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Review Article

Models for predicting venous thromboembolism in ambulatory patients with lung cancer: A systematic review and meta-analysis

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ABSTRACT

Aims: The incidence of venous thromboembolism (VTE) in patients with lung cancer is relatively high, and risk stratification models are vital for the targeted application of thromboprophylaxis. We aimed to review VTE risk prediction models that have been developed in patients with lung cancer and evaluated their performance.
Methods and results: Twenty-four eligible studies involving 123,493 patients were included. The pooled incidence of VTE within 12 months was 11 % (95 % CI 8 %–14 %). With the identified four VTE risk assessment tools, meta-analyses did not show a significant discriminatory capability of stratifying VTE risk for Khorana, PROTECHT and CONKO scores. The pooled sensitivity and specificity of the Khorana score were 24 % (95 % CI 11 %–44 %) and 84 % (95 % CI 73 %–91 %) at the 3-point cut-off, and 43 % (95 % CI 35 %–52 %) and 61 % (95 % CI 52 %–69 %) at the 2-point cut-off. However, a COMPASS-CAT score of $\geq$ 7 points indicated a significantly high VTE risk, with a RR of 4.68 (95 % CI 1.05–20.80).
Conclusions: The Khorana score lacked discriminatory capability in identifying patients with lung cancer at high VTE risk, regardless of the cut-off value. The COMPASS-CAT score had better performance, but further validation is needed. The results indicate the need for robust VTE risk assessment tools specifically designed and validated for lung cancer patients. Future research should include relevant biomarkers as important predictors and consider the combined use of risk tools.
PROSPERO registration number: CRD42021245907.

1. Introduction

Lung cancer is the second most common type of malignancy worldwide, with 2.2 million new cases diagnosed in 2020 which accounted for 11.4 % of all the new cancers diagnosed in that year [1]. The 5-year survival rate for this cancer was reported at 10–20 % [1], with nearly 1.8 million deaths reported in 2020 (approximately 18 % of cancer deaths from all sites in that year) [1]. Venous thromboembolism (VTE) is the leading cause of death after the progression of cancer per se [2]. Having VTE, either a pulmonary embolism (PE) or deep vein thrombosis (DVT), increased one-year mortality after lung cancer diagnosis by 53 % (HR 1.53, 95 % CI 1.20–1.95) and 26 % (HR 1.26, 95 % CI 1.01–1.57), respectively [3]. This burdensome complication of cancer, however, is preventable if patients at higher risk of VTE are identified in a timely manner and prophylactic anticoagulation is administered.

Guidelines for thromboprophylaxis in cancer patients do not recommend routine use of anticoagulation for primary prevention in ambulatory patients with cancer due to the risk of haemorrhage, but only to those at high VTE risk [4–6]. To identify those at high VTE risk, risk assessment models have been developed, such as the Khorana score, PROTECHT, CONKO and COMPASS-CAT [7–11]. The Khorana score is the most frequently used VTE risk tool and is incorporated into several

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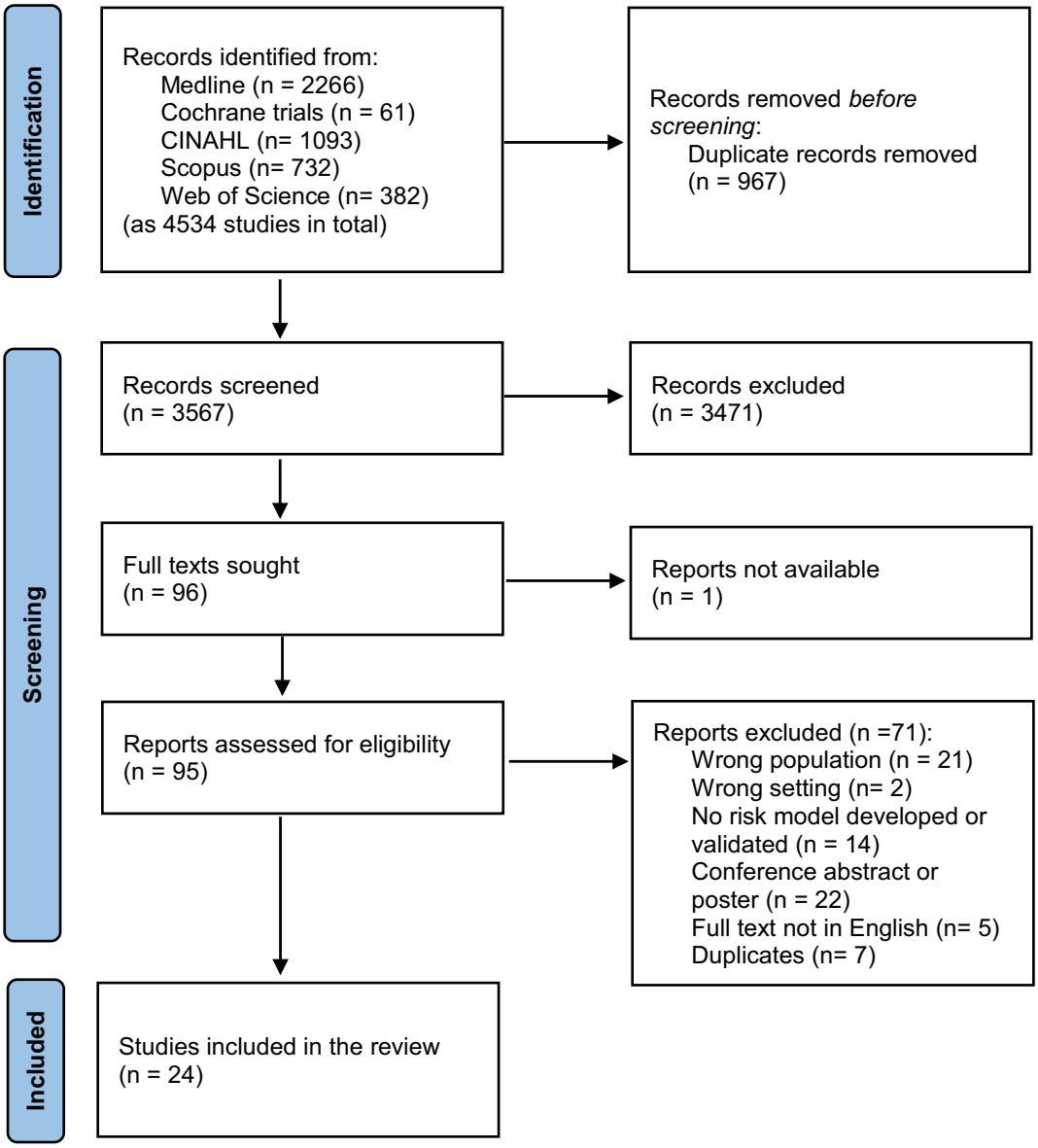

Fig. 1. PRISMA flow chart of the study selection.

international guidelines, including the American Society of Clinical Oncology (ASCO) [4], International Society for Thrombosis and Hemostasis (ISTH) [5], and the International Initiative on Thrombosis and Cancer (ITAC) guidelines [6]. The Khorana score was developed in cancer patients with various tumour types, and is composed of five items: cancer site — scoring 2 points for stomach or pancreas or 1 point for lung, lymphoma, gynaecologic, bladder, or testicular; platelet count at 350 $\times$ 10^9/L or more scoring 1 point; haemoglobin level <100 g/L or use of red cell growth factors scoring 1 point; white blood cell count >11 $\times$ 10^9/L scoring 1 point; and body mass index (BMI) at 35 kg/m^2 or more scoring 1 point [8]. Studies have shown that the Khorana score with the original 3-point cut-off for high VTE risk has a low sensitivity (23.4 %, 95 % CI: 18.4–29.4) for the prediction of VTE in patients with cancer in general [12]. More studies of the Khorana score with a cut-off value of 2 points have been conducted since 2020, after the ASCO guidelines was published in 2019, which recommended a Khorana score threshold of 2 points [13]. However, in patients with lung cancer it has been reported that the Khorana score with a 2-point cut-off lacks a high discriminatory capability (OR 1.1, 95 % CI 0.72–1.7) [14].

Some new risk models have been developed by modifying the Khorana score. For example, the PROTECHT score added 1 point for the use of gemcitabine or platinum-based chemotherapy, and the CONKO score replaced BMI by the Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\geq$ 2 for 1 point. The cut-off value is still 3 points in both scores, but their application in lung cancer patients showed a poor discrimination with a C-index around 0.50 [15,16].

The COMPASS-CAT score is another VTE risk score developed in cancer patients, which includes anthracycline treatment (6 points), time since cancer diagnosis $\leq$6 months (4 points), central venous catheter use (3 points), advanced stage of cancer (2 points), cardiovascular risk factors present (5 points), recent hospitalisation for acute medical illness (2 points), a history of VTE (1 point), and platelet count $\geq$350 $\times$ 10^9/L (2 points) [17]. With the original 7-point cut-off for high risk, the COMPASS-CAT score had a sensitivity of 83 % but a low specificity of 35 %. By altering the cut-off value to 11 points, the COMPASS-CAT score had a dramatically improved AUC of 0.89 [15].

There are also other risk scores, like the Vienna Modification (CATS score), which was developed by adding D-dimer and soluble P-selection to the Khorana score [18], a simpler CAT model with only two factors including distant metastases and platinum therapy [19], and the CATS-

Table 1
Characteristics of included studies.

Study	Study design	Population and sample size	Outcome/event	Follow-up in months	Risk tools
Ferroni 2012 Italy [26]	R	Lung cancer (n = 108)	21 VTE	Median 6.9	HS D-dimer
Mansfield 2016 USA [27]	R	Lung cancer (n = 719) (658 had a Khorana score)	83 VTE	Median 15.2	Khorana score
Xiong 2017 China [28]	C	Lung cancer (n = 9527)	1016 VTE	During hospitalisation	• TMs panel • CEA
Kuderer 2018 global (24 countries) [29]	P	Lung cancer (n = 1980) (1780 had a Khorana score)	121 VTE	≤6	Khorana score
Rupa-Matysek 2018 Poland [15]	R	Lung cancer (n = 118)	20 VTE	Median 14	• Khorana score • PROTECHT • CONKO • COMPASS-CAT
Syrigos 2018 Greece [30]	P	Lung adenocarcinoma (n = 150)	12 VTE	≤12	• ROADMAP-CAT • COMPASS-CAT • Combined ROADMAP and COMPASS-CAT
Vathiotis 2018 Greece [31]	R	Lung adenocarcinoma (n = 130)	13 VTE	Median 4	Khorana score
Alexander 2019 Australia [16]	P	NSCLC (n = 117) (83 had a Khorana score)	17 TE (13 VTE)	≤6	• Khorana score • PROTECHT • CONKO • BIOTEL
Castellon Rubio 2020 Spain [32]	P	Locally advanced or metastatic NSCLC (n = 90)	18 VTE	≤12	• Khorana score • PROTECHT • CONKO • Thrombo-NSCLC
Dapkeviciute 2020 Lithuania [33]	R	Lung cancer inpatients with IIIB and IV stages (n = 217)	26 PE	Median 10	Khorana score
Li 2020 China [34]	R	Lung cancer (n = 827)	102 VTE	During hospitalisation	Risk score system
Spyropoulos 2020 USA [35]	R	Lung cancer subgroup (n = 1108)	115 VTE	≤12	COMPASS-CAT
vanEs 2020 [14]	P*	Lung cancer (n = 1913)	118 VTE	≤6	Khorana score
Icht 2021 Israel [36]	R	NSCLC (n = 345)	20 VTE	Median 6	Khorana score
Li_J 2021 China [38]	P	Newly diagnosed NSCLC (n = 1014) (602 had a Khorana score)	111 VTE	≤6	• Khorana score • Tic-ONCO score
Li_S 2021 China [37]	R	Advanced lung cancer (n = 124)	24 VTE	During hospitalisation	• Khorana score • Modified Khorana score
Madison 2021 USA [39]	R	Lung cancer (n = 93,360)	6949 TE (5332 VTE)	≤6	Khorana score
Alma 2022 France [40]	R	Lung cancer (n = 481)	47 VTE (excluding CAT)	Median 9.8	Khorana score
Overvad 2022 Denmark [41]	R	Lung cancer (n = 6556)	209 VTE	≤6	Khorana score
Sahan 2022 Turkey [42]	R	Lung cancer (n = 284)	96 VTE	Mean 30.56 ± 21.82 (SD)	• Khorana score
Tsubata 2022 Japan [43,44]	P	Advanced lung cancer (n = 1008) (1003 had a Khorana score)	100 VTE	≤24	• Khorana score • Modified Khorana score
Zhang 2022 China [45]	R	Lung cancer (n = 369)	86 VTE	≤6	• Khorana score • Six-item nomogram
Khorana 2023 USA [46]	R	Stage IV NSCLC (n = 2299) (472 had a Khorana score)	387 VTE	Median 9.1	Khorana score
Zhu 2023 China [47]	R	Lung cancer (n = 649)	96 PE	≥6	7-Item nomogram score

R: retrospective cohort study; P prospective cohort study; C: case-control study.
* Individual patient data of control arms from 4 randomised controlled trials.

MICA model using cancer site and continuous D-dimer concentration [17].

There is limited research done on the predictive ability of the Khorana score in lung cancer and it is unclear if other risk scores are useful in this group of patients. Therefore, a review of the existing VTE risk tools and their performance in lung cancer was needed for risk model evaluation.

The aim of this systematic review was to identify and evaluate the VTE risk tools developed and validated in ambulatory patients with lung cancer. The objectives were to: (i) identify and summarise the existing VTE risk prediction models in ambulatory patients with lung cancer; and (ii) conduct a meta-analysis to evaluate the performance of the existing risk models for predicting VTE in ambulatory patients with lung cancer.

2. Methods

The protocol for this systematic review has been published [20].

2.1. Inclusion and exclusion criteria

This systematic review included all study designs in which risk prediction models for VTE were developed and/or validated in adult ambulatory patients with primary lung cancer diagnosed by histopathology. The primary outcome was VTE, objectively confirmed by ultrasonography, CT scan, venogram, angiography, magnetic resonance, or consensus by an expert panel. Studies of recurrent cancer-related VTE or VTE inpatients on chronic (>2 months) antithrombotic treatment at recruitment or during the follow-up period, or studies published in languages other than English were excluded.

2.2. Search strategies

The final search date was extended to 2nd February 2023. Full-text peer-reviewed journal articles published in English were identified by keywords using MEDLINE, Cochrane Library, CINAHL, Scopus and Web of Science for articles published from inception of the databases to the

Table 2
Performance of Khorana score in lung cancer patients.

Study ID	Cut-off for high VTE risk	High risk, n (%, 95 % CI)	Intermediate/ low risk, n (%, 95 % CI)	VTE incidence in high-risk stratum, n (%, 95 % CI)	VTE incidence in intermediate-risk stratum, n (%, 95 % CI)	*p*-Value	Sensitivity, % (95 % CI)	Specificity, % (95 % CI)	PPV, % (95 % CI)	NPV, % (95 % CI)	AUC/c-statistic, (95 % CI)	Effect size estimated from regression model (95 % CI)
Mansfield 2016 [27]	≥3 points	100 (15)	558 (84.8)	(12.4, 6.4–20.5) The cumulative incidences of VTE at 3, 6, 12 and 24 months were 5.2 %, 6.2 %, 7.2 % and 10.3 %	(12.1, 9.5–15.0) The cumulative incidences of VTE at 3, 6, 12 and 24 months were 5.1 %, 6.3 %, 7.4 % and 9.2 %	0.21	NA	NA	NA	NA	NA	NA
Kuderer 2018 [29]	Ordinal	≥3 points 298 (15.1) ≥2 points 601 (30.4)	1 point 881 (44.5) unknown 200 (10.1)	≥3 points 16 (5.4) 2 points 39 (6.5)	1 point 56 (6.4) unknown 10 (5.0)	Insignificant	NA	NA	NA	NA	NA	NA
Rupa-Matysek 2018 [15]	≥3 points	15 (13)	103 (87)	2 (13)	18 (17.5)	NA	10	100	17	83	0.81	NA
Vathiotis 2018 [31]	Ordinal	≥3 points 39 (30)* ≥2 points 82 (63)*	<3 points 91 (70)* <2 points 48 (37)*	≥3 points 4 (10)* ≥2 points 7 (9)*	<3 points 9 (10)* <2 points 6 (13)*	0.96	NA	NA	NA	NA	NA	NA
Alexander 2019 [16]	≥3 points	20 (24)	63 (76)	4* (20.2)	12* (18.9)	0.89	25 (7–52)	76 (64–86)	20 (6–44)	81 (69–90)	0.51 (0.39–0.63)	sHR 1.1 (0.4–3.3)
Castellon Rubio 2020 [32]	≥3 points	28 (31)*	62 (69)*	6 (21)*	12 (19)*	0.12	35	60	21.8 (11.9–30.3)	81.7 (77.4–85.4)	0.55 (0.44–0.66)	NA
Dapkeviciute 2020 [33]	≥2 points	80 (37)*	137 (63)*	PE 9 (11)	PE 17 (12)	0.80	NA	NA	NA	NA	NA	NA
van Es 2020 [14]	≥2 points	421* (22, 18–27)	1492 (78)*	28* (6.6, 4.7–9.2)	90* (6.0, 4.9–7.4)	NA	NA	NA	NA	NA	NA	OR 1.1 (0.72–1.7)
Icht 2021 [36]	≥2 points	All 165 (47.8) ICI cohort 80 (45.4) chemotherapy cohort 85 (50.3)	All 180 (52.2) ICI cohort 96 (54.5) Chemotherapy cohort 84 (49.7)	All 10 (6.1) ICI cohort 1 (11.3) Cumulative incidence at 6 m 1.2 (0.01–6) Chemotherapy cohort 9 (10.6) Cumulative incidence at 6 m 10.5 (5–18)	All 10 (5.6) ICI cohort 7 (7.3) Cumulative incidence at 6 m 7.3 (3–13) Chemotherapy cohort 3 (3.6) Cumulative incidence at 6 m 3.5 (1–9)	NA	NA	NA	NA	NA	NA	ICI cohort HR 0.17 (0.02–1.36) chemotherapy cohort HR 3.04 (0.82–11.22)
Li_J 2021 [38]	Ordinal	≥3 points 22 (4)* ≥2 points 138 (23)*	<3 points 580 (96)* <2 points 464 (77)*	≥3 points 3 (14)* ≥2 points 22 (16)*	<3 points 64 (11)* <2 points 45 (10)*	0.44	NA	NA	NA	NA	NA	NA
Li_S 2021 [37]	Ordinal	≥3 points 16 (13)* ≥2 points 52 (42)*	<3 points 108 (87)* <2 points 72 (58)*	≥3 points 6 (38)* ≥2 points 17 (33)*	<3 points 18 (17)* <2 points 7 (10)*	NA	70.83	65	NA	NA	0.706 (0.618–0.785)	NA
Madison 2021 [39]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.09 (1.06–1.13)
Alma 2022 [40]	≥2 points	161 (34)	313 (66)	15* (9.3)	32* (10)	0.87	NA	NA	NA	NA	NA	NA
Overvad 2022 [41]	≥3 points	1433	5123	118 (3.9, 3.0–5.2); cumulative	91 (3.4, 3.0–4.0); cumulative	NA	NA	NA	NA	NA	NA	sHR 0.96 (0.73–1.26)

(*continued on next page*)

Table 2 (*continued*)

Study ID	Cut-off for high VTE risk	High risk, n (%, 95 % CI)	Intermediate/ low risk, n (%, 95 % CI)	VTE incidence in high-risk stratum, n (%, 95 % CI)	VTE incidence in intermediate-risk stratum, n (%, 95 % CI)	*p*-Value	Sensitivity, % (95 % CI)	Specificity, % (95 % CI)	PPV, % (95 % CI)	NPV, % (95 % CI)	AUC/*c*-statistic, (95 % CI)	Effect size estimated from regression model (95 % CI)
				incidence 3.3, 2.4–4.3)	incidence 3.2, 2.7–3.7)							
Sahan 2022 [42]	≥3 points	41 (14.4)	243 (85.6)	16 (39.0)	80 (32.9)	0.45	NA	NA	NA	NA	NA	NA
Tsubata 2022 [44]	Ordinal	≥3 points 78 (7.8)	1 point 730 (72.8) 2 points 195 (19.4)	6 (7.6)	1 point 68 (9.3) 2 points 25 (12.8)	NA	6.1	92	NA	NA	0.518 (0.458–0.578), $p = 0.55$	NA
Zhang 2022 [45]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.600 (0.531–0.699)	NA
Khorana 2023 [46]	≥2 points	212 (44.9)	260 (55.1)	47* (22.4)	42* (16)	0.54	NA	NA	NA	NA	NA	HR 1.17 (0.71–1.92)

* Calculated from reported data.

final search date. The search by subject headings was also conducted in MEDLINE (via EBSCOhost) and CINAHL. The strategy was developed in consultation with a senior librarian. The detailed search strategy and results can be found in the supplementary material.

2.3. Data extraction

Covidence [21] was used for study selection and data extraction. A-RY and RM screened the titles and the abstracts and reviewed the full texts independently. Discrepancies were resolved by IS, A-RY and RM independently extracted data from the included studies with any discrepancies resolved by discussion with the other co-authors. The Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA) Checklist (Appendix Table A) was used for data extraction and result reporting [22]. The data extracted comprised first author, year of publication, study design, recruitment, description and treatment, sample size, follow-up period, the type of VTE risk model(s) and included predictors, the modelling method and evaluation, the number and/or incidence of VTE (both overall and stratified by risk models), the model performance indicators such as risk ratios or odds ratios, discriminating capacity indicators (e.g. AUC and Concordance index (C-index)) and classification measures (i.e. sensitivity, specificity, positive predictive value and negative predictive value).

2.4. Quality assessment

A-RY and RM independently assessed the quality of the included studies using the Prediction model Risk Of Bias ASsessment Tool (PROBAST) [23]. PROBAST includes the following domains: participants, predictors, outcome, and analysis, with two, three, six and nine signaling questions, respectively. The applicability of the original study findings was also assessed through PROBAST in the following three domains: participants, predictors, and outcome. According to the appraisal criteria, if one or more domains were assessed at high risk of bias, the overall outcome was evaluated at high risk of bias [24].

2.5. Statistical analysis

Meta-analysis of the incidence of VTE was conducted. Also, pooled data of VTE occurrence in patients having high risk scores were compared with those having low risk scores to determine the effect size [risk ratio (RR) and 95 % CI] for the risk of VTE in the meta-analysis of those using the same risk model. Heterogeneity across the studies were quantified with the I^2 statistic test, where an $I^2 > 75$ % indicates high heterogeneity, while an I^2 value between 50 % and 75 % indicates moderate heterogeneity. A fixed effect model was used when there were low levels of clinical or statistical heterogeneity, and a random effects model was used when $I^2 \geq 50$ %. To evaluate the publication bias, Egger's tests for funnel plot asymmetry were used when at least 10 studies were included in the meta-analysis. Further, the bivariate model was added for the estimation of a summary value of sensitivity and specificity of each risk score when at least four studies was included [25]. Between-study heterogeneity was explored by subgroup analysis in lung cancer and its subtypes. Stata 17.0 (STATA Corporation, Texas, USA) was used for data analysis and synthesis.

3. Results

3.1. Study selection

Fig. 1 depicts the study selection process. Of the 4534 studies found, after removing duplicates (n = 967) and excluding for irrelevant titles and abstracts (n = 3471), 96 studies were selected for full text review, out of which 72 studies were excluded (wrong population or setting, no risk scores identified, conference abstract or poster, non-English

Table 3
Performance of PROTECHT, CONKO and COMPASS-CAT score in lung cancer patients.

Study ID	Cut-off for high VTE risk	High risk, n (%)	Low risk, n (%)	VTE incidence in high-risk stratum, n (%)	VTE incidence in low-risk stratum, n (%)	Significance of the difference in VTE incidence, *p*-value	Sensitivity, % (95 % CI)	Specificity, % (95 % CI)	PPV, % (95 % CI)	NPV, % (95 % CI)	AUC/c-statistic, (95 % CI)	Effect size estimated from regression model (95 % CI)
PROTECHT												
Rupa-Matysek 2018 [15]	≥3	62 (52)	56 (48)	11 (17.7)	9 (16)	NA	20	78	18	84	0.51	NA
Alexander 2019 [16]	≥3	53 (64)	30 (36)	11* (20.9)	5* (16.3)	$p = 0.60$	69 (41–89)	37 (26–50)	21 (11–34)	83 (65–94)	0.53 (0.40–0.66)	sHR 1.3 (0.5–3.7)
Castellon Rubio 2020 [32]	≥3	61 (68)*	29 (32)*	15 (25)*	3 (10)*	NA	83.3	36.1	24.6 (14.5–37.3)	89.7 (72.6–97.8)	0.59 (0.49–0.70)	NA
CONKO												
Rupa-Matysek 2018 [15]	≥3	26 (22)	92 (78)	4 (15)	16 (17.4)	NA	55	48	15	82	0.49	NA
Alexander 2019 [16]	≥3	40 (48)	43 (52)	10 (25)	6 (13.8)	$p = 0.71$	63 (35–85)	55 (43–67)	25 (13–41)	86 (72–95)	0.59 (0.45–0.73)	sHR 1.9 (0.7–5.3)
Castellon Rubio 2020 [32]	≥3	20 (22)*	70 (78)*	4 (20)*	14 (20)*	NA	22.2	77.8	20.0 (5.7–43.7)	80.0 (68.7–88.6)	0.50 (0.39–0.61	NA
COMPASS-CAT												
Rupa-Matysek 2018 [15]	≥7	84 (71)	34 (29)	20 (24)	0 (0)	NA	100	35	24	100	0.89 (0.82–0.96)	OR 8.73 (1.01–75.22)
Syrigos 2018 [30]	≥7	51 (34)*	99 (66)*	10 (20)*	2 (2)*	NA	83	51	13	97	NA	NA
Spyropoulos 2020 [35]	≥7	1002 (90.4)	106 (9.6)	108 (10.8)	7 (6.6)	Insignificant	93.9	10.0	10.8	93.4	NA	NA

* Calculated from reported data.

Table 4
Other modified or newly developed risk scores and their performance in lung cancer patients.

Study ID	Ferroni 2012 [26]	Xiong 2017 [28]		Syrigos 2018 [30]		Alexander 2019 [16]	Castellon Rubio 2020 [32]	Li 2020 [34]	Li_J 2021 [38]	Li_S 2021 [37]	Tsubata 2022 [43,44]		Zhang 2022 [45]	Zhu 2023 [47]
Model name	HS D-dimer	CEA	TMs panel	ROADMAP	Combination of COMPASS-CAT with ROADMAP	BIOTEL	Thrombo-NSCLC	Risk score system	Tic-ONCO score	Modified Khorana score	Modified Khorana score	Rising-VTE/ NEJ037	Nomogram score	7-Item nomogram score
Predictors														
Khorana score	X									X	X			
COMPASS-CAT score					X									
Patient-related														
Age								X					X	
Gender								X				X		
BMI $\geq$ 25 kg/m^2											X			
ECOG PS									X			X		
Congestive heart failure														
Hypertension												X		
Cancer-related														
Adenocarcinoma								X				X		X
EGFR mutation									X					
Stage								X						X
Metastasis													X	
Antitumor treatment													X	
History of surgery								X						
History of chemotherapy								X						X
History of CVC								X						X
Biomarkers														
D-dimer	X					X		X	X	X			X	X
Fibrinogen						X								
Haemoglobin									X				X	X
Platelet count												X		
Neutrophil count									X					
Lymphocyte percentage												X		
Prothrombin fragment 1 + 2												X		
CEA		X	X						X					
SCC			X											
CYFRA21-1			X											
NSE			X											
ProGRP tumor markers			X											
Procoag-PPL < 44 s				X	X									
MRI < 125 nM/min				X	X									
sP-selectin							X							
mADU							X							
FVIII							X							
SII													X	
Serum albumin														X

Including previous MI, history of coronary revascularization, such as peripheral artery disease. 1: development cohort; 2: internal validation cohort; 3: external validation cohort.

Table 5
PROBAST results.

Study	Risk of Bias (ROB)				Applicability			Overall	
	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	ROB	Applicability
Ferroni 2012	−	+	+	−	+	+	+	−	+
Mansfield 2016	+	+	+	−	+	+	+	−	+
Xiong 2017	+	+	+	−	+	+	−	−	−
Kuderer 2018	+	+	+	−	+	+	+	−	+
Rupa-Matysek 2018	+	+	+	−	+	+	+	−	+
Syrigos 2018	+	+	+	−	+	+	+	−	+
Vathiotis 2018	+	+	+	−	+	+	+	−	+
Alexander 2019	+	+	+	+	+	+	−	+	−
Castellon Rubio 2020	+	+	+	−	+	+	+	−	+
Dapkeviciute 2020	+	+	+	−	+	+	−	−	−
Li 2020	+	+	+	−	+	+	+	−	+
Spyropoulos 2020	+	+	+	?	+	+	+	?	+
vanEs 2020	+	+	+	−	+	+	+	−	+
Icht 2021	+	+	+	−	+	+	+	−	+
Li_J 2021	+	+	+	+	+	+	+	+	+
Li_S 2021	+	+	+	−	+	+	+	−	+
Madison 2021	+	+	+	−	+	+	−	−	−
Alma 2022	+	+	+	−	+	+	+	−	+
Overvad 2022	+	+	+	−	+	+	+	−	+
Sahan 2022	+	+	+	−	+	+	+	−	+
Tsubata 2022/2023	+	+	+	−	+	+	+	−	+
Zhang 2022	+	+	+	−	+	+	+	−	+
Khorana 2023	+	+	+	−	+	+	+	−	+
Zhu 2023	+	+	+	−	+	+	−	−	−

language, duplicates, and full text unavailable). Finally, 24 studies were included [14–16,26–47].

3.2. Characteristics of the included studies

In total, 123,493 patients with lung cancer were involved in 16 retrospective cohort studies, 6 prospective cohort studies, 1 case-control study, and 1 post hoc analysis of control arms of randomised controlled trials (Table 1). Fifteen studies had a sample size <1000, with the smallest sample size being 90. Six studies had a sample size over 2000 with the largest sample size of 93,360. The lengths of follow-up varied across studies from a median period of 4 months to a mean time of over 30 months. Four studies followed patients for VTE occurrence beyond 12 months, and three studies followed patients during hospitalisation without specified time. Nineteen studies evaluated the risk score for predicting VTE; however, two studies investigated the risk scores for predicting thromboembolism (TE) risk, which included myocardial infarction (MI) and stroke events in addition to VTE. Three studies focused on PE risk without DVT or total VTE events reported.

Twenty studies reported the clinical practice of one or more of the four well-known risk tools, including Khorana score (Table 2), PROTECHT score, CONKO score and COMPASS-CAT score (Table 3), and twelve studies reported modified or newly developed risk scores (Table 4). No studies reported the validation of other known VTE risk scores in patients with lung cancer, such as the CATS score or the CATS/MICA score.

3.3. Quality assessment

The quality of the included studies was assessed by PROBAST [23] (Table 5). The included studies were generally at low risk of bias for 'participants', 'predictors' and 'outcomes', but almost all of them were judged to be at high risk of bias with regard to the domain 'analysis'. The major issues in model development studies were overfitting and statistical regression methods used without consideration of time effect and competing risk, while the model validation studies had low event rates and a lack of calibration. In addition, some studies investigated the outcomes of PE or thromboembolic events (TE) instead of VTE, and hence their findings may not be applicable for VTE prediction.

3.4. The incidence of VTE in patients with lung cancer

Due to very high heterogeneity (I^2 = 99.26 %), a random-effects model was used, and the pooled data from 21 studies showed that 12 % (95 % CI 9 %–15 %) of patients with lung cancer developed VTE during various follow-up periods (Fig. 2). The pooled data from three studies showed the incidence of PE was also 12 % (95 % CI 10 %–15 %). The funnel plots showed asymmetry, with 10 of the studies falling outside the pseudo 95 % confidence intervals (Fig. 3), and the significant result of Egger's test (p = 0.002) indicated publication bias.

By removing four studies followed the patients longer than one year, the pooled incidence of VTE within 12 months was 11 % (95 % CI 8 %–14 %).

Three studies followed inpatients in China were included, as most of these patients were considered ambulatory and had to be admitted to hospital for anticancer treatment due to China's medical insurance policy for reimbursement [34]. A subgroup analysis was conducted by removing these studies, and the pooled incidence of VTE was the same and the polled incidence of PE was similar (14 %, 95 % CI 11 %–16 %).

3.5. The Khorana score

Overall, 18 studies examined the Khorana score and reported its performance in lung cancer patients (Table 2), of which the study by Alexander et al. and the study by Madison et al. included arterial thrombosis were excluded for meta-analysis. Meta-analyses were conducted on the studies of Khorana score with a cut-off value of 2 and 3 points, respectively, for predicting VTE within a 12-month follow-up. Due to high heterogeneity (I^2 = 24.21 % and 80.84 %, respectively), a random-effects model was used. The meta-analysis results showed the RR was 1.20 (95 % CI 0.98–1.48) and 1.62 (95 % CI 0.88–2.99) for a Khorana score >2 and 3 points, respectively (Fig. 4). The pooled sensitivity and specificity of the Khorana score were 24 % (95 % CI 11 %–44 %) and 84 % (95 % CI 73 %–91 %) at the 3-point cut-off, and 43 % (95 % CI 35 %–52 %) and 61 % (95 % CI 52 %–69 %) at the 2-point cut-off. The hierarchical summary ROC showed that the Khorana score with the cut-off of either 2 or 3 points had low discrimination capability of VTE prediction in patients with lung cancer (Fig. 5).

Subgroup analyses showed that a Khorana score higher than 2 points

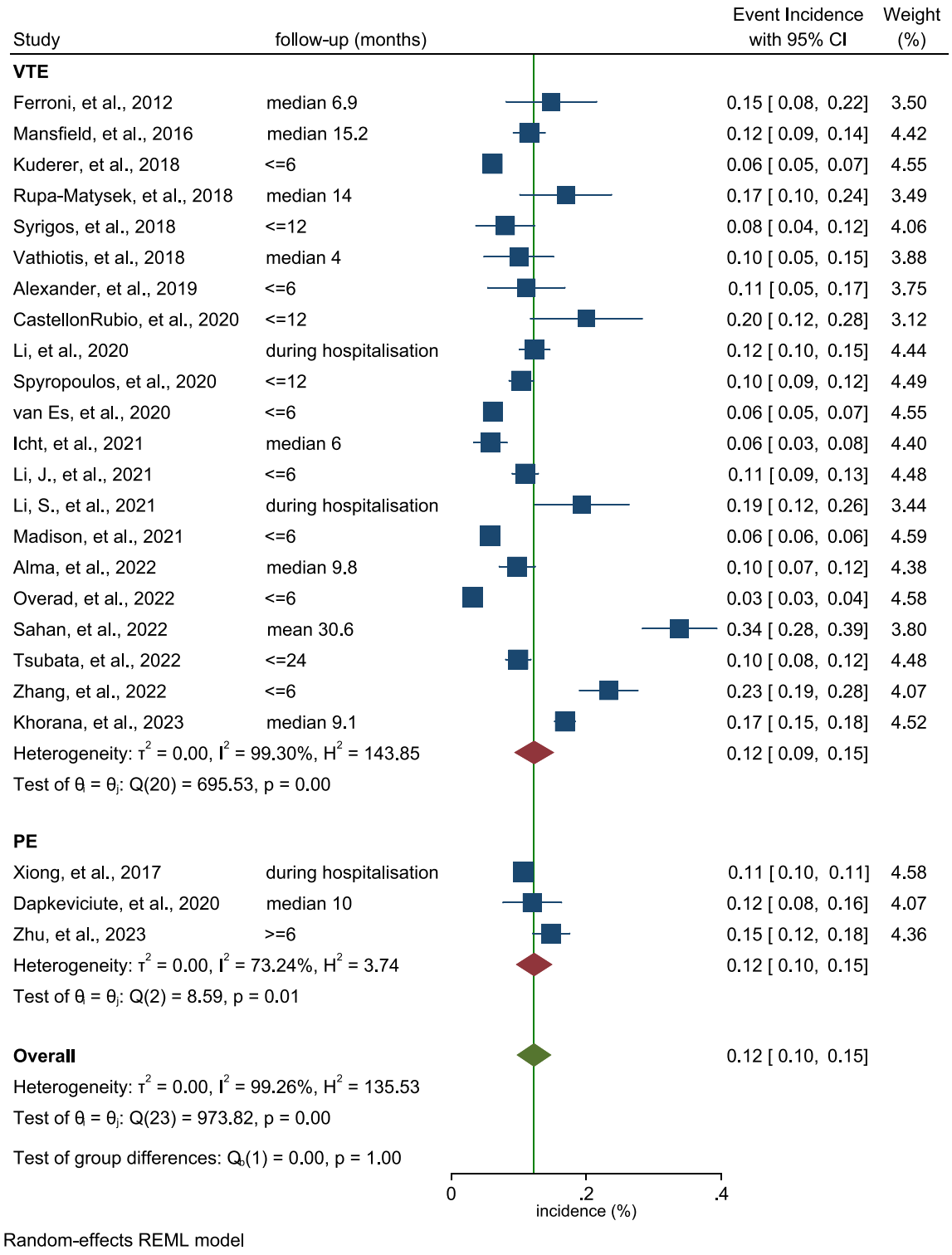

Fig. 2. Incidence of VTE/PE in patients with lung cancer.

in patients with non-small cell lung cancer (NSCLC) was associated with VTE occurrence (RR1.43, 95 % CI 1.08–1.88) (Fig. 4). However, the pooled sensitivity and specificity could not be estimated because of the insufficient number of included studies.

3.6. Other risk scores

PROTECHT and CONKO scores were each validated in three studies (Table 3). Both had poor discrimination capability, with an AUC around 0.50 [15,16,32]. The pooled data showed a RR of 1.41 (95 % CI 0.82–2.42) and 1.20 (95 % CI 0.69–2.08) with a high PROTECHT and CONKO score, respectively (Fig. 6). In terms of COMPASS-CAT score, the pooled data revealed a significant association between a score equal to or >7 points and VTE occurrence, with a RR of 4.68 (95 % CI 1.05–20.8) (Fig. 6). As the number of the included studies was less than four for the meta-analysis of each risk score, the pooled sensitivity and specificity were not estimated.

Another ten newly developed risk scores were identified in this

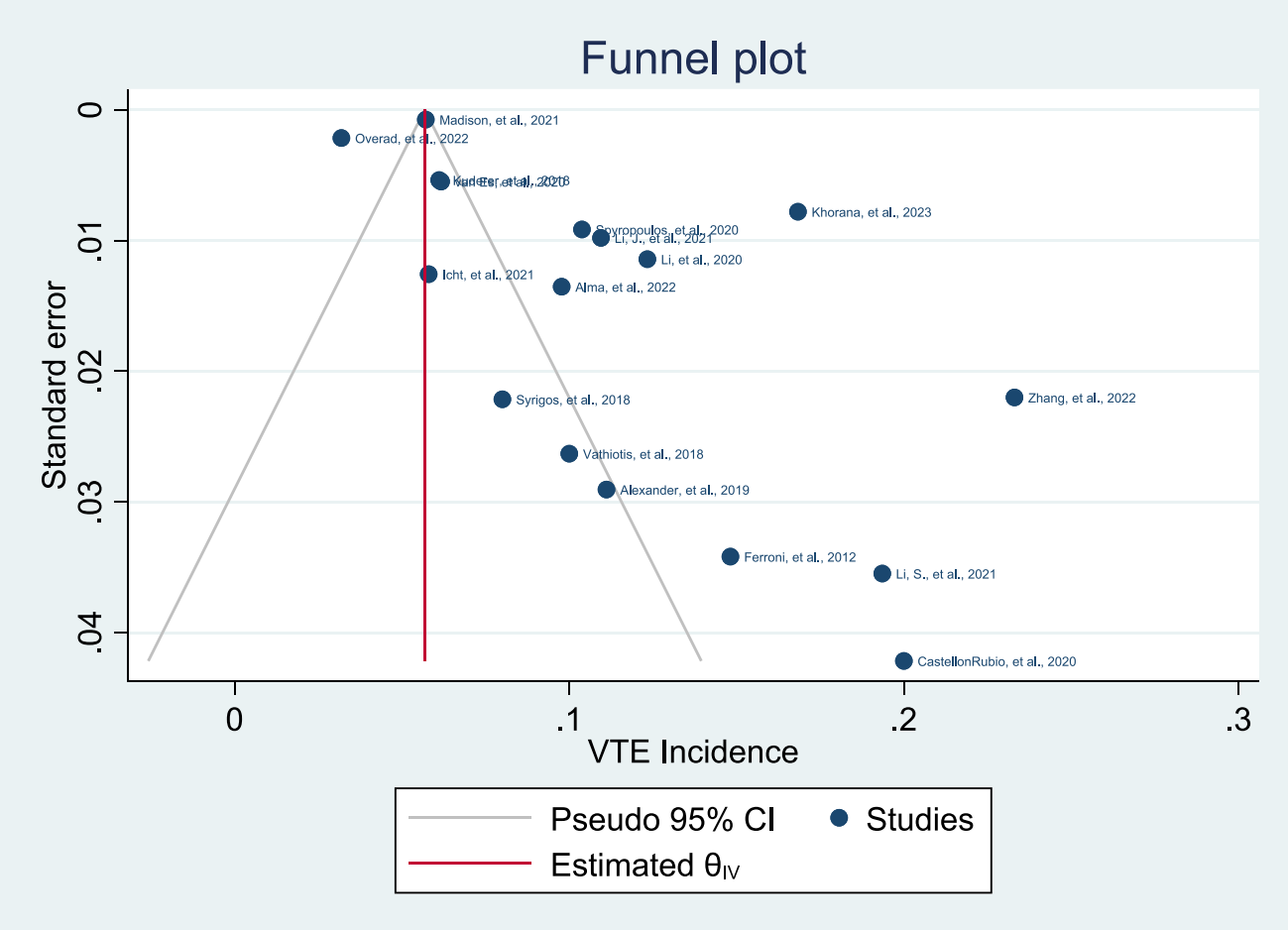

Fig. 3. Funnel plot of meta-analysis of 17 published studies with the incidence of VTE within 12 months.

systematic review, which included at least one biomarker and had a reasonably high AUC of between 0.67 and 0.93. Five of those risk scores solely consist of biomarkers [16,28,30,32] and the other five use a combination of biomarkers and patient-related and/or cancer-related factors [34,38,43,45,47] (Table 4). However, data could not be pooled for meta-analysis, because of their distinctive compositions.

4. Discussion

This review evaluated the risk of VTE in lung cancer patients with several validated risk assessment tools, including the Khorana, PROTECHT, CONKO and COMPASS-CAT scores. Of these risk tools, the Khorana score is the most studied (18 out of 24 (75 %) studies). However, meta-analyses showed that despite the change in the cut-off of 3 points to 2 points, the Khorana score was not able to stratify ambulatory lung cancer patients according to the risk of VTE. The current thromboprophylaxis guidelines for cancer patients only adopt the Khorana score for VTE risk stratification with the recommended cut-off value of 2 points [4–6]. Therefore, this review highlighted the need for updating the current guidelines for thromboprophylaxis for lung cancer patients.

The COMPASS-CAT score showed a significantly better discriminatory capability, but the pooled data was obtained from only three studies, with high heterogeneity. The study by Rupa-Matysek et al. had a median follow-up of 14 months [15], and the study by Syrigos et al. focused on PE instead of VTE [30], while the study by Spyropoulos et al. reported an insignificant discriminatory capability [35]. Further validation in patients with lung cancer is needed.

Although the Khorana score lacked discriminative capability in identifying patients at high VTE risk, its biomarker components (i.e., haemoglobin and platelet count) consistently showed an association with VTE risk in lung cancer patients [27] and were included in newly-developed risk models that demonstrated an intermediate to high discriminatory capability with an estimated AUC of 0.71–0.93 [43,45,47]. Also, the Khorana score was designed to be used in patients receiving chemotherapy [8], and it showed an association with VTE risk across the studies [15,27,28,34,36,39]; however, chemotherapy is not included in any of the risk models. With the investigation of VTE risk in patients receiving diverse anticancer treatment, it has been revealed that chemotherapy was related to a higher VTE risk than immunotherapy [46]. Therefore, VTE risk models should be treatment specific and expand their applicability by adjusting for treatment types.

Additionally, our review indicates that a combined use of more than one risk tool improves discrimination capability. When applying a risk tool with high specificity but low sensitivity, such as the Khorana score, patients in the intermediate risk group should be further stratified. All lung cancer patients score at least 1 point according to the Khorana score and are stratified as being at intermediate or higher VTE risk. Applying a second risk rule on the patients in the intermediate risk group could improve the sensitivity. As another example, a risk score consisting of more patient- and cancer-related factors (i.e., the COMPASS-CAT score) was used with a pure biomarker-based score (i.e., ROADMAP) [30]. Combined use of the two risk scores improved the specificity without loss of sensitivity [30].

While some other VTE risk factors were identified, discrepancies were seen within and between studies, such as smoking status and use of anticoagulation [29,32,39]. This may be caused by the different statistical techniques used. Three model-building methods were identified by this review: logistic regression model, Cox proportional hazard model

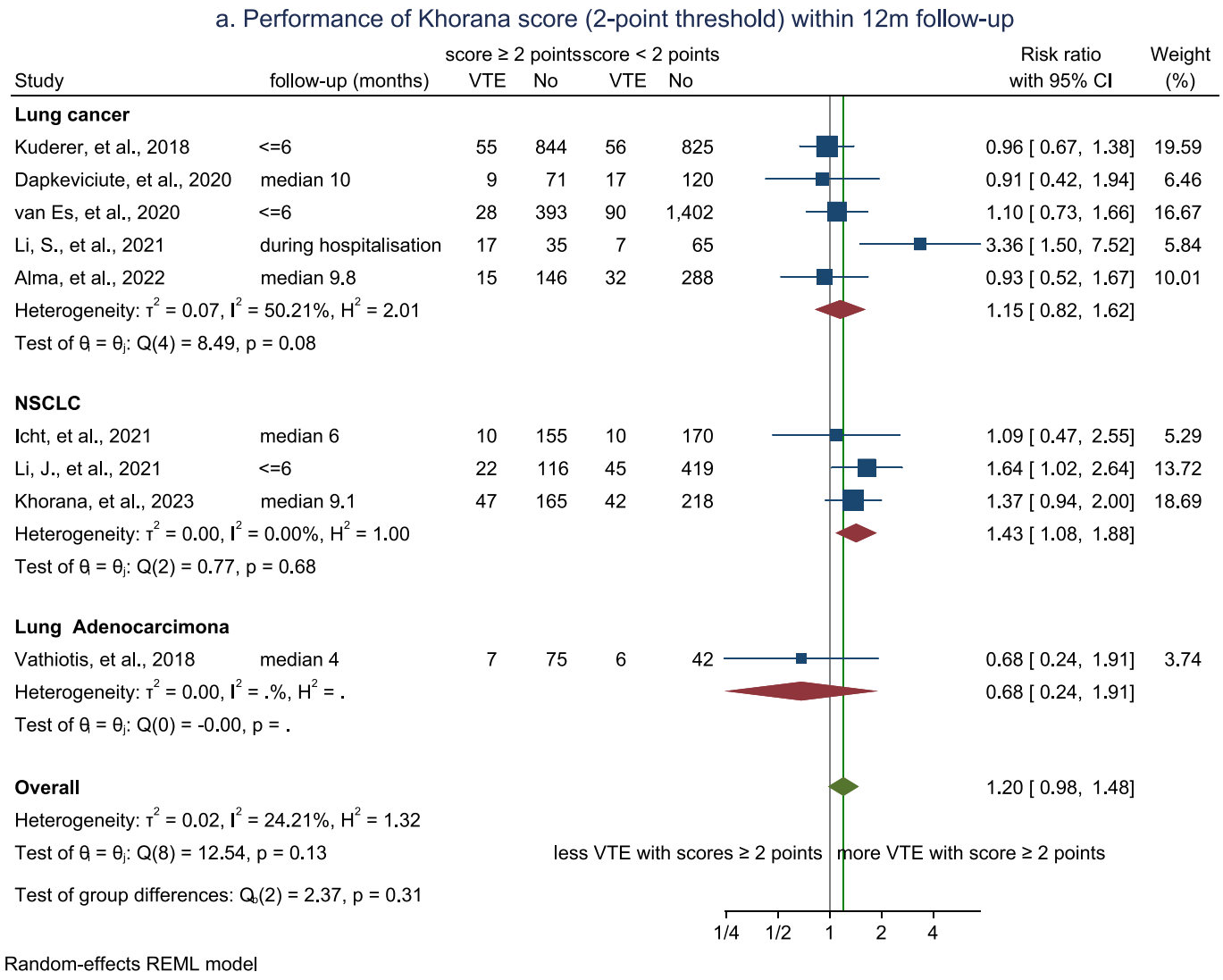

Fig. 4. Forest plots of overall and sub-group -analyses of performance of the Khorana score with threshold of 2 points (a) and 3 points (b), respectively, within 12-month follow-up.

and Fine-Gray subdistribution model. The latter two are time-to-event models. When competing risks exist, for example, cancer-related death is a competing risk for the VTE risk, a Fine-Gray subdistribution model is more accurate for risk prediction [48], while Cox proportional hazard models without competing risk overestimated VTE risk in lung cancer patients by 6.3 %–18.1 % [41]. More recently, joint models of longitudinal data and time-to-event have been developed, which are desired for investigating the predictive value of the changing-over-time biomarkers for VTE risk [49].

The high heterogeneity of the included studies is a major limitation of this review. Part of this heterogeneity is because of differences in the protocols of the included studies. For example, some studies recruited patients from diagnosis of lung cancer whereas others did this from the start of anticancer treatment, while other studies did not specify their patient recruitment time. Also, there were varying follow-up periods. Various VTE risk models with different thresholds for high VTE risk were tested in lung cancer patients or those with certain types of lung cancer, such as NSCLC or adenocarcinoma, and/or at a certain stage, such as IIIB and IV stages. Although the results showed the included studies were located globally, some limitation of this review is that the database Embase was not searched due to unavailability and only articles published in English were included, and it is possible that some other useful risk tools have not been identified and reviewed.

Another limitation of this study is the publication bias seen in the meta-analysis of the incidence of VTE in patients with lung cancer, which could have affected the accuracy of our findings. As shown in the funnel plot there might be an overestimation of the VTE incidence. The inconsistency in the incidence of VTE across the included studies could be caused by factors related to study designs, such as inclusion/exclusion criteria, sample size, and population characteristics. The study by Overad et al. reported the lowest VTE incidence and in this study patients with a history of VTE were excluded from the study [41]. This might have affected the reported incidence because having a history of VTE is a known risk factor of VTE in patients with cancer. On the other hand, among the four studies that reported the highest VTE incidence, two studies excluded patients without VTE assessment on vessel ultrasound examination or computed tomography pulmonary angiography [37,45]. By this criterion, the included patients with VTE assessment might have thrombotic symptoms or presence of VTE risk factors, and therefore were more likely to develop VTE. The study by Castellón Rubio et al. had a sample size of only 90 participants, which might have introduced bias due to small-study effects [32]; whereas, the study by Ferroni et al. had a very high proportion of metastasis (80 %) [26], which is related to high thrombotic risk [39,40].

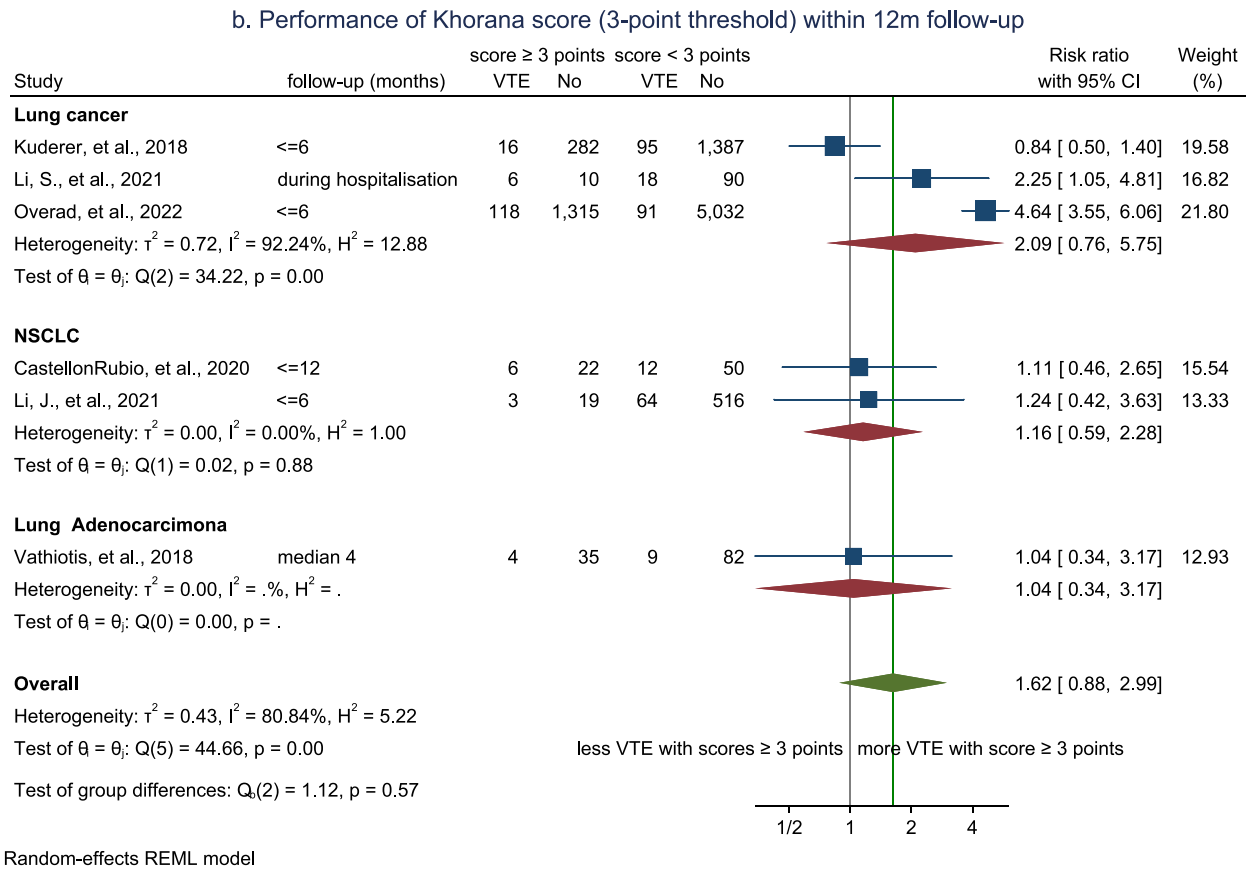

Fig. 4. (*continued*).

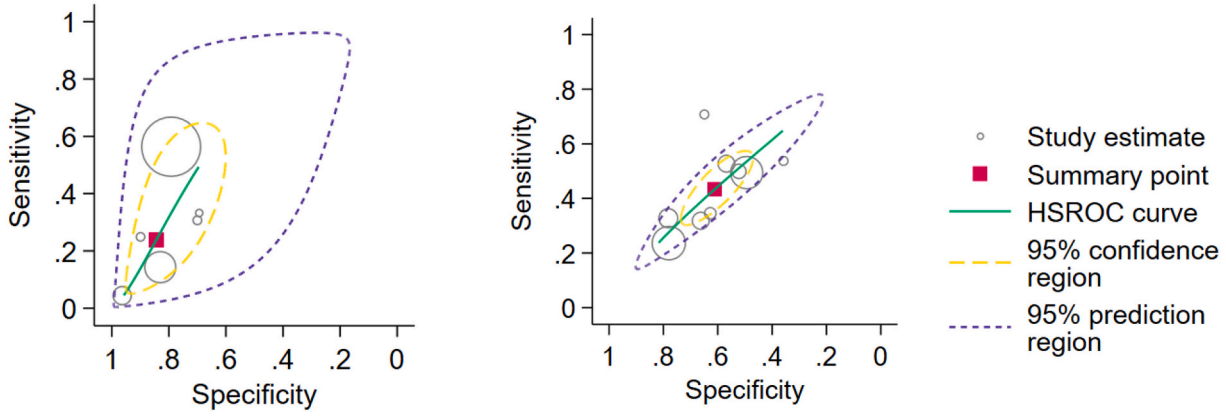

Fig. 5. HSROC curve. Left: the Khorana score with cut-off of 3 points; Right: the Khorana score with cut-off of 2 points.

Our review has also seen the improved discrimination capability of VTE risk models that contained biomarker(s). For instance, Tsubata et al. lowered the threshold of BMI from 35 kg/m^2 to 25 kg/m^2 to score 1 point, but the performance of the tool was not improved [44]. By contrast, when a high D-dimer value was added to the Khorana score for an additional 1 point, the modified tool had an improved AUC of 0.87 [37]. Notably, all the modified Khorana scores or new risk models that used D-dimer demonstrated significant associations with VTE occurrence. However, it was not possible to assess the usefulness of longitudinal biomarker risk assessment tools for VTE prediction as there was only one study reporting such a tool used in patients with lung cancer [16]. However, researchers have investigated longitudinal haemostasis biomarkers for VTE prediction in cancer patients and argued the repetition of VTE risk assessment over time [50,51]. Meanwhile, our review indicates the lack of other time-varying factors included in VTE risk tools, such as the administration of anticancer treatment changing over time. Incorporating longitudinal changes into risk tools would be of interest for future investigations.

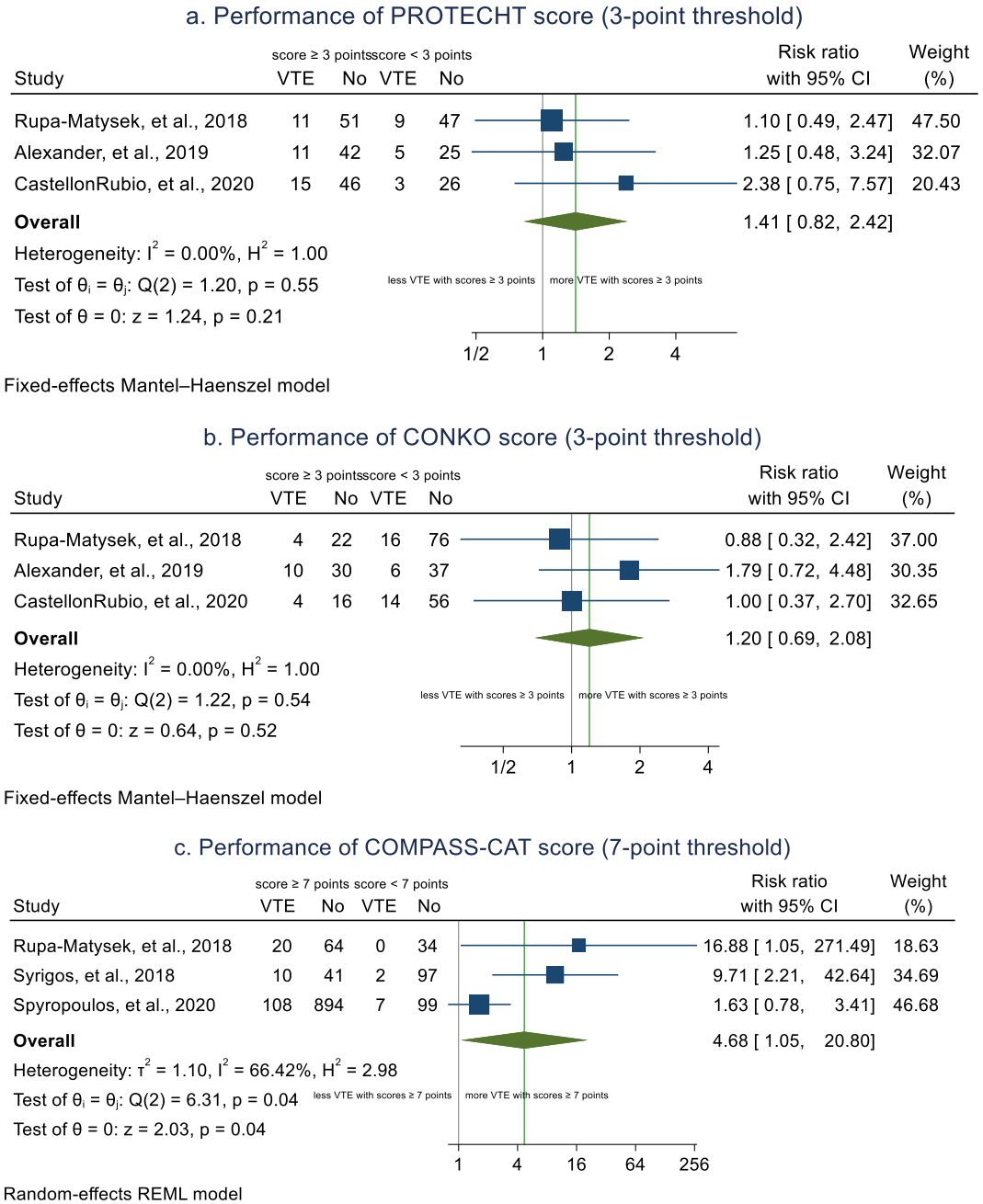

Fig. 6. Meta-analyses of performance of the PROTECHT (a), CONKO (b) and COMPASS-CAT (c) scores.

5. Conclusion

Our meta-analysis concluded that the Khorana score lacked the discriminatory capability of identifying patients with lung cancer at high VTE risk, regardless of the original 3-point cut-off value or the updated 2-point cut-off value. In addition, this review identified the COMPASS-CAT score had better performance, but further validation is needed. Our review also indicates the lack of time-varying factors included in VTE risk tools and therefore highlights the need for future research.

CRediT authorship contribution statement

Ann-Rong Yan: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Indira Samarawickrema:** Writing – review & editing, Validation, Supervision, Methodology. **Mark Naunton:** Writing – review & editing, Validation, Supervision, Methodology. **Gregory M. Peterson:** Writing – review & editing, Validation, Supervision, Methodology, Investigation. **Desmond Yip:** Writing – review & editing, Supervision. **Phillip Newman:** Writing – review & editing, Supervision, Methodology. **Reza Mortazavi:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2024.01.003.

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