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Models for predicting venous thromboembolism in ambulatory patients with lung cancer: a systematic review protocol

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ABSTRACT

Introduction Venous thromboembolism (VTE) is a common complication in patients with cancer and has a determining role in the disease prognosis. The risk is significantly increased with certain types of cancer, such as lung cancer. Partly due to difficulties in managing haemorrhage in outpatient settings, anticoagulant prophylaxis is only recommended for ambulatory patients at high risk of VTE. This requires a precise VTE risk assessment in individual patients. Although VTE risk assessment models have been developed and updated in recent years, there are conflicting reports on the effectiveness of such risk prediction models in patient management. The aim of this systematic review is to gain a better understanding of the available VTE risk assessment tools for ambulatory patients with lung cancer and compare their predictive performance.

Methods and analysis A systematic review will be conducted using MEDLINE, Cochrane Library, CINAHL, Scopus and Web of Science databases from inception to 30 September 2021, to identify all reports published in English describing VTE risk prediction models which have included adult ambulatory patients with primary lung cancer for model development and/or validation. Two independent reviewers will conduct article screening, study selection, data extraction and quality assessment of the primary studies. Any disagreements will be referred to a third researcher to resolve. The included studies will be assessed for risk of bias and applicability. The Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies will be used for data extraction and appraisal. Data from similar studies will be used for meta-analysis to determine the incidence of VTE and the performance of the risk models.

Ethics and dissemination Ethics approval is not required. We will disseminate the results in a peer-reviewed journal.

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Strengths and limitations of this study

► To the best of our knowledge, this is the first systematic review of venous thromboembolism risk assessment models for use in ambulatory patients with lung cancer.
► There will likely be heterogeneity among the included studies due to differences in study populations, research methods, anticancer treatments and the follow-up periods.
► The restriction to use articles published in English may introduce some bias.

the histological type, stage and aggressiveness of the cancer.[2] In patients with lung cancer receiving chemotherapy, the incidence of VTE during a median follow-up period of 12 months was reported to be as high as 13.9%.[3] It has been reported that having VTE is a significant predictor of death within 2 years in patients with primary lung cancer, with hazard ratios of 2.3 (95% CI 2.2 to 2.4) and 1.5 (95% CI 1.3 to 1.7) for non-small cell lung cancer and small cell lung cancer, respectively.[4]

The current American Society of Clinical Oncology Clinical Practice Guidelines for Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer only recommend thromboprophylaxis for patients whose risk of developing VTE has been assessed as high using a VTE risk prediction model called the Khorana Score.[5]

The Khorana Score was developed in 2008 for predicting VTE risk in ambulatory patients with cancer receiving chemotherapy.[6] It uses the following five items: cancer site, platelet count, leucocyte count, haemoglobin level and body mass index (BMI). In using this scoring tool, two points are allocated to very high-risk cancers (eg, stomach and pancreas), one point is given for high-risk cancers (eg, lung, lymphoma,

INTRODUCTION

Lung cancer is the second most common type of cancer globally and it has the highest mortality rate among all cancers.[1] Cancer is a risk factor for venous thromboembolism (VTE) and the incidence of VTE varies with

gynaecological, bladder, testicular), one point for baseline platelet count≥350 ×10^9/L, one point for baseline leucocyte count>11 ×10^9/L, one point for baseline haemoglobin level<100g/L or use of erythropoietin and one point for BMI≥35 kg/m^2.[6] In the original risk model, a total score of 0 indicates a low risk, a total score of 1–2 suggests an intermediate risk, and a score of 3 or more indicates a high-risk situation.[6] Recently, a different cut-off score of 2 was used in two randomised controlled trials to stratify the high-risk groups.[7 8]

An external validation study undertaken by Haltout *et al* on solid tumours reported a high specificity of 92.8% (95% CI 91.5% to 94.0%), but a poor sensitivity of 29.3% (95% CI 19.7% to 41.1%) for the original Khorana Score.[9] Furthermore, a meta-analysis of pooled data from 45 studies on outpatients with various types of cancer showed that only 23.4% (95% CI 18.4% to 29.4%) of the patients with cancer who developed VTE in the first 6months had been classified as high risk using the Khorana Score, no subgroup analysis was done on patients with lung cancer.[10] The Khorana Score may even have poorer predictive performance in ambulatory patients with lung cancer.[11] Several studies reported no statistically significant difference in the incidence of VTE between the stratified groups by the Khorana Score.[11–14] In another study, the poor discriminating capacity of the initial Khorana Score in ambulatory patients with lung cancer was also indicated by an area under the receiver operating characteristic curve (AUC) of only 0.51 (95% CI 0.39 to 0.63).[15]

Since its introduction, the Khorana Score has been modified several times by the addition and/or replacement of predictors. In the Vienna Modification or CATS Score, D-dimer and soluble P-selectin were added to the original list of predictors for the Khorana Score.[16] Similarly, in the PROTECHT Score, treatment-related factors, such as gemcitabine and platinum-based chemotherapy, have been added to the original score.[17] In another score (CONKO), which was developed in patients with advanced pancreatic cancer, the WHO Performance Status was added to the risk assessment model while BMI was removed.[18]

In terms of the complexity of the risk assessment tools, they range from a very simple model (e.g. the University of Texas MD Anderson Cancer Center Cancer-associated Venous Thromboembolim (MD-CAT) model) with only two factors, namely distant metastases and platinum therapy,[19] to more complicated models with both cancer-related and predisposing factors as well as platelet count (the COMPASS-CAT Score),[20] to a model which uses continuous D-dimer concentrations rather than a cut-off value (the Multinational Cohort Study to Identify Cancer Patients at High Risk of Venous Thromboembolism (the CATS-MICA) model.[21] Despite being potentially useful, having this many models may add to the practical complexity of VTE risk assessment in terms of choosing the best model for individual types of cancer or patients.

For assessing the risk of VTE in ambulatory patients with lung cancer, the PROTECHT Score and the CONKO Score both had a poor discriminating capacity, with an AUC of 0.53 (95% CI 0.40 to 0.66) and 0.59 (95% CI 0.45 to 0.73), respectively.[15] The COMPASS-CAT Score had an improved sensitivity of 83% but a worsened specificity of 51% (95% CIs were not reported).[22]

In our recent brief review, we identified some risk prediction models for VTE in ambulatory patients with lung cancer;[23] however, their performance is still largely unclear.[10 11 15 22 24] It is still uncertain how many VTE prediction models in total are available and which prediction model best suits the clinical purpose in terms of a reliable predictive performance in ambulatory patients with lung cancer.

This study will be performed with the following two key questions:
► What VTE prediction models are available to be used in adult ambulatory patients with lung cancer?
► Which VTE risk assessment model has the best predictive performance in adult ambulatory patients with lung cancer?

OBJECTIVES
The objectives of this systematic review are as follows:
1. Summarise the features of the existing VTE risk prediction models in ambulatory patients with lung cancer.
2. Conduct meta-analyses to estimate the overall performance of each risk model for predicting VTE in ambulatory patients with lung cancer within 12 months from the diagnosis of cancer.
3. Compare the performance of the existing models for predicting VTE in ambulatory patients with lung cancer by individual study findings or meta-analyses results.

METHODS AND ANALYSIS
Inclusion criteria
Patients
The systematic review will include published studies which were undertaken on adult ambulatory patients with primary lung cancer diagnosed by histopathology. For a study to be included, the diagnosis of VTE should be confirmed by appropriate reference methods (eg, ultrasonography or CT scan). A summary of inclusion and exclusion criteria can be found in box 1.

Type of studies to be included
This systematic review will include all study designs in which risk prediction models for VTE were developed and/or validated.

Time period
The follow-up period will be 12 months from the diagnosis of cancer or shorter if VTE or death from any cause occurs.

Box 1 Inclusion and exclusion criteria

Inclusion criteria
1. Full-text peer-reviewed journal articles of experimental or observational study types which developed or validated a prognostic model for venous thromboembolism (VTE) in adult ambulatory patients with primary lung cancer.
2. Primary lung cancer was diagnosed by histopathology.
3. VTE was confirmed by ultrasonography or CT scan or venogram or angiography or magnetic resonance or consensus by an expert panel.
4. VTE was identified within 1 year of the diagnosis of primary lung cancer.
5. Published from the inception of databases to 30 September 2021.
6. Published in English.

Exclusion criteria
1. Studies of VTE in patients on chronic (>2 months) antithrombotic or thrombolytic treatment at recruitment or during the follow-up period.
2. Studies of recurrent cancer-related VTE.
3. Duplication of the same study.
4. Full-text unavailable.

Predicted outcomes
The primary outcome (to be predicted) is VTE, confirmed by ultrasonography or CT scan or venogram or angiography or magnetic resonance or consensus by an expert clinical panel.

Secondary outcome (to be predicted) is death from any cause and other thrombotic events.

Search strategies
Full-text peer-reviewed journal articles will be searched on MEDLINE, Cochrane Library, CINAHL, Scopus and Web of Science for articles published in English from inception of the database to 30 September 2021. The search strategy is shown in online supplemental table S1. The strategy was developed in consultation with a medical librarian.

Study selection process
Two of the authors (A-RY and RM) will independently screen the preliminary search results for titles and abstracts using the inclusion and exclusion criteria (box 1) with discrepancies being referred to the third reviewer (MN) to resolve. Two reviewers (A-RY and RM) will then screen the full text of relevant articles and exclude irrelevant articles, with disagreements being resolved by a third reviewer (IS). The references of the included studies and additional sources (eg, systematic reviews) will be checked for any missed studies. The COVIDENCE platform will be used to record included/excluded studies.[25]

Data extraction
According to the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (the CHARMS checklist),[26] the following data will be extracted where available: first author, year of publication, study design, source of data, participant eligibility, recruitment, description and treatment, sample size, the number and/or incidence of outcomes defined above, missing data, follow-up period, the type of VTE risk model(s) and included predictors, the modelling method and evaluation, risk ratios or odds ratios (ORs) for the predictors (both overall and stratified), the model performance such as calibration (eg, calibration plot and Hosmer-Lemeshow test), discriminating capacity (eg, AUC and Concordance Index) and classification measures (ie, sensitivity, specificity, positive predictive value and negative predictive value), as well as the study limitations.

Data will be extracted from the included articles by A-RY using an Excel table and reviewed by RM and then double-checked by DY. If there are any required data that are not reported or unclearly presented in the paper, enquiries will be made from the corresponding authors via email. The COVIDENCE platform will be used to record extracted data from the included studies for assessment of study quality and evidence synthesis.[25]

Additional data
The risk of VTE is highest in the first three months following the diagnosis and remains relatively high during the first year (adjusted OR 53.5, 95% CI 8.6 to 334.3 for 0–3 months; adjusted OR 14.3, 95% CI 5.8 to 35.3 for 3–12 months and adjusted OR 3.6, 95% CI 2.0 to 6.5 between 1 and 3 years).[27] As a result, combining the numbers of VTE events that occurred within different follow-up periods will be meaningless. To facilitate a valid data synthesis, if the data for the 12-month follow-up period are not reported, the relevant information will be sought from the authors.

Quality assessment
The included studies will be assessed by the Prediction Model Risk of Bias Assessment Tool (PROBAST). PROBAST includes the following domains: participants, predictors, outcome and analysis, with two, three, six and nine signalling questions, respectively, to make a risk of bias (RoB) evaluation.[28]

The applicability of the original risk modelling studies to our review questions will also be assessed through PROBAST in the following three domains: participants, predictors and outcome.[28] Two reviewers (A-RY and RM) will independently assess the RoB and applicability for individual included studies and any discrepancies will be resolved by a third reviewer (GMP).

Data synthesis
All authors will participate in the development of the manuscript. Results will be reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidance.[29] A narrative synthesis will be reported with the characteristics of a range of VTE risk models from the included studies. Under each risk model, the data from the same follow-up period will be

synthesised for meta-analysis with Review Manager V.5.4 software (Copenhagen: the Nordic Cochrane Centre, the Cochrane Collaboration).

In the meta-analysis, studies will be weighted based on the assumptions about the distribution of the effect size and the definition of variance under the specific assumptions.[30] ORs with 95% CI of occurrence of VTE will be calculated to determine the pooled discriminating capacity of individual risk stratification models. Heterogeneity will be explored by using the χ^2 test, where a p value of <0.10 indicates significant heterogeneity. Inconsistency across studies will be then quantified with the I^2 statistic test, where an I^2 value between 50% and 75% indicates moderate heterogeneity, while a value of >75% indicates high heterogeneity. A fixed effect model will be used if there are low levels of clinical or statistical heterogeneity and a random effects model will be used when the heterogeneity is beyond 50%. A sensitivity analysis will be performed on subgroups based on cancer stages, metastases and anticancer treatment.

The analysis of publication bias will be assessed by using funnel plots with Egger's method if there are 10 or more studies included in the systematic review.[31] Sensitivity analysis will be performed to explore the source of heterogeneity, such as RoB.

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Supplementary Table 1. Search strategy on MEDLINE, Cochrane Library, CINAHL, Scopus and Web of Science.

MEDLINE via EBSCOhost, searching MeSH and keywords at all fields	
1	(MH "Lung Neoplasms+") OR lung-cancer OR lung-tumor* OR lung-tumour* OR lung-neoplasm* OR lung-adenocarcinoma* OR lung-carcinoma* OR lung-squamous-cell-carcinoma* OR SCLC OR large-cell-neuroendocrine-carcinoma* OR LCNEC OR carcinoid-tumor* OR carcinoid-tumour* OR NSCLC
2	(MH "Venous Thromboembolism") OR (MH "Venous Thrombosis+") OR (MH "Pulmonary Embolism+") OR venous-thrombosis OR thrombotic OR venous-thromboembolism OR thromboembolic OR VTE OR deep-vein-thrombosis OR DVT OR pulmonary-embolism OR PE OR catheter-related-thrombo* OR CRT OR cancer-associated-thrombo* OR CAT
3	(MH "Health Status Indicators+") OR (MH "Clinical Decision Rules") OR (MH "Risk Assessment+") OR (MH "Models, Statistical+") OR (MH "Multivariate Analysis+") OR (MH "Risk Factors+") OR (MH "Risk+") OR (MH "Predictive Value of Tests") OR (MH "ROC Curve") OR risk-model* OR risk-assessment OR risk-stratification OR risk-predicti* OR risk-scor* OR prediction-model* OR predictive-model* OR predictive-scor* OR prediction-tool* OR scoring-system* OR score-system* OR prognostic-model* OR multivariate-model* OR clinical-rul* OR prediction-rul*
4	1 AND 2 AND 3
Cochrane Library, searching keywords at All Text (MeSH search is not needed, because the results will be the duplicates of MeSH search in MEDLINE.)	
1	lung-cancer OR lung-tumor* OR lung-tumour* OR lung-neoplasm* OR lung-adenocarcinoma* OR lung-carcinoma* OR lung-squamous-cell-carcinoma* OR SCLC OR large-cell-neuroendocrine-carcinoma* OR LCNEC OR carcinoid-tumor* OR carcinoid-tumour* OR NSCLC
2	venous-thrombosis OR thrombotic OR venous-thromboembolism OR thromboembolic OR VTE OR deep-vein-thrombosis OR DVT OR pulmonary-embolism OR PE OR catheter-related-thrombo* OR CRT OR cancer-associated-thrombo* OR CAT

3	risk-model* OR risk-assessment OR risk-stratification OR risk-predicti* OR risk-scor* OR prediction-model* OR predictive-model* OR predictive-scor* OR prediction-tool* OR scoring-system* OR score-system* OR prognostic-model* OR multivariate-model* OR clinical-rul* OR prediction-rul*
4	1 AND 2 AND 3

CINAHL via EBSCOhost, searching CINAHL SH and keywords at all fields

1	(MH "Lung Neoplasms+") OR lung-cancer OR lung-tumor* OR lung-tumour* OR lung-neoplasm* OR lung-adenocarcinoma* OR lung-carcinoma* OR lung-squamous-cell-carcinoma* OR SCLC OR large-cell-neuroendocrine-carcinoma* OR LCNEC OR carcinoid-tumor* OR carcinoid-tumour* OR NSCLC
2	(MH "Venous Thromboembolism") OR (MH "Venous Thrombosis+") OR (MH "Catheter-Related Thrombosis") OR (MH "Pulmonary Embolism") OR venous-thrombosis OR thrombotic OR venous-thromboembolism OR thromboembolic OR VTE OR deep-vein-thrombosis OR DVT OR pulmonary-embolism OR PE OR catheter-related-thrombo* OR CRT OR cancer-associated-thrombo* OR CAT
3	(MH "Clinical Assessment Tools+") OR (MH "Risk Assessment") OR (MH "Models, Statistical+") OR (MH "ROC Curve") OR (MH "Multivariate Analysis+") OR (MH "Risk Factors+") OR (MH "Predictive Value of Tests") OR (MH "Sensitivity and Specificity") OR risk-model* OR risk-assessment OR risk-stratification OR risk-predicti* OR risk-scor* OR prediction-model* OR predictive-model* OR predictive-scor* OR prediction-tool* OR scoring-system* OR score-system* OR prognostic-model* OR multivariate-model* OR clinical-rul* OR prediction-rul*
4	1 AND 2 AND 3

Scopus, searching keywords at Article Title/Abstract/Keywords

1	TITLE-ABS-KEY (lung-cancer OR lung-tumor* OR lung-tumour* OR lung-neoplasm* OR lung-adenocarcinoma* OR lung-carcinoma* OR lung-squamous-cell-carcinoma* OR SCLC OR large-cell-neuroendocrine-carcinoma* OR LCNEC OR carcinoid-tumor* OR carcinoid-tumour* OR NSCLC)

2	TITLE-ABS-KEY (venous-thrombosis OR thrombotic OR venous-thromboembolism OR thromboembolic OR VTE OR deep-vein-thrombosis OR DVT OR pulmonary-embolism OR PE OR catheter-related-thrombo* OR CRT OR cancer-associated-thrombo* OR CAT)
3	TITLE-ABS-KEY (risk-model* OR risk-assessment OR risk-stratification OR risk-predicti* OR risk-scor* OR prediction-model* OR predictive-model* OR predictive-scor* OR prediction-tool* OR scoring-system* OR score-system* OR prognostic-model* OR multivariate-model* OR clinical-rul* OR prediction-rul*)
4	1 AND 2 AND 3

Web of Science Core Collection, searching keywords at Topic

1	lung-cancer OR lung-tumor* OR lung-tumour* OR lung-neoplasm* OR lung-adenocarcinoma* OR lung-carcinoma* OR lung-squamous-cell-carcinoma* OR SCLC OR large-cell-neuroendocrine-carcinoma* OR LCNEC OR carcinoid-tumor* OR carcinoid-tumour* OR NSCLC (Topic)
2	venous-thrombosis OR thrombotic OR venous-thromboembolism OR thromboembolic OR VTE OR deep-vein-thrombosis OR DVT OR pulmonary-embolism OR PE OR catheter-related-thrombo* OR CRT OR cancer-associated-thrombo* OR CAT (Topic)
3	risk-model* OR risk-assessment OR risk-stratification OR risk-predicti* OR risk-scor* OR prediction-model* OR predictive-model* OR predictive-scor* OR prediction-tool* OR scoring-system* OR score-system* OR prognostic-model* OR multivariate-model* OR clinical-rul* OR prediction-rul* (Topic)
4	1 AND 2 AND 3