BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-055322
Article Type:	Protocol
Date Submitted by the Author:	08-Jul-2021
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Keywords:	Respiratory tract tumours < THORACIC MEDICINE, Thromboembolism < CARDIOLOGY, Anticoagulation < HAEMATOLOGY

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

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Word count: 2113

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, Embase, and Web of Science databases from inception to current time, to identify all 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 (CHARMS) 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 waived for this research since the study is carried out on published papers. We will disseminate the results in a peer-reviewed journal.

Keywords: thromboembolism; respiratory tract tumours; anticoagulant

PROSPERO registration number: CRD42021245907

Strengths and limitations of this study

- To the best of our knowledge, this is the first systematic review of VTE 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, anti-cancer treatments, and the follow-up periods.
- The restriction to use articles published in English may introduce some bias.

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 the histological type, stage and aggressiveness of the cancer.[2] In lung cancer patients 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 two years in patients with primary lung cancer, with hazard ratios of 2.3 (95% CI 2.2-2.4) and 1.5 (95% CI 1.3-1.7) for non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), respectively.[4]

The current American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines for Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer, only recommend thromboprophylaxis in 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 cancer patients 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, 2 points are allocated to very high-risk cancers (e.g. stomach and pancreas), 1 point is given for high-risk cancers (e.g. lung, lymphoma, gynaecological, bladder, testicular), 1 point for baseline platelet count $\geq 350 \times 10^9$/L, 1 point for baseline leukocyte count $> 11 \times 10^9$/L, 1 point for baseline haemoglobin level < 100 g/L or use of erythropoietin, and 1 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 to 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 to stratify high-risk groups in two randomised controlled trials of anticoagulant thromboprophylaxis.[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%-94.0%), but a poor sensitivity of 29.3% (95% CI 19.7%-41.1%) for the initial 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% - 29.4%) of the cancer patients who developed VTE in the first six months had been classified as high risk using the Khorana score; no subgroup analysis was done on lung cancer patients.[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 lung cancer patients was also indicated by an area under the receiver operating characteristic curve (AUC) of only 0.51 (95% CI 0.39-0.63).[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 advanced pancreatic cancer patients, the World Health Organization (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 (the 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 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 0.40-0.66) and 0.59 (95% CI 0.45-0.73), 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, 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; and
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

This report adheres to the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) guidance (Table 1).[24]

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 (e.g. ultrasonography or computerised tomography). 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.

Predicted outcomes

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

Secondary outcomes (to be predicted) are death from any cause and other thrombotic events.

Patient and public involvement

It is not applicable, because this is a protocol for a systematic review.

Search strategies

Full-text peer-reviewed journal articles will be searched on Medline, Cochrane, CINAH, Embase and Web of Science for articles published in English from inception of the database to the current time.

The search syntax will be:

1. “lung cancer” OR “lung tumo?r” 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 tumo?r" OR NSCLC

2. "venous thromboembolism" OR thrombosis, thromboemboli*, VTE OR "deep vein thrombosis" OR DVT OR "pulmonary embolism" OR PE
3. "risk model*" OR "risk assessment" OR "risk stratification" OR "risk prediction" OR "risk scor*" OR "predict* model*" OR "predictive scor*" OR "prediction tool*" OR "scoring system*" OR "score system*" OR "prognos* predict*" OR "multivaria* predict*"
4. #1 AND #2 AND #3

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 (e.g. 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 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 for the predictors (both overall and stratified), the model performance such as calibration (e.g. calibration plot and Hosmer-Lemeshow test), discriminating capacity (e.g. AUC and Concordance index (C-index)) and classification measures (i.e. sensitivity, specificity, positive predictive value and negative predictive value), as well as the study limitations.

Data will be extracted from the included articles by author (A-RY) using an Excel table and reviewed by a second author (RM), and then double-checked by a third reviewer (DY). If there are any required data that are not reported or unclearly presented in the paper, enquiries will 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 diagnosis and remains relatively high during the first year (adjusted OR 53.5, 95% CI 8.6-334.3 for 0-3 months; adjusted OR 14.3, 95% CI 5.8-35.3 for 3-12 months and adjusted OR 3.6, 95% CI 2.0-6.5 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 ASessment 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 risk of bias 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 (PRISMA) 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 (RevMan) 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] Odds ratios (OR) with 95% confidence intervals (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 chi-square 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%.

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

CONCLUSION

Although some VTE risk prediction models have been developed and validated in ambulatory patients with cancer,[6 16-21] their performance is still largely unclear in patients with lung cancer.[10 11 15 22 32] Only with a reliable and robust VTE risk stratification can thromboprophylaxis be effectively administrated.[5] The results of this systematic review will help identify VTE risk prediction models with the best performance in ambulatory lung cancer patients.

Author Statement A-RY and RM initiated and designed the study. IS, MN, GMP and DY contributed to the study design. A-RY drafted the manuscript. All the authors took part in the revision and development of the manuscript and approved the final version.

Conflicts of interests None

Funding None

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Table 1 PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) 2015 checklist

Section and topic	Item No.	Checklist item	Reported on page No.
Administrative information			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	9
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	3-4

Section and topic	Item No.	Checklist item	Reported on page No.
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6-7
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7,13
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7-8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6

Section and topic	Item No.	Checklist item	Reported on page No.
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA

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 VTE in adult ambulatory patients with primary lung cancer; and
(2) Primary lung cancer was diagnosed by histopathology; and
(3) VTE was confirmed by ultrasonography or computerised tomography or venogram or angiography or magnetic resonance, or consensus by an expert panel; and
(4) VTE was identified within one year of the diagnosis of primary lung cancer; and
(5) Published from the inception of databases to 30/09/2021; and
(6) Published in English.

Exclusion criteria:

(1) Studies of VTE with genetic profiling only; or
(2) Studies of VTE in patients on chronic (>2 months) antithrombotic or thrombolytic treatment at recruitment or during the follow-up period; or
(3) Studies of recurrent cancer related VTE; or
(4) Duplication of the same study; or
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Models for predicting venous thromboembolism in ambulatory patients with lung cancer: a systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-055322.R1
Article Type:	Protocol
Date Submitted by the Author:	08-Nov-2021
Complete List of Authors:	Yan, Ann-Rong; University of Canberra Faculty of Health, School of Health Sciences Samarawickrema, Indira; University of Canberra Faculty of Health, School of Nursing, Midwifery and Public Health Naunton, Mark; University of Canberra Faculty of Health, School of Health Sciences Peterson, Gregory; University of Canberra Faculty of Health, School of Health Sciences; University of Tasmania College of Health and Medicine Yip, Desmond; Australian National University, Medical School; Canberra Hospital, Department of Medical Oncology Mortazavi, Reza; University of Canberra Faculty of Health, School of Health Sciences; University of Canberra Faculty of Health, Prehab Activity Cancer Exercise Survivorship research group
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Haematology (incl blood transfusion)
Keywords:	Respiratory tract tumours < THORACIC MEDICINE, Thromboembolism < CARDIOLOGY, Anticoagulation < HAEMATOLOGY

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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 Sept 30, 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 (CHARMS) 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.

Keywords: thromboembolism; respiratory tract tumours; anticoagulant

PROSPERO registration number: CRD42021245907

Strengths and limitations of this study

- To the best of our knowledge, this is the first systematic review of VTE 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, anti-cancer treatments, and the follow-up periods.
- The restriction to use articles published in English may introduce some bias.

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 the histological type, stage and aggressiveness of the cancer.[2] In lung cancer patients 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 two years in patients with primary lung cancer, with hazard ratios of 2.3 (95% CI 2.2-2.4) and 1.5 (95% CI 1.3-1.7) for non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), respectively.[4]

The current American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines for Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer, only recommend thromboprophylaxis in 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 cancer patients 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, 2 points are allocated to very high-risk cancers (e.g. stomach and pancreas), 1 point is given for high-risk cancers (e.g. lung, lymphoma, gynaecological, bladder, testicular), 1 point for baseline platelet count $\geq 350 \times 10^9$/L, 1 point for baseline leukocyte count $> 11 \times 10^9$/L, 1 point for baseline haemoglobin level < 100 g/L or use of erythropoietin, and 1 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 to 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 to stratify high-risk groups in two randomised controlled trials of anticoagulant thromboprophylaxis.[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%-94.0%), but a poor sensitivity of 29.3% (95% CI 19.7%-41.1%) for the initial 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% - 29.4%) of the cancer patients who developed VTE in the first six months had been classified as high risk using the Khorana score; no subgroup analysis was done on lung cancer patients.[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 lung cancer patients was also indicated by an area under the receiver operating characteristic curve (AUC) of only 0.51 (95% CI 0.39-0.63).[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 advanced pancreatic cancer patients, the World Health Organization (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 (the 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 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 0.40-0.66) and 0.59 (95% CI 0.45-0.73), 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; and
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 (e.g. ultrasonography or computerised tomography). 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.

Predicted outcomes

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

Secondary outcomes (to be predicted) are 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 Sept 30, 2021. The search strategy is shown in *Supplementary 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 (e.g. 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 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 for the predictors (both overall and stratified), the model performance such as calibration (e.g. calibration plot and Hosmer-Lemeshow test), discriminating capacity (e.g. AUC and Concordance index (C-index)) and classification measures (i.e. sensitivity, specificity, positive predictive value and negative predictive value), as well as the study limitations.

Data will be extracted from the included articles by author (A-RY) using an Excel table and reviewed by a second author (RM), and then double-checked by a third reviewer (DY). If there are any required data that are not reported or unclearly presented in the paper, enquiries will 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 diagnosis and remains relatively high during the first year (adjusted OR 53.5, 95% CI 8.6-334.3 for 0-3 months; adjusted OR 14.3, 95% CI 5.8-35.3 for 3-12 months and adjusted OR 3.6, 95% CI 2.0-6.5 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 ASessment 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 risk of bias 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 (PRISMA) 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 (RevMan) 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] Odds ratios (OR) with 95% confidence intervals (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 chi-square 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 anti-cancer treatment.

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

Patient and public involvement

There will be no patient or public involvement in the study.

Ethics and dissemination

Ethics approval is not required for this research. We will disseminate the results in a peer-reviewed journal.

Acknowledgements

We would like to acknowledge Mr Murray Turner (Faculty of Health, University of Canberra) for his professional advice on search strategies for all the databases.

Author Statement A-RY and RM initiated and designed the study. IS, MN, GMP and DY contributed to the study design. A-RY drafted the manuscript. All the authors took part in the revision and development of the manuscript and approved the final version.

Conflicts of interests None

Funding None

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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 VTE in adult ambulatory patients with primary lung cancer; and
(2) Primary lung cancer was diagnosed by histopathology; and
(3) VTE was confirmed by ultrasonography or computerised tomography or venogram or angiography or magnetic resonance, or consensus by an expert panel; and
(4) VTE was identified within one year of the diagnosis of primary lung cancer; and
(5) Published from the inception of databases to Sept 30, 2021; and
(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; or
(2) Studies of recurrent cancer related VTE; or
(3) Duplication of the same study; or
(4) full text unavailable.

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

Table 1 PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) 2015 checklist

Section and topic	Item No.	Checklist item	Reported on page No.
Administrative information			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	9
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	3-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5-6

Section and topic	Item No.	Checklist item	Reported on page No.
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5,6,12
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Suppl. Table
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6-7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility, and inclusion in meta-analysis)	6,12
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7-8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7-8

Section and topic	Item No.	Checklist item	Reported on page No.
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8,9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA