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REVIEW

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A systematic review of risk prediction model of venous thromboembolism for patients with lung cancer

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Abstract

Background: Venous thromboembolism (VTE) increases the risk of death or adverse outcomes in patients with lung cancer. Therefore, early identification and treatment of high-risk groups of VTE have been the research focus. In this systematic review, the risk assessment tools of VTE in patients with lung cancer were systematically analyzed and evaluated to provide a reference for VTE management.

Methods: Relevant studies were retrieved from major English databases (The Cochrane Library, Embase, Web of Science, PubMed, Scopus, Medline) and Chinese databases (China National Knowledge Infrastructure [CNKI] and WanFang Data) until July 2023 and extracted by two researchers. This systematic review was registered at PROSPERO (no. CRD42023409748).

Results: Finally, two prospective cohort studies and four retrospective cohort studies were included from 2019. There was a high risk of bias in all included studies according to the Prediction Model Risk of Bias Assessment tool (PROBAST). In the included studies, Cox and logistic regression were used to construct models. The area under the receiver operating characteristic curve (AUC) of the model ranged from 0.670 to 0.904, and the number of predictors ranged from 4 to 11. The D-dimer index was included in five studies, but significant differences existed in optimal cutoff values from 0.0005 mg/L to 2.06 mg/L. Then, three studies validated the model externally, two studies only validated the model internally, and only one study validated the model using a combination of internal and external validation.

Conclusion: VTE risk prediction models for patients with lung cancer have received attention for no more than 5 years. The included model shows a good predictive effect and may help identify the risk population of VTE at an early stage. In the future, it is necessary to improve data modeling and statistical analysis methods, develop predictive models with good performance and low risk of bias, and focus on external validation and recalibration of models.

KEYWORDS

lung cancer, risk prediction model, systematic review, venous thromboembolism

INTRODUCTION

Lung cancer is one of the malignant tumors with the highest incidence and mortality in the world,[1] and also with a high incidence and recurrence of venous

Yan Wang and Qiuyue Li are co-first authors.

[Correction added on 25 January 2024, after first online publication: a footnote stating that Yan Wang and Qiuyue Li were co-first authors was added.]

thromboembolism (VTE).[2] VTE is a venous return disorder in which blood clots abnormally in the veins, causing complete or incomplete blockage of the blood vessels, including deep vein thrombosis (DVT) and pulmonary embolism (PE).[3,4] There have been extensive studies and discussions on the relationship between tumor and VTE, and many have confirmed that cancer is a risk factor for VTE.[5] Compared with patients without cancer, patients with active cancer have a 5–6 times increased risk of VTE.[6,7] Especially in patients with lung cancer, the incidence of VTE was reported to be as high as 13.9% during a median follow-up period of 12 months among patients receiving chemotherapy.[8] In addition, the occurrence of VTE makes patients with lung cancer face a higher death risk and worse prognosis, and PE is the second leading cause of death in cancer.[9] Relevant studies have shown that patients with lung cancer with VTE as the primary manifestation have higher early mortality, which greatly increases the disease burden.[10,11] In a study of patients with primary lung cancer, VTE was a significant predictor of death within 2 years, with risk 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.[12]

A large amount of evidence has shown that VTE primary prevention can reduce the relative risk of VTE in cancer patients, which depends on the implementation of a VTE risk assessment model to achieve early screening, identification and intervention of high-risk groups of VTE.[13–15] However, the existing risk assessment tools have some shortcomings. At present, the Khorana score is the most used risk assessment tool for patients who plan to receive chemotherapy. It is often used to assess the risk of VTE in ambulatorized tumor patients during chemotherapy, mainly including tumor site, tumor type, platelet count, white blood cell count, hemoglobin and body mass index. The Khorana score ≥3 is classified as high-risk. However, in previous studies, its sensitivity and specificity were revealed to be low.[16,17] Other commonly used tools include the Vienna Cancer and Thrombosis Study (CATS), PROTECHT, CONKO, and Tic-ONCO scores, which are not tumor type-specific. In addition, the Caprini risk assessment model recommended by many guidelines cannot distinguish risk levels and is not suitable for patients with lung cancer.[18–25] Therefore, there is an urgent need to establish new risk prediction models to meet the needs of patients with lung cancer.

In recent years, there have been studies to explore the risk prediction model of VTE in patients with lung cancer, but whether it makes up for the shortcomings of the original risk prediction model is still unclear. Hence, this study systematically analyzed and evaluated the development process and effectiveness of existing VTE risk prediction models for patients with lung cancer, aiming to provide a basis and reference for the selection and in-depth development of VTE risk prediction models for patients with lung cancer.

#1 "Lung Neoplasms"[MeSH Terms]
#2 "Lung Neoplasms"[All Fields]
#3 "Lung cancer"[All Fields]
#4 "Lung tumor" [All Fields]
#5 "Lung neoplasia" [All Fields]
#6 ("lung"[All Fields] AND "neoplasms"[All Fields])
#7 "lung malignant neoplasm" [All Fields]
#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

#9 "venous thromboembolism"[MeSH Terms]
#10 "venous thromboembolism"[All Fields]
#11 "VTE"[All Fields]
#12 #9 OR #10 OR #11

#13 "risk assessment" [MeSH Terms]
#14 "predictive risk model" [All Fields]
#15 "prediction tool" [All Fields]
#16 "risk score"[All Fields]
#17 "prediction model" [All Fields]
#18 "risk prediction" [All Fields]
#19 #13 OR #14 OR #15 OR #16 OR #17 OR #18

#20 #8 AND #12 AND #19

FIGURE 1 The search strategy takes PubMed as an example.

METHODS

Study design

This systematic review was reported by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[26] The protocol of this systematic review has been registered in PROSPERO (registration no.: CRD42023409748).

Inclusion and exclusion criteria

Inclusion criteria: (1) Population: patients diagnosed with lung cancer by pathological examination and clinical imaging examination, and over 18 years old. (2) Research content: the construction of a VTE risk prediction model (excluding diagnostic model) describing the establishment, verification, and evaluation process. (3) Study types: cohort study, cross-sectional study and case–control study. (4) Literature language: Chinese or English.

Exclusion criteria: (1) Research content: validate and compare previously developed models. (2) Research method: predictive models based on artificial intelligence technology (such as neural networks or decision trees) only have the modeling process, but do not reflect the influencing factors and model effectiveness. (3) Study types: Review, review, systematic review, meta-analysis and other secondary literature. (4) Repeated publications. (5) Full text of the study is not available, (6) Informally published documents such as conference abstracts and disserations.

Literature search

Relevant studies were retrieved from major English databases (The Cochrane Library, Embase, Web of Science, PubMed, Scopus, Medline) and Chinese databases (China National Knowledge Infrastructure [CNKI] and WanFang Data) and searched until July 2023. At the same time, relevant reviews and included references were tracked.

Keywords: "lung tumor" "lung neoplasms" "venous thromboembolism" "risk prediction model" "risk assessment" free word "lung cancer" "lung tumor" "lung neoplasm" "lung neoplasia" "lung and neoplasms" "lung malignant neoplasm" "pulmonary malignant tumor" "venous thromboembolism" "VTE" "risk assessment" "the risk prediction model" "predictive tool" "risk score" "prediction model" "risk assessment" "risk prediction." The retrieval method takes PubMed as an example, as shown in Figure 1

Data extraction and quality assessment

Two researchers, Li Qiuyue and Wang Yan independently screened the literature, extracted the data, and then cross-checked it. If there was any disagreement, a third party's opinion was sought. After EndNote20 was used to deduplicate, the titles and abstracts were preliminarily screened, and then obviously irrelevant literature was excluded, further, the full texts were read through according to the inclusion and exclusion criteria to finally determine whether to include (rescreening).

Standardized tables were developed based on the factors and data extraction content of the prediction model research bias risk and suitability assessment. The data extraction content mainly includes the first author, publication year, country (region), study type, study object, sample size (excluding missing data), data source, prediction results, number of candidate predictors, processing methods of continuous variables, number of missing data and processing methods, sample size and number of result events of modeling group and validation group, events per variable (EPV), modeling method, and variable sieve method selection, degree of differentiation (C-index), degree of calibration, clinical utility, method of validation model, predictors included in model, model presentation form.

The Prediction Model Risk of Bias Assessment tool (PROBAST) was independently used by Li Qiuyue and Wang Yan to rigorously assess the bias risk and applicability of the included literature. If there was any disagreement, the opinions of the third party were solicited. PROBAST was launched in 2019 by Moons et al.,[27] Wolff et al.,[28] and consists of four fields: study subjects (2 questions), predictors (3 questions), results (6 questions), and data analysis (9 questions). The evaluation results in each area are classified as "low," "high," and "unclear." Each question is answered with "yes/maybe yes," "probably not/no," or "no information." If the results of bias risk assessment in the four areas are all "low", the overall risk of bias is judged to be "low." If the assessment result of bias risk in ≥1 domains is "high," the overall risk of bias is "high." If the risk assessment of bias in one area is "unclear" and the risk assessment of bias in other areas is "low," the overall risk of bias is considered "unclear." In addition, for model building studies, even if the risk of bias is assessed as "low" in all areas, the overall risk of bias is still "high" if the model is not externally validated. PROBAST mainly evaluates the applicability in the first three fields, and the applicability evaluation method is similar to the bias risk evaluation method.[27,28]

Statistical analysis

All results were narratively summarized and described without any quantitative synthesis due to variations in predictors and characteristics of participants among the included prediction models.

RESULTS

Search results and study characteristics

A total of 5155 relevant studies were retrieved, and after screening, six studies were finally included.[29–34] The literature screening process is shown in Figure 2.

The six included studies were mainly from China ($n = 5$) and Australia ($n = 1$). Two were prospective and four were retrospective studies. Among them, there were five English papers and one Chinese paper. Sample size (excluding missing data) ranged from 47 to 3398. The predicted results were VTE, as shown in Table 1.

Basic features of prediction model

The number of candidate predictors ranged from 5 to 11, and no study maintained the continuity of continuous variables. All the six studies converted all continuous variables into categorical variables. In terms of data missing and its processing methods, five studies did not mention whether there was data missing, only Li et al. used multiple interpolation to process missing values, but did not indicate the number of missing data. In the included studies, Cox and logistic regression were used to establish models. Univariate analysis was used for variable screening in all included studies, with EPV ranging from 5 to 15, and more details are presented in Table 2.

In terms of model performance, the area under the curve (AUC) of the overall receiver operating characteristic (ROC) curve ranged from 0.670 to 0.904. Except AUC <0.7 in the study by Alexander et al.,[29] AUC of other models were all >0.7, indicating that the models had a good performance. The calibration graph of Hosmer-Lemeshow goodness of fit test was used in two studies to verify the model,[30,32] while the calibration degree of the other four prediction models was not tested. Three studies used decision curve analysis to confirm the clinical utility of the prediction model.[31,32,34]

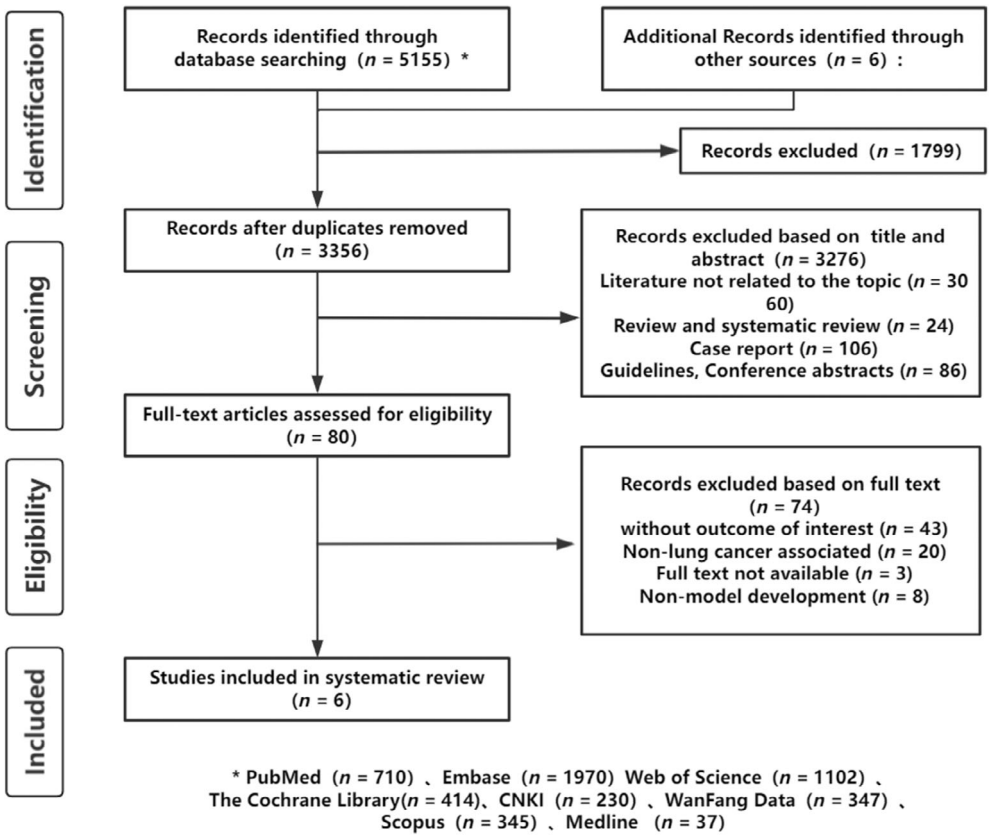

FIGURE 2 Literature screening process.

TABLE 1 General characteristics of the included studies ($n = 6$).

Author	Year	Region	Study design	Participants	Sample size	Data source	Outcome
Alexander et al.[29]	2019	Australia	P	A	170	A	VTE
Li et al.[30]	2020	China	R	B	827	B	VTE (DVT/PE)
Li et al.[31]	2021	China	P	C	1014	B	VTE
Li et al.[32]	2022	China	RC	D	819	C	VTE
Zhang et al.[33]	2022	China	R	E	47	C	VTE
Lei et al.[34]	2023	China	RC	D	3398	C	VTE

Abbreviations: DVT, deep vein thrombosis; P, prospective cohort study; PE, pulmonary embolism; R, retrospective cohort study; RC, retrospective case–control study; VTE, venous thromboembolism.

A, patients with NSCLC; B, patients with lung cancer; C, inpatients with NSCLC; D, inpatient with lung cancer; E, preoperative patient with lung cancer. A, cohort study data; B, case data; C, electronic medical record.

Three studies carried out external validation,[29,31,33] two studies carried out internal validation,[30,32] and one carried out both internal and external validation.[34] The model is presented in three main forms: additive scoring, scoring system and nomogram. The predictors can be divided into three categories: demographic factors, disease-related factors and laboratory examination indicators. Demographic factors are less involved, mainly gender and age.[30,33] Disease-related factors include clinical stage,[34,35] pathological type,[29,30,32] chemotherapy history,[30,32] central venous catheter,[30,32,34] Eastern Cooperative Oncology Group (ECOG) performance score, and so forth.[29,31] Laboratory indicators such as D-dimer, neutrophil count and hemoglobin level are more common,[29–33] as shown in Table 3.

Assessment of bias risk and applicability

All included studies had a high risk of bias.

In the object domain, two prospective studies were rated as low risk, and four retrospective studies were rated as high risk, among which two were retrospective cohort studies and two were retrospective case–control studies. Zhang et al. did not explicitly point out in the exclusion criteria that the diagnosis of VTE occurred after the diagnosis of lung cancer.[33] This may lead to bias in the study results, as shown in Table 4.

In the predictor domain, four studies were rated as high risk and two studies were rated as low risk. All the studies were single-center studies with no difference in evaluation. All the predictors involved were objective indicators, and

TABLE 2 Establishment of a VTE risk prediction model in patients with lung cancer.

	Candidate prediction variable		Missing data		Sample size	Number of outcome		Model development	
Author	Quantity	Continuous variables are converted into categorical variables	Quantity	Method	Build/verify	Build/verify	EPV	Method	Selection of variables
Alexander et al.[29]	5	ALL	-	-	129/—	25/—	5	A	Multifactor analysis
Li et al.[30]	8	ALL	-	-	496/331	62/39	8	B	Multifactor analysis
Li et al.[31]	6	ALL	-	-	602/412	66/45	11	B	Multifactor analysis
Li et al.[32]	11	ALL	-	Multiple interpolation method	819/351	165/69	15	B	Multifactor analysis
Zhang et al.[33]	4	ALL	-	-	141/51	47/17	12	B	Multifactor analysis
Lei et al.[34]	11	ALL	-	-	2379/1019	89/36	8	B	Multifactor analysis

Abbreviations: A, Cox's proportional hazards; B, logistic regression; EPV, events per variable; VTE, venous thromboembolism.

TABLE 3 Performance and predictive factors of VTE risk prediction models in critically ill patients.

	Model performance			Verification method		
Author	Distinction (AUC) Build/verify	Calibration	Clinical effectiveness (DCA)	Internal/external	Model presentation	Predictor
Li et al.[30]	0.819/0.827	H-L	-	Internal	Scoring system	(8) Gender, age, clinical stage, pathological type, chemotherapy history, surgical history, D-dimer, central venous catheter
Li et al.[31]	0.779/0.853	-	DCA	External	Scoring system	(6) ECOG, *EGFR* mutation, neutrophil count, hemoglobin level, CEA, D-dimer
Li et al.[32]	0.865/0.904	H-L	DCA	Internal	Nomograph	(11) BMI, adenocarcinoma, disease stage, central venous catheter, D-dimer level, PT level, fasting blood glucose, TG level, ROS1 rearrangement, history of chemotherapy, history of radiotherapy.
Alexander et al.[29]	0.670/—	-	-	External	Scoring system	(5) Chemotherapy, baseline D-dimer ≥1.5 mg/L, first month D-dimer ≥1.5 mg/L, baseline fibrinogen ≥4 g/L and D-dimer ≥0.5 mg/L, ECOG PS≥2
Zhang et al.[33]	0.880/0.878	-	-	External	Scoring system	(4) Age, homocysteine, D-dimer and fibrinogen concentration
Lei et al.[34]	0.843/0.791	-	DCA	Internal + external	Nomograph	(11) Karnofsky score, clinical stage, varicose veins, COPD, CVC, albumin, PT, white blood cell count, EGFR-TKI, dexamethasone, and beizumab

Abbreviations: AUC, area under the curve; BMI, body mass index; CEA, carcinoembryonic antigen; COPD, chronic obstructive pulmonary disease; CVC, central venous catheter; DCA, decision curve analysis; ECOG PS, Eastern Cooperative Oncology Group performance score; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; PT, prothrombin time; TG, triglyceride.

the evaluation and measurement methods tended to be consistent. On the question of the relationship between predictors and outcome information, prospective studies were rated "yes" and retrospective studies were rated "probably yes."

In the result domain, three studies were rated as low risk and three studies were rated as unclear. For the classification and definition of results, except Lei et al., which mentioned the specific definition and diagnostic methods of outcome indicators, the definition, diagnosis, and measurement

TABLE 4 Evaluations of the bias risk and applicability of the included models.

	Risk of bias				Applicability			Overall evaluation	
Author	Participant	Predictor	Outcome	Analysis	Participant	Predictor	Outcome	Risk of bias	Risk of applicability
Li et al.[30]	H	H	U	H	L	L	L	H	L
Li et al.[31]	L	L	L	H	L	L	L	H	L
Li et al.[32]	H	H	L	H	L	L	L	H	L
Alexander et al.[29]	L	L	L	H	L	L	L	H	L
Zhang et al.[33]	H	H	U	H	L	L	L	H	L
Lei et al.[34]	H	H	U	H	L	L	L	H	L

Note: H, high risk of bias, high applicability risk; L, low risk of bias, low applicability risk; U, unclear.

methods of VTE in other studies were all derived from clinical guidelines, and the definition did not include predictive factors, so they were all judged as "yes/possibly yes." The outcome indicator of VTE has clear evaluation criteria and has little relationship with whether the predictor was known. Therefore, the questions "Does the definition of outcome exclude information about predictors" were all rated "Yes" or "Probably yes"; As to whether the time interval between the assessment of the predictor and the determination of the result is reasonable, three studies have given clear time intervals, which are 6 months, 6 months and 22 months respectively, which have been proved reasonable by similar studies.[29,31,32] Another three studies have not mentioned the time interval and were evaluated as "unclear."[30,33,34]

In the data analysis domain, all included studies generally performed poorly in terms of "analysis" and were at high risk of bias. The events per variable (EPV) of three studies was less than 10,[29,30,34] and the EPV of the other three studies was between 10 and 20, which failed to meet the requirements.[31–33] The six studies did not maintain the continuity of variables, and all continuous variables were transformed into categorical variables. Only Li et al. mentioned the use of multiple interpolation method to deal with missing data,[32] while other studies did not mention the processing method of missing values. In the aspect of prediction factor screening, the multifactor analysis was carried out on the basis of single factor analysis. The processing of complex data is not mentioned in all studies; In terms of model performance evaluation, four studies did not report the calibration degree of the model, and two studies only reflected the calibration degree of the model with the statistical value and *p*-value of H-L goodness of fit test,[30,32] but failed to provide calibration charts, and did not normatively evaluate the model, so it was evaluated as "no/can" on the corresponding issues, as shown in Table 4.

The overall inclusion of the model and its applicability in various fields are good, as shown in Table 4.

DISCUSSION

The study of VTE risk prediction model for patients with lung cancer is still at the growing stage. This study systematically searched relevant studies on VTE risk prediction models for lung cancer, and finally included six studies after layer by layer screening. This study was first reported in 2019,[29] and other studies were also published in the last 2–3 years, indicating that this research problem has attracted the attention of scholars in related fields recently, especially Chinese scholars. It is of important clinical value to explore a VTE risk prediction model for patients with lung cancer that truly meets the needs of clinical application. The AUC of the included models ranged from 0.670 to 0.904, among which the AUC of the models developed in four studies was >0.8,[30,32–34] and that of the validated model in one study was >0.9,[32] indicating that the model had good prediction performance. All the included studies had a high risk of bias, mainly due to unreasonable processing of continuous variables, unreasonable processing of missing data, ignoring the overfitting problem of the model, small EPV, unstandardized evaluation of the model, and lack of external validation. There are few existing large-scale prospective studies, and multicenter large-scale prospective cohort studies are needed.

There is homogeneity in the VTE risk prediction model. The most common predictors of VTE risk prediction model in patients with lung cancer were age, clinical stage, pathological type, chemotherapy history, D-dimer, ECOG, central venous catheter, fibrinogen and lipid indexes. It suggests that clinical workers should pay attention to the early warning effect of the above indicators on the incidence of VTE in patients with lung cancer and strengthen the evaluation of it. However, it also shows that the risk prediction model of VTE shows a serious homogenization problem. Exploring new, personalized predictors could help break through existing development dilemmas.

Epidemiological studies have shown that VTE shares common risk factors with some arterial diseases, especially with atherosclerosis like smoking, obesity, hypercholesterolemia, hypertension, diabetes, and so forth. Myocardial infarction and heart failure can also increase the risk of VTE.[36–38] However, to facilitate practical evaluation, patients with the above risk factors were often excluded in the study process, and few researchers listed them as candidate predictors or included them in the prediction model, resulting in no precise exploration of their actual impact on

VTE in patients with lung cancer. Next, conducting relevant real-world studies should be considered to develop predictive models that are more operable in clinical applications. For instance, considering that the occurrence of VTE in patients with lung cancer is different in gender and age, it is also possible to further develop a gender and age-based differential prediction model.

At the same time, it is necessary to further explore the mechanism of VTE formation at the genetic level. Studies have shown that genotype may be a key factor in hypercoagulability and the occurrence of VTE.[35] A prospective study investigating the relationship between common driver oncogene alterations and VTE development in the NSCLC cohort showed that epidermal growth factor receptor (EGFR) mutation was inversely associated with VTE risk, while anaplastic lymphoma kinase (ALK) rearrangement was positively associated with VTE risk.[39,40] However, it has not been widely confirmed, and more research is needed in the future.

The optimal cutoff value of D-dimer needs further study. D-dimer, the smallest degradation product of fibrin, is produced by the hydrolysis of fibrin by fibrinase and is a specific marker indicating the activation of the fibrinolytic system and hypercoagulability in patients.[41] Among the included studies, the D-dimer index was involved in five studies, but there were significant differences in the determination of the optimal cutoff value, which were 0.55 mg/L,[30] 0.00014 mg/L,[31] 2.06 mg/L,[32] 1.5 mg/L,[33] 0.0005 mg/L,[29] respectively.

Studies have confirmed that the increase in D-dimer concentration is a sensitive indicator of preoperative VTE occurrence.[33] However, the concentration of D-dimer will also increase in cases such as infection, heart failure, tumor, myocardial infarction, stroke and chronic kidney disease.[42] Chinese Expert Consensus on perioperative VTE prevention of thoracic malignant tumors pointed out that the increased D-dimer concentration is highly sensitive in the diagnosis of suspected VTE, and normal D-dimer level can assist the diagnosis of VTE, which reduces unnecessary clinical examination and avoids unnecessary anticoagulant therapy.[43] However, the guidelines focused on perioperative lung cancer patients and did not take into account the impact of chemotherapy on patients. In fact, patients with tumors could also be affected by chemotherapy drugs, some of which may interfere with coagulation factors and lead to abnormal coagulation function, thereby causing the increase of D-dimer.[13] In the future, the effects of surgery and chemotherapy on patients should be comprehensively considered. In addition, previous studies have shown that the plasma D-dimer level of patients with lung cancer is generally high, which is greatly affected by age, and the difference in lung cancer stage and pathological type may change the optimal critical value for the diagnosis of PE with plasma D-dimer.[44,45] Subgroup analysis based on lung cancer stage and pathological type needs to be further explored in future studies.

In conclusion, this systematic review showed that VTE risk prediction models for patients with lung cancer have only been paid attention to in the past 3 years. There are few newly developed risk prediction models, and the predictive performance of most models has not been evaluated. The high AUC of the models included in this study suggests that the models have good predictive performance, but all models have significant statistical processing problems, so that there is generally a high risk of bias. Second, the existing models have obvious homogeneity and poor clinical operability. It is suggested that large-scale real-world studies should be conducted based on the actual situation of patients in view of the particularity of the treatment of patients with lung cancer, various risk factors should be fully verified and analyzed, and the internal mechanism of the formation of VTE in lung cancer patients should be explored further, such as the relationship with tumor genotypes. In addition, the optimal threshold value of D-dimer is still controversial, and subgroup analysis based on lung cancer stage and pathological type needs to be further explored in future studies.

There are some limitations in this study. The heterogeneous results of different studies are not quantitatively integrated, which limits the comparability of the research model. Second, despite our exhaustive literature search, some gray literature may have been missed, which may have resulted in an underestimation of the number of models.

AUTHOR CONTRIBUTIONS

Yan Wang was involved in the conception of the project, extraction and analysis of the data, and drafting and revision of the manuscript. Qiuyue Li was involved in the conception of the project, performed the extraction, acquisition, and analysis of the data, and drafted the manuscript. Yanjun Zhou was involved in the processing of the data and the data analysis. Jinping Li was involved in the processing of the data and the data analysis. Yiting Dong critically revised the manuscript for important intellectual content. Tao Liang was involved in the conception of the project and critically revised the manuscript for important intellectual content.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there is no competing interest.

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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