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Prediction models for venous thromboembolism in ambulatory adults with pancreatic and gastro-oesophageal cancer: protocol for systematic review and meta-analysis

Asma Zaheer ,[1,2] Nenad Naumovski ,[2,3] Kellie Toohey,[1,4] Theophile Niyonsenga ,[2,5] Desmond Yip,[6,7] Nicholas Brown,[2,8] Reza Mortazavi [1,2]

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For numbered affiliations see end of article.

Correspondence to
Dr Reza Mortazavi; reza.mortazavi@canberra.edu.au

ABSTRACT

Introduction Venous thromboembolism (VTE) is a common complication of cancer. Pancreatic and gastro-oesophageal cancers are among malignancies that have the highest rates of VTE occurrence. VTE can increase cancer-related morbidity and mortality and disrupt cancer treatment. The risk of VTE can be managed with measures such as using anticoagulant drugs, although the risk of bleeding may be an impeding factor. Therefore, a VTE risk assessment should be performed before the start of anticoagulation in individual patients. Several prediction models have been published, but most of them have low sensitivity and unknown clinical applicability in pancreatic or gastro-oesphageal cancers. We intend to do this systematic review to identify all applicable published predictive models and compare their performance in those types of cancer.

Methods and analysis All studies in which a prediction model for VTE have been developed, validated or compared using adult ambulatory patients with pancreatic or gastro-oesphageal cancers will be identified and the reported predictive performance indicators will be extracted. Full text peer-reviewed journal articles of observational or experimental studies published in English will be included. Five databases (Medline, EMBASE, Web of Science, CINAHL and Cochrane) will be searched. Two reviewers will independently undertake each of the phases of screening, data extraction and risk of bias assessment. The quality of the selected studies will be assessed using Prediction model Risk Of Bias Assessment Tool. The results from the review will be used for a narrative information synthesis, and if the same models have been validated in multiple studies, meta-analyses will be done to pool the predictive performance measures.

Ethics and dissemination There is no need for ethics approval because the review will use previously peer-reviewed articles. The results will be published.

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Strengths and limitations of this study

- This review will seek to stratify risk models according to their predictive performance for venous thromboembolism risk.
- The methodological issues identified by this review may help design more robust predictive models.
- High levels of heterogeneity across the studies may affect the feasibility of a meta-analysis.
- Exclusion of journal articles published in languages other than English is a limitation of this study.

INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), occurs as a serious complication of cancer.[1] The relationship between malignancy and a hypercoagulable state was first described by Armand Trousseau in early 19th century.[2] VTE is the second most common cause of death in patients with cancer.[3] Compared with the general population, patients with upper gastrointestinal cancer including gastro-oesophageal and pancreas have a 60-fold increased risk of developing a VTE[4] with approximately 13% diagnosed with a VTE prior to any intervention (eg, surgery or chemotherapy)[5] and 21% diagnosed with a VTE within 12 months from cancer diagnosis.[6 7]In addition to cancer itself, other factors such as treatment modalities (chemotherapy and surgery), and venous access devices may contribute to the risk or VTE in these patients.[8] Studies have suggested that development of VTE in patients with pancreatic or upper gastrointestinal cancer is associated with a poor prognosis.[8 9]

Several studies have demonstrated that thromboprophylaxis can significantly decrease the rate of VTE events in patients with pancreatic and gastric cancer, especially in outpatients.[10–14] However, the management of VTE risk in patients with cancer represents

a major challenge for clinicians, as the use of anticoagulants can increase the risk of potentially dangerous haemorrhage.[15] This risk is even higher in outpatients because they are beyond the observation of medical staff most of the time. Furthermore, although patients with pancreatic cancer have a higher risk for VTE compared with other types of cancer,[16] generally, they have twice the risk of major bleeds.[7] This highlights a need for the assessment of the risk of VTE in patients with ambulatory cancer before starting anticoagulation. This can be attained through using sensitive and reliable VTE risk prediction tools.

Predictive models in healthcare are statistical tools that use individual patient data (eg, demographics, patient history and biomarkers) to help estimate the likelihood of occurring an event, such as VTE, in a defined time.[17 18] An appropriately built and validated model can improve clinical decision making and improve patient management. Examples of clinical prediction models include the updated Vienna prediction model for the recurrence of VTE[19]; the Wells rule to predict DVT and PE in hospitalised patients[20 21]; and a well-known risk stratification tool called the Khorana score (KS),[22] designed to stratify cancer outpatients prior to the start of chemotherapy according to their risks of developing VTE.

A reliable predictive model for VTE in ambulatory patients with cancer may help reduce the number of patients needed to be treated for VTE by guiding clinicians towards taking a prophylactic approach in high-risk patients. As noted above, a widely used clinical VTE risk assessment tool is the KS which was derived and validated based on a split-sample method.[22] The KS was developed in 2008, using the data from a cohort of 2701 ambulatory patients with different types of cancer and it was further validated in another cohort of 1365 patients.[22] In the development of this score, a logistic regression model was used with five clinical and laboratory variables including the type of cancer, the patient's body mass index (BMI), the pretreatment platelet count, leucocyte count and haemoglobin level as well as the administration of erythropoietin stimulating agents.[22] Notably, for pancreatic and gastric cancers they assigned a score of 2 points, which means that these types of cancer are associated with very high risk of VTE. In the derivation as well as validation cohorts, rates of VTE were 0.8% and 0.3% in the low-risk category (score=1), 1.8% and 2% in the intermediate category (score 1–2) respectively, and 7.1% and 6.7% in the high-risk category (score ≥3) for a median follow-up period of 2.5 months. The two biggest advantages of KS are that first it uses patient data which are routinely available during the diagnosis or at the start of chemotherapy; and second, it has a high specificity of 93%.[23] However, the disadvantages include the model's low sensitivity (23%)[24] and its failure in differentiating patients with cancer with a low from those with a high risk of VTE.

Several independent investigators have validated the KS,[25–27] but its generalisability to all types of tumours remains controversial as different cancer types have produced mixed results. Studies in patients with pancreatic cancer have shown that the KS failed to discriminate high-risk patients from those at intermediate risk for VTE.[28–30] A possible explanation for the poor performance of this score in patients with pancreatic cancer may be that only <2% of patients who were included in the development and validation cohorts were patients with pancreatic cancer.[22] Furthermore, recent studies have reported no significant association between VTE risk and KS.[30–33] For instance, a randomised control trial enrolling 312 patients with pancreatic cancer showed that none of the KS parameters was associated with risk of VTE.[29] Similarly, a study including 112 participants found that risk stratification using KS was not predictive of VTE in the cohort of patients with gastric cancer.[33]

For outpatients with cancer, initially, a KS cutoff ≥3 was suggested to identify patients who are at high risk of VTE.[34] However, as mentioned above, it was realised that the KS has low sensitivity for certain types of cancer such as pancreatic cancer[30] and gastric cancer.[33] This issue is also applied to lung cancer.[31 35] A key reported disadvantage of KS was that more than 50% of patients fell into the intermediate risk group, making it difficult for the physicians to decide whether to use anticoagulation. To alleviate those shortcomings, in two independent trials,[36 37] undertaken to evaluate the effects of direct oral anticoagulation in ambulatory patients with cancer, a modified KS cut-off value of ≥2 was used. CASSINI[37] (Clinical Trials.gov identifier: NCT2555878) assessed the use of rivaroxaban in patients with solid tumours (over 50% of the study participants had diagnosis with very high-risk cancer types, ie, pancreatic or gastro-oesophageal) starting systemic antineoplastic therapy. The results not only showed significantly reduced VTE and VTE-related death during the treatment period, but also showed that the revised cut-off was able to identify patients with cancer who were at high risk of VTE both at baseline (4.53%) and during study (8.79%) (HR 0.66; 95% CI 0.40 to 1.09). The practicability of this revised cut-off value was recently confirmed by Mulder *et al* in a meta-analysis, using the KS cut-off value of two points or more reported a marked increase in proportion of patients from 17% to 47% in high-risk group with a decreased absolute risk of VTE from 11% (95% CI 8.8% to 13.8%) to 9% (95% CI 7.3% to 10.8%) in this group.[38]

To improve the predictive performance of KS, several modifications have been proposed, such as the addition of D-dimer and P-selectin by the Vienna group of Cancer And Thrombosis Study investigators (CATS score),[25] the inclusion of chemotherapeutic agents such as platinum-based regimens and gemcitabine as in the PROphylaxis of ThromboEmbolism during CHemoTherapy (PROTECHT) score,[39] or replacing BMI with the performance status (used to quantify general well-being and daily life activities in patients with cancer) as in the Charitié-ONKOlogie score.[29] The clinical usefulness of these risk assessment models remains a matter of debate

because most of these models performed well in the initial derivation studies but when externally validated, showed conflicting results.[28 40] A multinational prospective cohort study evaluated and compared the performance of all the above-mentioned risk scores for VTE in patients with solid cancer and found a poor discriminatory performance for all the scores. However, Vienna CATS and PROTECHT scores were found to distinguish better in low-risk and high-risk patients.[41]

Several clinical trials have also demonstrated that the risk of VTE can be reduced in patients with pancreatic cancer on anticoagulant prophylaxis.[10–14] Based on the results of these studies, the National Comprehensive Cancer Network recommended prophylactic treatment for patients with locally advanced or metastatic pancreatic cancer who are receiving chemotherapy.[42] The American Society of Clinical Oncology's (ASCO) practice guidelines does not recommend routine thromboprophylaxis in all ambulatory patients with cancer; however, they do recommend thromboprophylaxis for patients with KS of ≥2[43] if there are no contraindications. On the other hand, the National Institute for Health and Care Excellence recommended thromboprophylaxis only for patients with myeloma or pancreatic cancer.[44]

Because of the above-mentioned controversies, a better understanding of the strengths and limitations of the available published VTE risk prediction models applicable to the ambulatory patients with pancreatic or gastro-oesophageal cancer will be highly useful. To date, no systematic review has been conducted to assess the predictive performance of risk assessment models of VTE in those groups of patients with cancer. Therefore, this systematic review will seek to analyse and synthesise information regarding the predictive performance measures of the available models in assessing the risk of VTE in ambulate patients with pancreatic or gastro-oesophageal cancer.

Research question

In adult ambulatory patients with pancreatic or gastro-oesophageal cancer, which VTE risk prediction model has the best predictive performance (discrimination and calibration) during the first year following cancer diagnosis?

The research question has been outlined according to the PICOTS system[45] in table 1 below.

Table 1 PICOTS system for predictive models

Population	Adult ambulatory patients with pancreatic, gastric or oesophageal cancer receiving one or more of the treatment options including systemic chemotherapy, radiation therapy, immunotherapy and targeted therapy
Intervention	Use of internally/externally validated predictive models for VTE
Comparator	No predefined comparator. However, models will be compared with each other
Outcome to be predicted	Venous thromboembolism within 12 months from the cancer diagnosis
Follow-up period	12 months from diagnosis of cancer
Setting	Models used in ambulatory settings

VTE, venous thromboembolism.

Objectives of the systematic review

The objectives are as follows.

1. Identify all internally and/or externally validated prediction models in the published literature, which can be used to predict the risk of VTE in ambulatory patients with pancreatic, gastric or oesophageal cancer separately.
2. Summarise the characteristics of these prediction models according to valid guidelines such as 'Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies: The CHARMS Checklist'.[46]
3. Appraise the predictive accuracy (calibration, discrimination and classification measures) for the identified models.
4. If possible, compare the model performance measures of available risk prediction models by meta-analysing the reported performance statistics for the same time points across the studies.
5. Identify the predictors/risk factors for the occurrence of VTE in patients with ambulatory pancreatic, gastric or oesophageal cancers.

METHODS AND ANALYSIS

This study protocol is prepared in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Protocol[47] and the outcomes of the review will follow PRISMA statement 2020.[48] The methodology for data extraction and evaluation will be guided by the CHRAMS checklist[46] and the recommendations reported by Debray and colleagues.[45] The start date for this review is 1 August 2021, and the anticipated completion date will be the end of July 2022.

Eligibility criteria

Inclusion criteria

Study design

This review will include cohort studies (prospective or retrospective), case–control studies and clinical trials with at least one prediction model developed and/or validated. For randomised trials evaluating thromboprophylaxis, only control arms will be included for analysis. Also, reference list of systematic reviews and included articles will be searched to identify additional original studies

which were not found through the standard database searching.

Patient group

We will include studies which have developed or validated a prediction model for VTE on patients ≥18 years of age with pancreatic, gastric or oesophageal cancers diagnosed by histopathology, who were receiving one or more of the treatment options including systemic chemotherapy, radiation therapy, immunotherapy and targeted therapy. For a study to be included, the diagnosis of VTE should be confirmed by appropriate reference methods (eg, ultrasonography or CT). There is no restriction on the stage or grade of cancer. Studies with mixed population/cancer types will also be included provided that they report the relevant information for pancreatic, gastric or oesophageal cancer subgroups.

Intervention

Studies must report a prognostic model using multiple prognostic factors to predict the risk of VTE in ambulatory patients with pancreatic or gastro-oesophageal cancer.

Outcome

Primary outcome to be predicted: Composite of VTE events which includes symptomatic or incidentally detected VTE (including upper and lower deep and superficial venous thrombosis, splanchnic thrombosis and PE) and catheter-related thrombosis.

Settings

Studies developing models to be used in adult ambulatory patients with cancer.

Exclusion criteria

The review will exclude the following:

1. Studies enrolling patients under 18 years of age only.
2. Cancers other than pancreatic, gastric and oesophageal types.
3. Animal models, and *in vitro* studies.
4. Studies of VTE diagnosed 6 months prior to or more than 12 months after the diagnosis of cancer.
5. Studies enrolling patients on long-term (>2 months) anticoagulants, antithrombotic or thrombolytic treatment within 3 months prior to recruitment or within the follow-up period.
6. Studies on mixed types of cancer with no subgroup analysis for pancreatic, gastric or oesophageal cancers.
7. Studies occasionally reporting VTE as an adverse effect of intervention rather than a study outcome.
8. Studies purely focused on finding potential predictors of VTE rather than estimating the predictive performance of associated models.
9. Studies based on genetic profiling only.
10. Studies published in languages other than English.
11. Full text unavailable.

Information sources

We will search all records in the following databases.

1. Medline via EBSCOhost.
2. Cumulative Index to Nursing and Allied Health Literature via EBSCOhost.
3. Web of science.
4. EMBASE (Scopus).
5. Cochrane library.

Use of multiple databases will minimise the selection bias.[49 50]

Search strategy

We will use both electronic search and manual search strategies to identify relevant articles. The search strategy (below) was designed with assistance from a liaison librarian at the Faculty of Health, University of Canberra, and approved by all the coauthors.

One reviewer (AZ) will search the above-mentioned databases using a combination of subject terms with free-text terms and search filters suggested by Geersing *et al*.[51] The following search words are adopted for each data base : ("Venous Thromboembolism" OR VTE OR Thromboemboli* OR "cancer associated thrombosis" OR CAT OR thrombosis OR "Pulmonary embolism" OR PE OR "deep vein thrombosis" OR DVT) AND ("pancreatic cancer*" OR "pancreatic carcinoma*" OR "carcinoma of pancreas" OR "pancreatic tumor*" OR "pancreatic tumour*" OR "upper gastrointestinal cancer*" OR "upper gastrointestinal carcinoma*" OR "upper gastrointestinal neoplasm*"OR "Pancreatic Neoplasm*" OR "stomach cancer*" OR "gastric cancer*" OR "oesophageal cancer*" OR "esophageal cancer*" OR "cancer of the pancreas") AND ("risk model*" OR "risk assessment" OR "risk stratification" OR "risk prediction" OR "risk scor*" OR "predict* model*" OR "predictive scor*" OR "prediction tool*" OR "nomogram" OR "scoring system*" OR "score system*" OR "prognos* predict*" OR "multivaria* predict*" OR "stratification" OR "ROC curve" OR "discriminate" OR "c-statistics" OR " c statistic" OR " area under the curve" OR "AUC" OR "calibration" OR "indices" OR "algorithm" OR "Multivariable").

Boolean and proximity operators, parentheses, truncation commands will be used in line with the interfaces used for searching the databases. The search will cover from the start of indexing up to the date of publication submission. We will read the reference lists of included studies and relevant review articles to identify additional studies. If required, forward or backward citation will be used in the searching. Furthermore, relevant 'grey literature' will be searched via Google or MedNar. Each of the stages of systematic review including title and abstract screening, full text screening, risk-of-bias assessment and data extraction will be undertaken by two of the reviewers and the conflicts at each stage will be referred to a third reviewer for resolution.

An example of Medline search strategy is provided in online supplemental additional file 1. The outcomes of the review will be reported using PRISMA checklist 2020[48]

and PRISMA flow diagram will be used to show the selection process.

Study records

Data management

All study records will be processed through an electronic reference tool, EndNote V.20 (Clarivate Analytics), which will facilitate removing the duplicate results. Covidence (Veritas Health Innovation, Melbourne, Australia) will be used for streaming, extracting and recording included and excluded studies.

Study selection and data collection process

Title, abstract and full text screening will be performed by two researchers independently (AZ and RM) according to predefined criteria for inclusion and exclusion. Disagreements will be resolved by a third researcher (KT). Data extraction will be conducted by two researchers (AZ) and (RM). The extracted data will be checked by TN and NN.

Data items

Data extraction from selected studies will be guided primarily by CHARMS checklist.[46] The data extraction, where available, will include author, year of publication, study design, sample size, source of participants (eg, country, facility type, setting), eligibility criteria of selected participants, treatment or type of chemotherapy and description, study outcome(s),patient's performance status, stage of cancer, grade of cancer, missing data and methods of handling missing data, follow-up period, lost to follow-up, type of VTE risk model(s) and candidate predictors, number of events/sample size, incidence of VTE as well as ORs or risk ratios for the predictors, the modelling method and evaluation, model validated internally or externally (yes/no), model presentation (eg, full presentation of model is given including all variables and their beta weights), model performance such as discrimination (assessed using area under the receiver operating characteristic curve or C-statistics (Harrell's C-index),[52] calibration measures (eg, calibration plot and Hosmer-Lemeshow test), and classification measures (ie, sensitivity, specificity, positive predictive value and negative predictive values). Where an essential piece of information has not been reported for a study, the corresponding author will be contacted via an email for enquiries. Data from all included studies will be extracted using a Microsoft Excel spread sheet (version 2016, Microsoft Office).

Risk of bias assessment

Two researchers AZ and RM will independently assess the risk of bias and applicability of each included study using the Prediction model Risk of Bias ASsessment Tool (PROBAST).[53] Difficulties encountered, and the conflicts will be discussed and resolved by TN or NB. The PROBAST tool consists of signalling questions divided to four different domains: participants, predictors, outcome and statistical analysis. Risk of bias in each of the domains will be considered low if signalling questions can be answered with ('probably') 'yes'. Applicability assessment examines whether the model development/validation study matches our systematic review question in terms of the target population, predictors, or outcome of interest. An overall rating for each domain will be assigned as low, high, or unclear risk of bias.

Data synthesis

For each individual study, we will provide a qualitative overview of the model used. Study characteristics and results extracted using CHARMS[46]checklist, as guidance will be tabulated. This will include: (1) source of data; (2) participant population; (3) number of events/sample size; (4) type of model; (5) outcome type; (6) follow-up time; (7) number of predictors; (8) discrimination; (9) calibration; (10) internal/external validation (yes/no) and (11) presentation of the risk model.

We will use qualitative information synthesis to evaluate the performance characteristics of the models both individually and in comparison, to each other. The OR or HRs of risk factors/predictors (derived from published articles) will also be reported.

Clinical and methodological heterogeneity across studies will be assessed by considering variability in the participant's characteristics (e. g., age and sex distribution, setting), definition and measurement methods of outcome assessments and risk of bias. Statistical heterogeneity will be identified using Cochran's Q statistic, which indicates the presence ($p<0.05$) or absence ($p>0.05$) of heterogeneity. To quantify statistical heterogeneity, the I^2 statistic will be used. I^2 values between 0%–30%, 31%–50% and >50% will indicate mild, moderate and marked heterogeneity, respectively. A high amount of clinical or statistical heterogeneity may affect our choice of meta-analysis.

Meta-analysis will be undertaken to combine the reported performance measures of the individual models and estimate the overall performance index. If there is clinical heterogeneity among the included studies (or subsets of them), the random effects model approach will be used instead of the fixed effect approach. Depending on the availability of data, we will undertake separate meta-analyses for prospective and retrospective studies.

Meta-biases

If more than 10 studies are included in the review, reporting bias will be explored graphically using funnel plot, and statistically by Egger's test. As suggested, $p<0.05$ will be considered to indicate publication bias.

DISCUSSION

Studies have shown that VTE incidence is highest among pancreatic and gastro-oesophageal cancer. Several risk assessments models have been developed to help assess the risk of VTE in ambulatory patients with these types of cancer, but their predictive performance is less known. To the best of our knowledge, no systematic review or VTE prediction models in pancreatic or gastro-oesophageal

patients has been published. Thus, we plan to conduct a systematic review and meta-analysis on this subject topic. This review will identify various risk models currently in existence/use, identify their methodological strengths and limitations, and compare their performance measures. The results of this review will provide the clinicians and researchers with clearer evidence about the usefulness of the current VTE prediction models which can be used in ambulatory patients with pancreatic or gastro-oesophageal cancers. This protocol provides a detailed and complete description of the methodology of our intended systematic review.

This systematic review will have some limitations. First, only studies published in English will be included, which could make us lose data published in other languages. Second, we expect to find some heterogeneity across the included studies in the study population, study design, or other elements which may affect the feasibility of a meta-analysis. This could limit the generalisability of our systematic review's findings. The assessment of bleeding risk and identification of its predictors and risk factors will not be reviewed as it was considered to be out of scope of this review.

ETHICS AND DISSEMINATION

The proposed systematic review and meta-analyses will collect and analyse data from the published literature; therefore, ethical approval is not required. The results will be submitted for publication in a peer-reviewed journal and presented in a relevant conference. Data generated during the research will be available from the corresponding author on reasonable request.

Author affiliations
[1]Prehab, Activity, Cancer, Exercise and Survivorship (PACES) research Group, University of Canberra Faculty of Health, Canberra, Australian Capital Territory, Australia
[2]Faculty of Health, University of Canberra, Bruce, Australian Capital Territory, Australia
[3]Functional Foods and Nutritional Research (FFNR) Laboratory, University of Canberra Faculty of Health Sciences, Canberra, Australian Capital Territory, Australia
[4]School of Health Sciences, University of Canberra, Canberra, Australian Capital Territory, Australia
[5]School of Health Sciences, University of South Australia, Adelaide, South Australia, Australia
[6]Department of Medical Oncology, Canberra Hospital, Canberra, Australian Capital Territory, Australia
[7]ANU Medical School, Australian National University, Canberra, Australian Capital Territory, Australia
[8]Office of Executive Director of Allied Health,Canberra Health Services, Garran, Canberra, Australian Capital Territory, Australia

Twitter Kellie Toohey @kellietoohey and Reza Mortazavi @reza_mortazavi4

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ORCID iDs
Asma Zaheer http://orcid.org/0000-0002-7998-3446
Nenad Naumovski http://orcid.org/0000-0002-2841-4497
Theophile Niyonsenga http://orcid.org/0000-0002-6723-0316
Reza Mortazavi http://orcid.org/0000-0001-8885-0891

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