict*[tiab] (*N*=2083983)
4.	1 AND 2 AND 3 (*N*=2094)
5.	"Infant"[Mesh] OR "infant"[MeSH Terms:noexp] OR "child"[MeSH Terms] OR "child"[MeSH Terms:noexp] OR infant,newborn[Mesh] OR child,preschool[Mesh] (*N*=2299792)
6.	4 NOT 5 (*N*=2030)
7.	Review[ptyp] OR meta-analysis[ptyp] OR editorial[ptyp] OR practice guideline[ptyp] OR case reports[ptyp] (*N*=4649720)
8.	6 NOT 7 (*N*=1685)
9.	"2008/01/01"[Date - Create] : "2019/01/01"[Date - Create] (*N*=10747919)
10.	8 AND 9 (*N*=1296)
EMBASE	
1.	exp neoplasm/ or exp/ carcinoma or cancer$.mp or tum*r$.tw. or malign$.tw. (*N*= 5326817)
2.	exp Lung Embolism/ or pulmonary embolism*.mp. or lung embolism*.ti,ab. or pulmonary thromboembolism*.ti,ab. or exp Venous thrombosis/ or exp venous thromboembolism/ or deep vein thrombosis.mp. (*N*=206441)
3.	Khorana.mp. or scor$.tw. or stratif$.tw. or predict$.tw. or exp prediction/ (*N*= 2944162)
4.	1 and 2 and 3 (*N*=8031)
5.	limit 4 to yr="2008 -Current" (*N*=7018)
6.	limit 5 to exclude medline journals (*N*=530)

Supplementary Table 3. Criteria used in QUIPS bias risk assessment tool

Study participation	Low	Prospective study with adequately described inclusion and exclusion criteria.
	moderate/unclear	Retrospective study with not adequately described criteria or unclear selection.
	high	Bias possible due to selection procedure
Study attrition	low	Loss to follow-up was <5%
	moderate/unclear	Loss to follow-up not described
	high	Loss to follow up >5%
Prognostic Factor measurement	low	Khorana score determined for most op the population (>95%)
	moderate/unclear	Khorana score could not be calculated fot >5%
	high	Khorana score could not be calculated fot >10%
Outcome measurement	low	Blind measurement by an independant assessor.
	moderate/unclear	No blind measurement
	high	No blind measurement, outcome ascertainment not reported and duration of follow-up not described.
Confounding	low	Patients using thromboprophylaxis were excluded.
	moderate	Not described whether patients using thromboprophylaxis were excluded.
	high	>5% of the population received thromboprophylaxis.
Statistical analysis & reporting	low	The selected statistical model is adequate for the design of the study. No selective reporting.
	moderate	Not sufficient presentation of data to assess the adequacy of the analysis.
	high	Selective reporting, abstract
Applicability patient selection	low	The study evaluated outpatients with cancer who started chemotherapy and did not receive thromboprophylaxis
	moderate/unclear	Selected population
	high	Chemotherapy was started before determination of the Khorana score. Selected population
Applicability Khorana score	low	Khorana score applied without modifications
	moderate/unclear	Modified Khorana score applied: tumor types added to the high risk and very high risk sites
	high	Major modifications or unsure whether score was modified or not.
Applicability outcome	low	LEDVT, UEDVT, PE and/or CSVT as outcome.
	moderate/unclear	Superficial or abdominal thrombosis included. Unclear whether incidental was included. Unclear which types of VTE were included.
	high	Arterial thrombosis included.

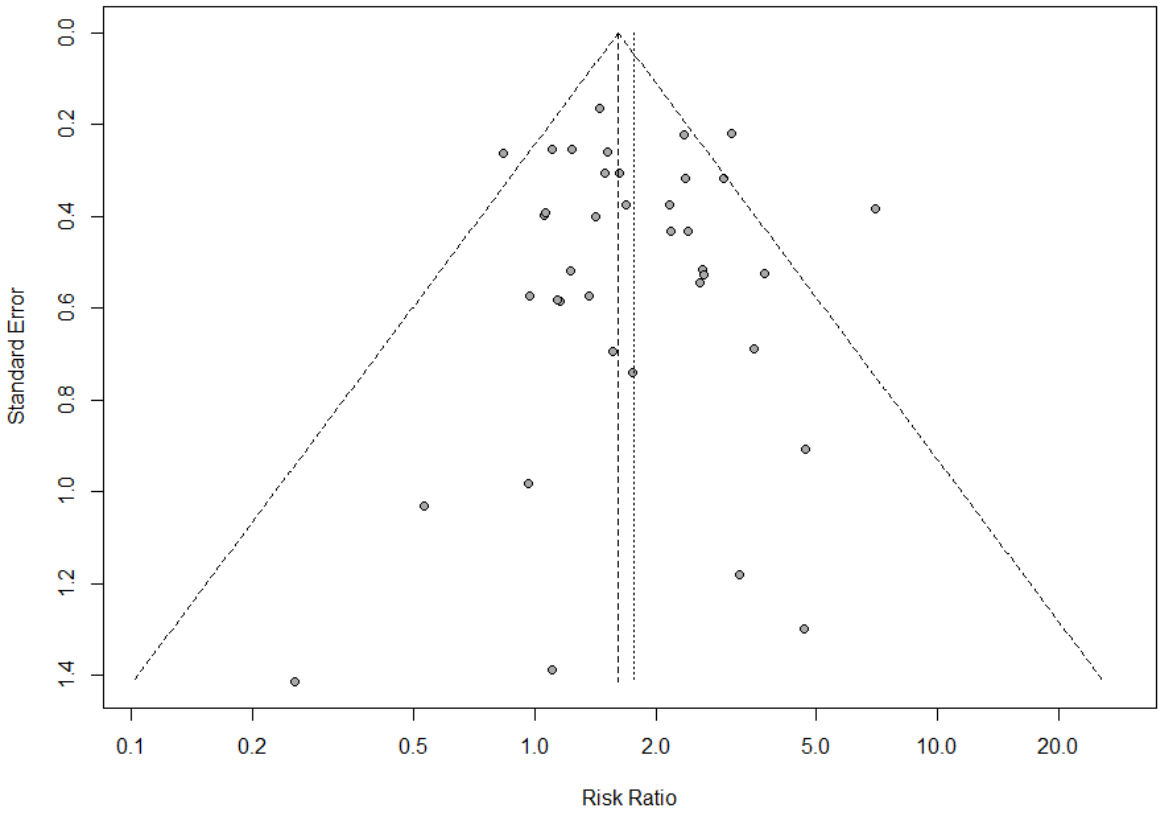
Supplementary Table 4. Bias risk assessment.ǂ

Author	Study outcome	Incidental VTE included	Patients that received anticoagulation included	Applicability patient selection	Applicability Khorana score	Applicability outcome	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Confounding	Statistical analysis and reporting
Abdel-Razeq (2017)	DVT, PE	No	No	-*	-	-	?	?	-	?	-	?
Ades (2015)	DVT, PE	Yes	NR	-	-	?	?	-	?	?	?	+
Austin (2017)	DVT, PE, catheter-associated	Yes	No	?	?	?	?	-	-	?	?	+
Ayyappan (2016)	VTE	Yes	Yes	?	?	?	?	-	+	?	+	+
Bezan	DVT, PE, SVT	Yes	Yes (3.3%)	?	?	?	?	-	?	?	?	-
Borchman (2016)	DVT, PE, catheter-associated	No	Yes (1%)	?	?	?	?	?	?	?	?	+
Cella (2017)	DVT,PE, head/neck VTE	Yes	No	?	-	?	-	?	-	?	?	-
Ferroni (2015)	DVT, PE	Yes	No	-	-	?	-	?	-	?	-	-
Ferroni (2012)	DVT, PE	Yes	No	?	-	-	?	-	-	+	-	-
Fuentes (2017)	DVT, PE	Yes	No	?	-	-	-	-	-	?	-	-
George (2011)	DVT, PE	Yes	No	-	-	-	-	-	-	-	-	-
Guadagni (2017)	DVT, PE, catheter-associated	Yes	No	?	?	?	-	-	-	?	-	-
Kearney (2009)	VTE	NR	NR	-	-	?	?	?	-	+	-	+
Khorana (2017)	VTE	Yes	No	?	-	?	-	-	-	-	-	-
Khorana (2014)	DVT, PE	Yes	No	?	-	?	-	-	-	-	-	-
Khorana (2008)	DVT, PE	No	No	-	-	?	-	-	-	?	-	-
Kim (2012)	DVT, PE	NR	Yes	?	-	?	?	-	-	+	-	-
Kruger (2017)	DVT, PE	No	No	+	-	?	?	-	+	?	-	-
Kuderer (2017)	DVT, PE, SVT, catheter-associated	Yes	NR	?	-	?	-	?	+	?	?	-
Kuk (2017)	NR	NR	No	-	-	+	+	-	-	+	-	+
Kunapareddy (2017)	NR	NR	NR	?	-	?	-	?	-	?	?	+
Lim (2015)	DVT, PE	Yes	No	?	-	?	+	?	-	?	-	-
Lubberts (2016)	DVT, PE	Yes	No	-	-	-	-	+	-	?	-	+
Lustig (2015)	DVT, PE	Yes	No	?	+	?	-	?	-	?	-	-
Mandala (2012)	DVT, PE, SVT	No	Yes	?	-	?	-	?	-	?	?	-
Mansfield (2016)	DVT, PE, SVT	Yes	No	-	-	?	-	-	?	?	-	-
Misch (2013)	DVT, PE, head/neck VTE	No	Yes	+	?	?	+	?	-	+	-	-
Moore (2011)	DVT, PE, head/neck VTE	Yes	NR	?	?	+	?	-	-	?	?	-
Munoz-Martin (2017)	DVT, PE, head/neck VTE	NR	No	-	-	-	-	-	-	?	-	-
Munoz-Martin (2014)	DVT, PE, SVT	Yes	No	?	-	?	?	?	-	?	-	-
Noble (2015)	DVT, PE, ATE	Yes	No	-	-	-	-	-	-	?	-	-
Panizo (2015)	DVT, PE, SVT	Yes	Yes	+	?	?	-	?	-	?	-	-
Papaxoinis (2018)	DVT, PE	Yes	No	-	-	?	-	-	-	?	-	-
Park (2017)	DVT, PE	Yes	No	-	-	-	-	-	?	?	-	?
Patel (2015)	DVT, PE	Yes	No	?	-	?	-	?	-	?	?	-
Pelzer (2013)	DVT,PE	No	No	-	-	-	-	?	?	-	?	-
Petitto (2017)	NR	NR	No	?	-	?	?	?	-	?	?	+
Posch (2016)	DVT, PE	Yes	NR	-	-	-	-	?	-	-	?	-
Ramos (2016)	DVT, PE, catheter-associated	NR	NR	?	-	?	?	-	-	?	-	-
Ruch (2012)	DVT, PE, SVT	NR	Yes	?	-	?	?	?	-	?	?	+
Rupa-Matysek (2018)	DVT, PE, SVT, head/neck VTE	No	No	-	-	?	?	-	-	?	-	-
Rupa-Matysek (2018)	DVT, PE	NR	Yes	-	-	-	?	-	-	?	+	-
Santi (2017)	DVT, PE	NR	Yes (6%)	?	-	-	-	?	?	?	?	-
Sohal (2016)	DVT, PE, SVT, catheter-associated	Yes	Yes	?	-	?	?	?	?	?	+	+
Srikanthan (2015)	DVT, PE	NR	No	-	?	?	?	-	-	?	-	-
Tafur (2015)	DVT, PE, SVT	Yes	No	-	-	-	-	?	-	-	-	-
van Es (2017)	DVT, PE	Yes	No	+	-	-	-	-	-	-	-	-
van Es (2017)	DVT, PE	Yes	No	-	-	-	?	-	-	?	-	-
Vathiotis (2018)	DVT, PE	Yes	No	?	-	-	?	-	-	?	-	-
Verso (2012)	DVT, PE, SVT, ATE	No	No	-	-	+	-	+	-	-	-	-
Wang (2017)	DVT, PE, SVT	Yes	No	?	-	?	-	-	-	-	?	-
Yust-Katz (2015)	DVT,PE, head/neck VTE	No	Yes	?	?	-	+	?	-	?	+	-
Zahir (2017)	DVT, PE	Yes	No	-	-	-	-	-	-	?	-	+

*- : low risk of bias, ?: moderate/unclear risk of bias, +; high risk of bias Abbreviations: VTE, venous thromboembolism; DVT, deep-venous thrombosis; PE, pulmonary embolism; SVT, splanchnic vein thrombosis; ATE, arterial thromboembolism; NR, not reported.‡ bias assessment can be altered than original report if additional data was acquired.

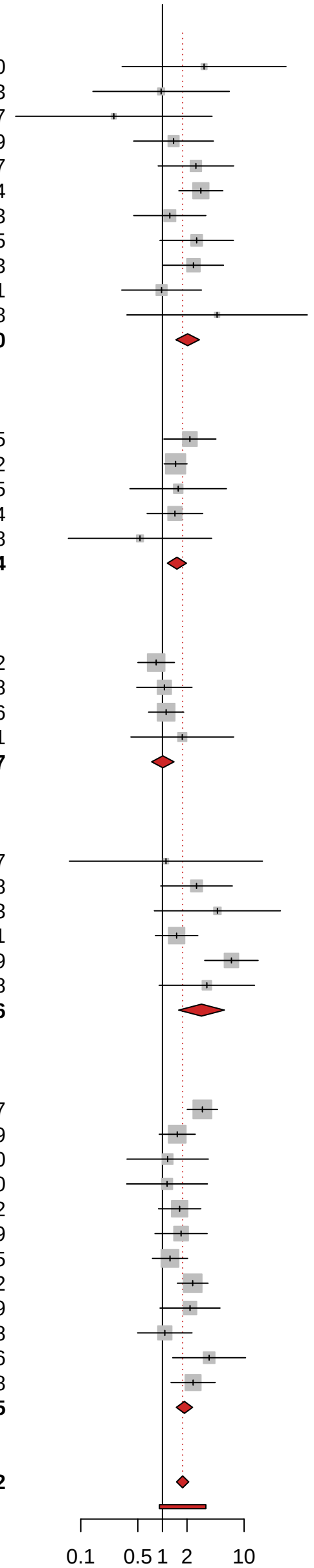
Supplementary Figures

Supplementary Figure 1. Funnel plot of risk ratio of venous thromboembolic events in the Khorana score high-risk group versus the lower risk groups for all individual studies.



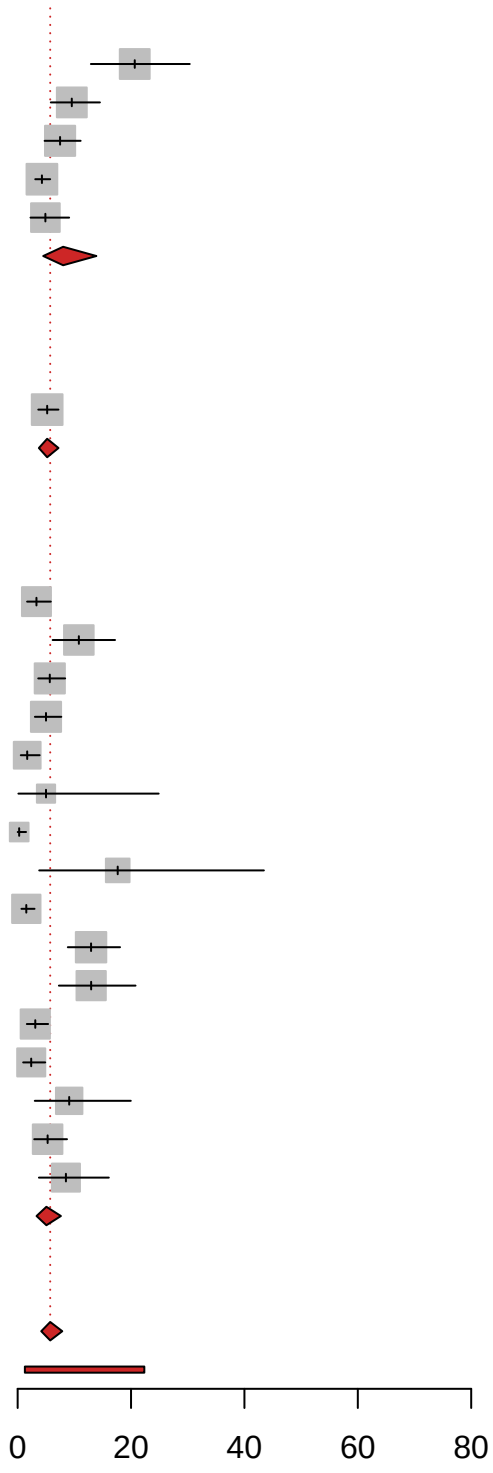
Supplementary Figure 2. Relative risk of VTE incidence with 95% confidence intervals in high-risk group (Khorana score ≥3) versus low- and intermediate-risk groups during 6-month follow-up.

Study − Year	Cancer type	High risk group VTE	High risk group Patients	Other groups VTE	Other groups Patients	Relative risk	95% − CI	Weight
Gastrointestinal cancer								
Ades − 2015	Colorectal	0	1	15	150	3.2	[0.3; 32.7]	0.5%
Fuentes − 2017	Gastric	2	55	2	53	1.0	[0.1; 6.6]	0.7%
Guadagni − 2017	Various GI	0	25	24	317	0.3	[0.0; 4.1]	0.4%
Kruger − 2017	Pancreatic	5	42	6	69	1.4	[0.4; 4.2]	1.8%
Munoz−Martin − 2014	Pancreatic	10	36	4	37	2.6	[0.9; 7.5]	1.9%
Papaxoinis − 2018	Various GI	10	42	39	484	3.0	[1.6; 5.5]	3.9%
Park − 2017	Gastric	7	108	7	133	1.2	[0.4; 3.4]	2.1%
Pelzer − 2013	Pancreatic	17	89	4	55	2.6	[0.9; 7.4]	2.0%
Sohal − 2016	Colorectal	5	40	81	1553	2.4	[1.0; 5.6]	2.7%
van Es − 2017	Pancreatic	4	46	9	101	1.0	[0.3; 3.0]	1.8%
Wang − 2017	Hepatocellular	0	2	11	268	4.7	[0.4; 59.4]	0.4%
Random effects model		**60**	**486**	**202**	**3220**	**2.0**	**[1.5; 2.8]**	**18.2%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.60								
Hematological cancer								
Ayyappan − 2016	DLBCL	8	36	21	205	2.2	[1.0; 4.5]	3.2%
Borchman − 2016	HL	53	1397	105	4012	1.4	[1.0; 2.0]	6.1%
Lim − 2015	DLBCL	2	17	23	305	1.6	[0.4; 6.1]	1.3%
Rupa−Matysek − 2018	DLBCL and HL	7	64	28	364	1.4	[0.6; 3.1]	3.0%
Santi − 2017	NHL	1	141	14	1048	0.5	[0.1; 4.0]	0.7%
Random effects model		**71**	**1655**	**191**	**5934**	**1.5**	**[1.1; 2.0]**	**14.3%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.73								
Lung cancer								
Kuderer − 2017	Lung	16	298	95	1482	0.8	[0.5; 1.4]	4.6%
Mansfield − 2016	Lung	7	100	37	558	1.1	[0.5; 2.3]	3.0%
Noble − 2015	Lung	21	302	48	766	1.1	[0.7; 1.8]	4.7%
Vathiotis − 2018	Lung	3	39	4	91	1.8	[0.4; 7.5]	1.2%
Random effects model		**47**	**739**	**184**	**2897**	**1.0**	**[0.7; 1.4]**	**13.5%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.75								
Urogenital cancer								
Bezan (Graz) − 2017	Testicular	0	9	27	577	1.1	[0.1; 16.8]	0.4%
Bezan (Zurich) − 2017	Testicular	4	25	17	278	2.6	[1.0; 7.2]	2.1%
Patel − 2015	Prostate	1	5	40	943	4.7	[0.8; 27.9]	0.8%
Ramos − 2016	Urothelial	13	162	42	781	1.5	[0.8; 2.7]	4.0%
Srikanthan (cohort 1) − 2015	Testicular	8	18	12	189	7.0	[3.3; 14.9]	3.1%
Srikanthan (cohort 2) − 2015	Testicular	2	7	8	98	3.5	[0.9; 13.5]	1.3%
Random effects model		**28**	**226**	**146**	**2866**	**3.0**	**[1.6; 5.7]**	**11.8%**
Heterogeneity: I^2 = 54%, τ^2 = 0.2951, p = 0.05								
Various cancers								
Abdel−Razeq − 2017	Various	30	260	53	1417	3.1	[2.0; 4.7]	5.3%
Austin − 2017	Various	19	161	45	579	1.5	[0.9; 2.5]	4.7%
Cella − 2017	Various	3	57	35	770	1.2	[0.4; 3.6]	1.7%
Ferroni − 2015	Various	3	50	40	760	1.1	[0.4; 3.6]	1.8%
George − 2011	Various	14	281	39	1272	1.6	[0.9; 3.0]	4.0%
Kunapareddy − 2017	Various	14	82	11	109	1.7	[0.8; 3.5]	3.2%
Munoz−Martin − 2018	Various	16	74	55	315	1.2	[0.8; 2.0]	4.7%
Posch − 2016	Various	26	232	65	1362	2.3	[1.5; 3.6]	5.2%
Tafur − 2015	Various	6	32	18	209	2.2	[0.9; 5.1]	2.7%
van Es − 2017	Various	7	105	46	738	1.1	[0.5; 2.3]	3.0%
Verso − 2012	Various	5	45	10	336	3.7	[1.3; 10.4]	2.0%
Zahir − 2017	Various	11	52	31	348	2.4	[1.3; 4.4]	3.8%
Random effects model		**154**	**1431**	**448**	**8215**	**1.9**	**[1.5; 2.3]**	**42.2%**
Heterogeneity: I^2 = 30%, τ^2 = 0.0513, p = 0.15								
Random effects model		**360**	**4537**	**1171**	**23132**	**1.8**	**[1.5; 2.1]**	**100.0%**
Prediction interval							**[0.9; 3.4]**	
Heterogeneity: I^2 = 36%, τ^2 = 0.0968, p = 0.02								



Supplementary Figure 3A. VTE incidence with 95% confidence intervals in low-risk group during total follow-up.

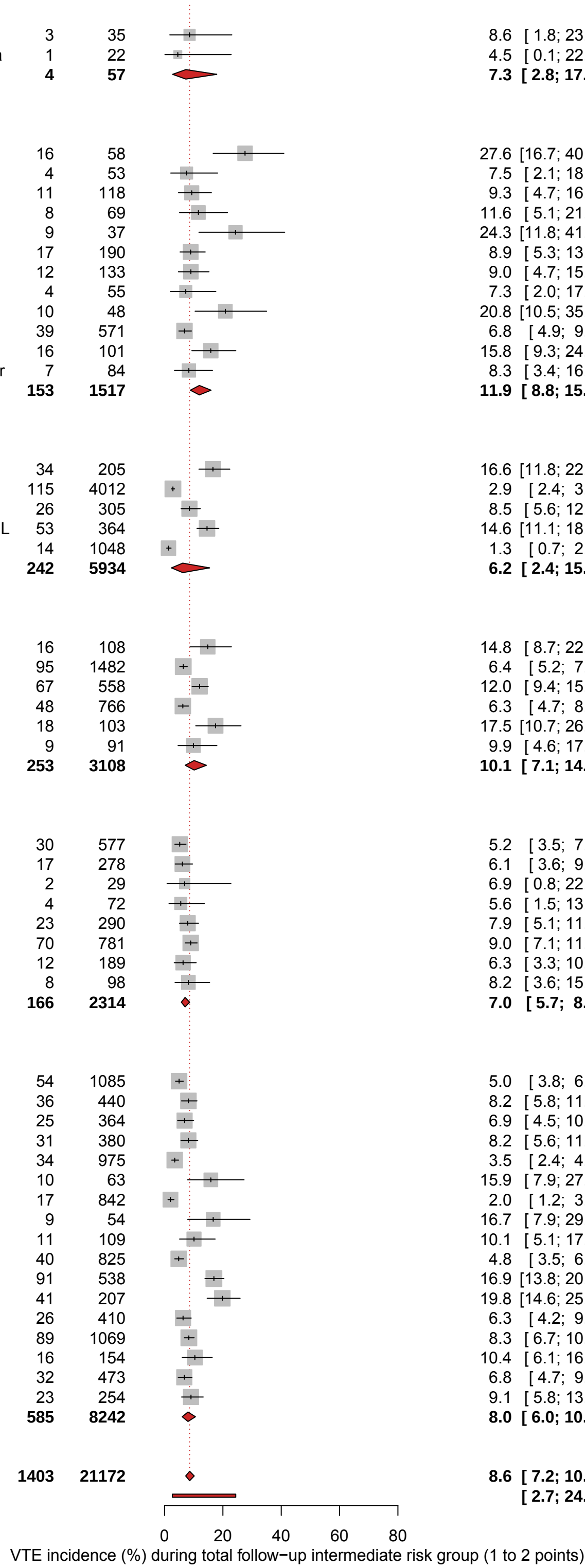
Study − Year	Cancer type	VTE	Patients	Incidence (%)	95% − CI	Weight
Gastrointestinal cancer						
Ades − 2015	Colorectal	19	92	20.7	[12.9; 30.4]	5.1%
Guadagni − 2017	Various GI	19	199	9.5	[5.8; 14.5]	5.1%
Papaxoinis − 2018	Various GI	22	294	7.5	[4.7; 11.1]	5.2%
Sohal − 2016	Colorectal	42	982	4.3	[3.1; 5.7]	5.4%
Wang − 2017	Hepatocellular	9	184	4.9	[2.3; 9.1]	4.7%
Random effects model		**111**	**1751**	**8.0**	**[4.5; 13.9]**	**25.5%**
Heterogeneity: I^2 = 89%, τ^2 = 0.4294, p < 0.01						
Urogenital cancer						
Patel − 2015	Prostate	34	653	5.2	[3.6; 7.2]	5.4%
Random effects model		**34**	**653**	**5.2**	**[3.7; 7.2]**	**5.4%**
Heterogeneity: not applicable						
Various cancers						
Abdel−Razeq − 2017	Various	11	332	3.3	[1.7; 5.9]	4.8%
Austin − 2017	Various	15	139	10.8	[6.2; 17.2]	5.0%
Cella − 2017	Various	23	406	5.7	[3.6; 8.4]	5.2%
Ferroni − 2015	Various	19	380	5.0	[3.0; 7.7]	5.2%
George − 2011	Various	5	297	1.7	[0.5; 3.9]	4.1%
Kearney − 2009	Various	1	20	5.0	[0.1; 24.9]	1.9%
Khorana − 2008	Various	1	374	0.3	[0.0; 1.5]	2.0%
Kim − 2012	Various	3	17	17.6	[3.8; 43.4]	3.2%
Mandala − 2012	Various	8	525	1.5	[0.7; 3.0]	4.6%
Moore − 2011	Various	29	224	12.9	[8.8; 18.1]	5.3%
Munoz−Martin − 2018	Various	14	108	13.0	[7.3; 20.8]	4.9%
Panizo − 2015	Various	12	386	3.1	[1.6; 5.4]	4.9%
Posch − 2016	Various	7	293	2.4	[1.0; 4.9]	4.5%
Tafur − 2015	Various	5	55	9.1	[3.0; 20.0]	4.0%
van Es − 2017	Various	14	265	5.3	[2.9; 8.7]	5.0%
Zahir − 2017	Various	8	94	8.5	[3.7; 16.1]	4.5%
Random effects model		**175**	**3915**	**5.1**	**[3.3; 7.6]**	**69.1%**
Heterogeneity: I^2 = 83%, τ^2 = 0.6224, p < 0.01						
Random effects model		**320**	**6319**	**5.7**	**[4.2; 7.9]**	**100.0%**
Prediction interval					**[1.3; 22.3]**	
Heterogeneity: I^2 = 84%, τ^2 = 0.5239, p < 0.01						



Abbreviations: CI, confidence interval; DLBCL, Diffuse large B-cell lymphoma; HL, Hodgkin lymphoma; NHL, Non-Hodgkin lymphoma; VTE, Venous thromboembolism.

Supplementary Figure 3B. VTE incidence with 95% confidence intervals in intermediate-risk group during total follow-up.

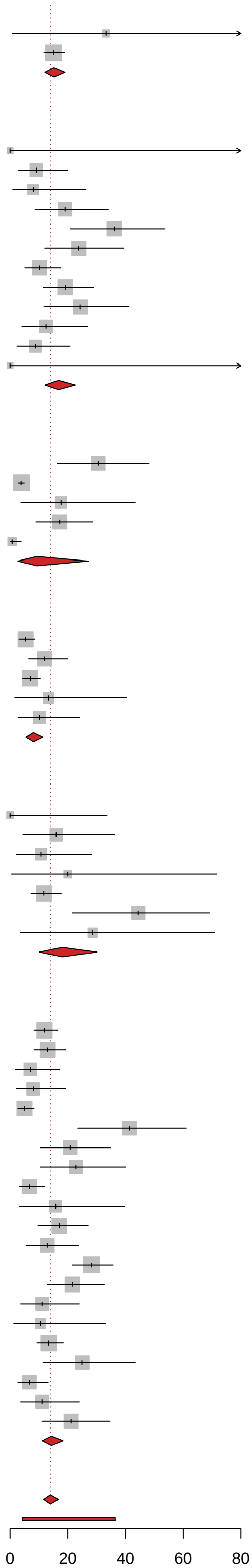
Study − Year	Cancer type	VTE	Patients	Incidence (%)	95% − CI	Weight
Central nervous cancer						
Misch − 2013	Glioma	3	35	8.6	[1.8; 23.1]	1.2%
Yust−Katz − 2015	Glioblastoma	1	22	4.5	[0.1; 22.8]	0.6%
Random effects model		**4**	**57**	**7.3**	**[2.8; 17.9]**	**1.9%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.57						
Gastrointestinal cancer						
Ades − 2015	Colorectal	16	58	27.6	[16.7; 40.9]	2.0%
Fuentes − 2017	Gastric	4	53	7.5	[2.1; 18.2]	1.4%
Guadagni − 2017	Various GI	11	118	9.3	[4.7; 16.1]	1.9%
Kruger − 2017	Pancreatic	8	69	11.6	[5.1; 21.6]	1.8%
Munoz−Martin − 2014	Pancreatic	9	37	24.3	[11.8; 41.2]	1.7%
Papaxoinis − 2018	Various GI	17	190	8.9	[5.3; 13.9]	2.1%
Park − 2017	Gastric	12	133	9.0	[4.7; 15.2]	2.0%
Pelzer − 2013	Pancreatic	4	55	7.3	[2.0; 17.6]	1.4%
Ruch − 2012	Pancreatic	10	48	20.8	[10.5; 35.0]	1.8%
Sohal − 2016	Colorectal	39	571	6.8	[4.9; 9.2]	2.3%
van Es − 2017	Pancreatic	16	101	15.8	[9.3; 24.4]	2.0%
Wang − 2017	Hepatocellular	7	84	8.3	[3.4; 16.4]	1.7%
Random effects model		**153**	**1517**	**11.9**	**[8.8; 15.9]**	**22.1%**
Heterogeneity: I^2 = 73%, τ^2 = 0.2376, p < 0.01						
Hematological cancer						
Ayyappan − 2016	DLBCL	34	205	16.6	[11.8; 22.4]	2.2%
Borchman − 2016	HL	115	4012	2.9	[2.4; 3.4]	2.4%
Lim − 2015	DLBCL	26	305	8.5	[5.6; 12.2]	2.2%
Rupa−Matysek − 2018	DLBCL and HL	53	364	14.6	[11.1; 18.6]	2.3%
Santi − 2017	NHL	14	1048	1.3	[0.7; 2.2]	2.0%
Random effects model		**242**	**5934**	**6.2**	**[2.4; 15.4]**	**11.2%**
Heterogeneity: I^2 = 98%, τ^2 = 1.2903, p < 0.01						
Lung cancer						
Ferroni − 2012	Lung	16	108	14.8	[8.7; 22.9]	2.0%
Kuderer − 2017	Lung	95	1482	6.4	[5.2; 7.8]	2.4%
Mansfield − 2016	Lung	67	558	12.0	[9.4; 15.0]	2.3%
Noble − 2015	Lung	48	766	6.3	[4.7; 8.2]	2.3%
Rupa−Matysek − 2018	Lung	18	103	17.5	[10.7; 26.2]	2.1%
Vathiotis − 2018	Lung	9	91	9.9	[4.6; 17.9]	1.8%
Random effects model		**253**	**3108**	**10.1**	**[7.1; 14.3]**	**13.0%**
Heterogeneity: I^2 = 87%, τ^2 = 0.1974, p < 0.01						
Urogenital cancer						
Bezan (Graz) − 2017	Testicular	30	577	5.2	[3.5; 7.3]	2.2%
Bezan (Zurich) − 2017	Testicular	17	278	6.1	[3.6; 9.6]	2.1%
Kuk − 2017	Ovarian	2	29	6.9	[0.8; 22.8]	1.0%
Lubberts − 2016	Testicular	4	72	5.6	[1.5; 13.6]	1.4%
Patel − 2015	Prostate	23	290	7.9	[5.1; 11.7]	2.2%
Ramos − 2016	Urothelial	70	781	9.0	[7.1; 11.2]	2.3%
Srikanthan (cohort 1) − 2015	Testicular	12	189	6.3	[3.3; 10.8]	2.0%
Srikanthan (cohort 2) − 2015	Testicular	8	98	8.2	[3.6; 15.5]	1.8%
Random effects model		**166**	**2314**	**7.0**	**[5.7; 8.6]**	**15.0%**
Heterogeneity: I^2 = 16%, τ^2 = 0.0292, p = 0.30						
Various cancers						
Abdel−Razeq − 2017	Various	54	1085	5.0	[3.8; 6.4]	2.3%
Austin − 2017	Various	36	440	8.2	[5.8; 11.1]	2.3%
Cella − 2017	Various	25	364	6.9	[4.5; 10.0]	2.2%
Ferroni − 2015	Various	31	380	8.2	[5.6; 11.4]	2.2%
George − 2011	Various	34	975	3.5	[2.4; 4.8]	2.3%
Kearney − 2009	Various	10	63	15.9	[7.9; 27.3]	1.8%
Khorana − 2008	Various	17	842	2.0	[1.2; 3.2]	2.1%
Kim − 2012	Various	9	54	16.7	[7.9; 29.3]	1.8%
Kunapareddy − 2017	Various	11	109	10.1	[5.1; 17.3]	1.9%
Mandala − 2012	Various	40	825	4.8	[3.5; 6.5]	2.3%
Moore − 2011	Various	91	538	16.9	[13.8; 20.4]	2.4%
Munoz−Martin − 2018	Various	41	207	19.8	[14.6; 25.9]	2.3%
Panizo − 2015	Various	26	410	6.3	[4.2; 9.2]	2.2%
Posch − 2016	Various	89	1069	8.3	[6.7; 10.1]	2.4%
Tafur − 2015	Various	16	154	10.4	[6.1; 16.3]	2.1%
van Es − 2017	Various	32	473	6.8	[4.7; 9.4]	2.2%
Zahir − 2017	Various	23	254	9.1	[5.8; 13.3]	2.2%
Random effects model		**585**	**8242**	**8.0**	**[6.0; 10.6]**	**36.9%**
Heterogeneity: I^2 = 92%, τ^2 = 0.3672, p < 0.01						
Random effects model		**1403**	**21172**	**8.6**	**[7.2; 10.2]**	**100.0%**
Prediction interval					**[2.7; 24.4]**	
Heterogeneity: I^2 = 90%, τ^2 = 0.3674, p < 0.01						



Abbreviations: CI, confidence interval; DLBCL, Diffuse large B-cell lymphoma; HL, Hodgkin lymphoma; NHL, Non-Hodgkin lymphoma; VTE, Venous thromboembolism.

Supplementary Figure 3C. VTE incidence with 95% confidence intervals in high-risk group during total follow-up.

Study − Year	Cancer type	VTE	Patients	Incidence (%)	95% − CI	Weight
Central nervous cancer						
Misch − 2013	Glioma	1	3	33.3	[0.8; 90.6]	0.6%
Yust−Katz − 2015	Glioblastoma	63	418	15.1	[11.8; 18.9]	2.8%
Random effects model		**64**	**421**	**15.2**	**[12.1; 19.0]**	**3.4%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.40						
Gastrointestinal cancer						
Ades − 2015	Colorectal	0	1	0.0	[0.0; 97.5]	0.4%
Fuentes − 2017	Gastric	5	55	9.1	[3.0; 20.0]	1.9%
Guadagni − 2017	Various GI	2	25	8.0	[1.0; 26.0]	1.2%
Kruger − 2017	Pancreatic	8	42	19.0	[8.6; 34.1]	2.1%
Munoz−Martin − 2014	Pancreatic	13	36	36.1	[20.8; 53.8]	2.3%
Papaxoinis − 2018	Various GI	10	42	23.8	[12.1; 39.5]	2.2%
Park − 2017	Gastric	11	108	10.2	[5.2; 17.5]	2.4%
Pelzer − 2013	Pancreatic	17	89	19.1	[11.5; 28.8]	2.5%
Ruch − 2012	Pancreatic	9	37	24.3	[11.8; 41.2]	2.2%
Sohal − 2016	Colorectal	5	40	12.5	[4.2; 26.8]	1.9%
van Es − 2017	Pancreatic	4	46	8.7	[2.4; 20.8]	1.7%
Wang − 2017	Hepatocellular	0	2	0.0	[0.0; 84.2]	0.4%
Random effects model		**84**	**523**	**16.8**	**[12.2; 22.7]**	**21.1%**
Heterogeneity: I^2 = 49%, τ^2 = 0.2055, p = 0.03						
Hematological cancer						
Ayyappan − 2016	DLBCL	11	36	30.6	[16.3; 48.1]	2.2%
Borchman − 2016	HL	54	1397	3.9	[2.9; 5.0]	2.8%
Lim − 2015	DLBCL	3	17	17.6	[3.8; 43.4]	1.4%
Rupa−Matysek − 2018	DLBCL and HL	11	64	17.2	[8.9; 28.7]	2.3%
Santi − 2017	NHL	1	141	0.7	[0.0; 3.9]	0.8%
Random effects model		**80**	**1655**	**9.2**	**[2.7; 27.1]**	**9.6%**
Heterogeneity: I^2 = 93%, τ^2 = 1.8952, p < 0.01						
Lung cancer						
Kuderer − 2017	Lung	16	298	5.4	[3.1; 8.6]	2.5%
Mansfield − 2016	Lung	12	100	12.0	[6.4; 20.0]	2.4%
Noble − 2015	Lung	21	302	7.0	[4.4; 10.4]	2.6%
Rupa−Matysek − 2018	Lung	2	15	13.3	[1.7; 40.5]	1.2%
Vathiotis − 2018	Lung	4	39	10.3	[2.9; 24.2]	1.7%
Random effects model		**55**	**754**	**8.0**	**[5.6; 11.4]**	**10.5%**
Heterogeneity: I^2 = 34%, τ^2 = 0.0755, p = 0.20						
Urogenital cancer						
Bezan (Graz) − 2017	Testicular	0	9	0.0	[0.0; 33.6]	0.5%
Bezan (Zurich) − 2017	Testicular	4	25	16.0	[4.5; 36.1]	1.7%
Kuk − 2017	Ovarian	3	28	10.7	[2.3; 28.2]	1.5%
Patel − 2015	Prostate	1	5	20.0	[0.5; 71.6]	0.7%
Ramos − 2016	Urothelial	19	162	11.7	[7.2; 17.7]	2.6%
Srikanthan (cohort 1) − 2015	Testicular	8	18	44.4	[21.5; 69.2]	1.9%
Srikanthan (cohort 2) − 2015	Testicular	2	7	28.6	[3.7; 71.0]	1.0%
Random effects model		**37**	**254**	**18.1**	**[10.2; 30.1]**	**9.8%**
Heterogeneity: I^2 = 56%, τ^2 = 0.3846, p = 0.04						
Various cancers						
Abdel−Razeq − 2017	Various	31	260	11.9	[8.2; 16.5]	2.7%
Austin − 2017	Various	21	161	13.0	[8.3; 19.2]	2.6%
Cella − 2017	Various	4	57	7.0	[1.9; 17.0]	1.7%
Ferroni − 2015	Various	4	50	8.0	[2.2; 19.2]	1.7%
George − 2011	Various	14	281	5.0	[2.8; 8.2]	2.5%
Kearney − 2009	Various	12	29	41.4	[23.5; 61.1]	2.2%
Khorana − 2017	Various	10	48	20.8	[10.5; 35.0]	2.2%
Khorana − 2014	Various	8	35	22.9	[10.4; 40.1]	2.1%
Khorana − 2008	Various	10	149	6.7	[3.3; 12.0]	2.3%
Kim − 2012	Various	3	19	15.8	[3.4; 39.6]	1.5%
Kunapareddy − 2017	Various	14	82	17.1	[9.7; 27.0]	2.4%
Mandala − 2012	Various	8	62	12.9	[5.7; 23.9]	2.2%
Moore − 2011	Various	48	170	28.2	[21.6; 35.6]	2.8%
Munoz−Martin − 2018	Various	16	74	21.6	[12.9; 32.7]	2.5%
Panizo − 2015	Various	5	45	11.1	[3.7; 24.1]	1.9%
Petitto − 2017	Various	2	19	10.5	[1.3; 33.1]	1.2%
Posch − 2016	Various	31	232	13.4	[9.3; 18.4]	2.7%
Tafur − 2015	Various	8	32	25.0	[11.5; 43.4]	2.1%
van Es − 2017	Various	7	105	6.7	[2.7; 13.3]	2.1%
Verso − 2012	Various	5	45	11.1	[3.7; 24.1]	1.9%
Zahir − 2017	Various	11	52	21.2	[11.1; 34.7]	2.3%
Random effects model		**272**	**2007**	**14.4**	**[11.2; 18.3]**	**45.6%**
Heterogeneity: I^2 = 77%, τ^2 = 0.3187, p < 0.01						
Random effects model		**592**	**5614**	**14.0**	**[11.7; 16.7]**	**100.0%**
Prediction interval					**[4.4; 36.4]**	
Heterogeneity: I^2 = 81%, τ^2 = 0.3785, p < 0.01						



Abbreviations: CI, confidence interval; DLBCL, Diffuse large B-cell lymphoma; HL, Hodgkin lymphoma; NHL, Non-Hodgkin lymphoma; VTE, Venous thromboembolism.

Supplementary list 1

Data sources and search strategy

A comprehensive search was performed in Embase and MEDLINE from January 2008 to June 2018 to identify randomized controlled trials, prospective cohort studies, or historical cohort studies that had evaluated the Khorana score in ambulatory cancer patients receiving chemotherapy. Studies that lacked radiological confirmation of VTE, those with a case-control design, and those in languages other than English, French, Dutch, Spanish, or German were excluded. As patients with multiple myeloma are ought to receive a form of thromboprophylaxis[1], studies that primarily included these patients were excluded. The search strategy is displayed in Supplementary Table 2. In addition, studies presented as abstracts at conferences of the American Society of Hematology (ASH) or the International Society on Thrombosis and Haemostasis (ISTH) from 2008 to 2018 were identified by a manual search. Two reviewers (F.I.M. and M.C.) independently screened studies and assessed bias with the Quality in Prognosis Studies (QUIPS) tool[2].

Data extraction and bias assessment

Two reviewers (F.I.M. and M.C.) independently screened titles, abstracts, and full text-articles for potentially eligible studies. Risk of bias assessment and data extraction were performed in duplicate by both reviewers using standardized forms. Discrepancies were solved by discussion. For persisting disagreements, a third reviewer (N.v.E) was consulted.

The Quality in Prognosis Studies (QUIPS) tool[2] was used for risk of bias assessment in the following domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. Predefined reasons to consider a study as having a high risk of bias for a specific domain included a loss to follow-up of more than 5%, the inability to calculate the Khorana score for more than 10% of the cohort, thromboprophylaxis given to more than 5% of the cohort, start of chemotherapy before calculation of the Khorana score, and inclusion of arterial thromboembolism in the outcome. All criteria applied in the critical appraisal and bias assessment are listed in Supplementary Table 3.

The following variables were extracted from the report of each included study: design, proportion of males, mean or median age at baseline, proportion of patients with metastatic cancer, mean or median follow-up duration, outcomes, and incidence of VTE for all Khorana score groups (low, intermediate, or high risk). For randomized trials evaluating thromboprophylaxis, only patients in the placebo or observation arm were included in present analysis.

References supplementary documents

1. International Myeloma Working Group (IMWG). IMWG Guidelines for the Prevention of Thalidomide- and Lenalidomide-Associated Thrombosis in Myeloma [Epub ahead of print].
2. Hayden J a, Windt D a Van Der, Cartwright JL, Co P. Research and Reporting Methods Annals of Internal Medicine Assessing Bias in Studies of Prognostic Factors. Ann Intern Med 2013;144427–437.