Stratification of Risk Factors of Lung Cancer-Associated Venous Thromboembolism and Determining the Critical Point for Preemptive Intervention: A Systematic Review With Meta-analysis

Clinical Medicine Insights: Oncology
Volume 17: 1–10

DOI: 10.1177/11795549231175221

Theresa Nwagha[1] and Martins Nweke[2,3]

[1]Department of Haematology and Immunology, Faculty of Medicine, University of Nigeria Teaching Hospital Ituku-Ozalla, Enugu, Nigeria. [2]Department of Physiotherapy, Evangel University, Akaeze, Nigeria. [3]Fledgelight Evidence Consult, Enugu, Nigeria.

ABSTRACT

BACKGROUND: Several biomarkers or risk factors have been identified and several prediction models exist. The major limitations inherent in these models include cost-ineffectiveness and lack of systematic stratification of risk factors resulting in the inclusion of clinically insignificant biomarkers in the models. This review aimed to systematically stratify the risk factors of lung cancer-associated venous thromboembolism (VTE) and determine the critical point for preemptive intervention.

METHODS: This systematic review was structured as per the Preferred Reporting Item for Systematic Reviews and Meta-analyses. We searched MEDLINE, PubMed, Cochrane Library, CINAHL, Academic Search Complete, and PsycINFO from the onset to June 2022. We included studies that reported the risk factors of lung cancer-associated VTE and corresponding risk estimates, irrespective of treatment status but studies were excluded if patients were on anti-VTE medications. We employed random effects models of meta-analysis and computed risk stability index and risk weight (Rw) to achieve the review objectives. The review protocol is registered with PROSPERO (CRD42022336476).

RESULTS: The clinically significant risk factors of VTE in lung cancer patients were D-dimer (odds ratio [OR] = 5.510, 95% CI = 2.6-11.7; Rw = 5.0), albumin (OR = 2.2, 95% CI = 1.0-4.8; Rw = 1.79), leukocyte (OR = 2.48, 95% CI = 1.9-3.2; Rw = 1.77), histological type (OR = 1.69, 95% CI = 1.2-2.4; Rw = 1.3), age (OR = 1.56; Rw = 0.99), and hemoglobin (OR = 1.85, 95% CI = 1.3-2.6; Rw = 0.92). Based on the distribution of Rw across risk factors, the critical point (upper third of the upper quartile class) was 4.5 and may mark the point at which preemptive intervention should be commenced.

CONCLUSIONS: Targeted screening for VTE in lung cancer patients could be patient-specific and should be based on a combination of the most significant risk factors required to meet the critical point, provided that such a combination is affordable as illustrated in the ALBAH model.

REGISTRATION: The review protocol is registered with PROSPERO (ID: CRD42022336476).

KEYWORDS: Lung cancer, venous thromboembolism, risk stratification, preemptive intervention, evidence synthesis

RECEIVED: January 08, 2023. **ACCEPTED:** April 20, 2023.

TYPE: Systematic Review

FUNDING: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The research cost was borne by Nwagha T.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Martins Nweke, Department of Physiotherapy, Evangel University, Akaeze, Ebonyi, Nigeria. Email: martins.nweke@gmail.com

Introduction

Cancer-related thrombosis is a leading cause of death in people with cancer, with venous thromboembolism (VTE) being the most prevalent kind.[1] VTE is four to seven times more likely in cancer patients than in non-cancer patients, with roughly 15% of cancer patients experiencing a VTE event.[2] Lung cancer is one of the most prevalent types of malignant tumor and the main cause of cancer-related death worldwide.[3-5] After the onset of VTE, the 1-year mortality rate is as high as 61%.[6] The risk of VTE in lung cancer patients can be as high as 4% to 20%.[6] The prognosis for VTE related to cancer is poor, increasing morbidity, death, and medical costs.[7] Due to the considerable death and economic burden associated with VTE in lung cancer patients, early identification and prophylaxis remain the mainstay intervention.[8]

Several VTE risk factors have been identified in pursuit of early detection of VTE and prophylaxis in lung cancer patients.[6] Risk factors of lung cancer-associated VTE have been classified into patient-, disease-, and treatment-related factors.[6] Some examples include body mass index (BMI),[9] age,[10] lower extremity varicose veins,[11,12] cardiovascular disease risk factors such as hypertension[13] and atrial fibrillation,[8] ALK rearrangements,[14] KRAS mutation,[15] histological type,[16] clinical stages,[17] tumor grade,[18] time after diagnosis,[6] chemotherapy,[16] high D-dimer level,[19] platelets,[20] P-selectin,[21] leukocytes,[22,23] hemoglobin,[22] among others. Likewise, risk assessment models have been developed to predict VTE in lung cancer patients and improve the efficacy of prophylaxis.[7] They include the Khorana risk score (KRS),[23] Vienna CATS,[24] PROTECHT score,[2] CONKO score,[25] and COMPASS-CAT,[26] although they generic models

for solid tumors. There is currently no VTE model specific to lung cancer.

Although systematic approach was employed toward risk identification, and estimating risk weight (Rw), the lack of systematic pooling of data representative of global community as well as lack of data on risk stability index (Ri) otherwise known as reliability of risk factors measured by the preponderance of risk factors are of fundamental flaws in these models. Furthermore, some of the preexisting models[24,26] assimilate biomarkers that an average person in low- and middle-income countries (LMICs) cannot afford. Interestingly, although most of the model were built from a large database of data, the models were limited in terms of geographical boundaries, with data drawn mostly from high-income American and European countries. The use of systematic pooling of data across the globe and estimation of risk stability will certainly improve model performance amid proffering cost-effective options. Without doubt, the current state-of-the-art cancer-associated VTE risk assessment approach, unsurprisingly, leaves a lot of room for improvement. For example, the most validated KRS has been associated to some drawbacks including not being validated or discriminatory in lung cancers,[27,28] the inability to identify patients with low KRS who develop cancer-associated VTE,[29] among others. These flaws could be linked to a lack of systematic pooling and stratification of cancer-related VTE risk factors resulting in the inclusion of clinically unreliable risk factors/biomarkers in the models. Also, the current models failed to account for racial disparities in the distribution of cancer-associated VTE, especially where there is enough data to construct regional-specific risk assessment models. Hence, this study aimed to systematically pool data and stratify the risk factors of lung cancer-associated VTE and determine the critical point for preemptive intervention.

Methods

Design

This is a systematic review of epidemiological studies to systematically pool relevant data and stratify the risk of lung cancer-associated VTE. The protocol was structured using the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) checklist.[30] The protocol was registered with PROSPERO (Registration ID: CRD42022336476).

Eligibility criteria

The review included cross-sectional, case-control, and cohort studies that documented the risk of lung cancer-associated VTE. We included articles written and published in English and French. Quantitative observational studies were included irrespective of the sample size, sampling technique, and test statistics. However, only studies with a low or moderate risk of bias were included. The participants in the included studies were lung cancer patients.

Inclusion criteria

1. Peer-reviewed studies examining risk factors or correlates of VTE in lung cancer patients.
2. Observational studies (cross-sectional, case-control, and cohort) and systematic review.
3. Peer-reviewed studies of low and moderate risk of bias.

Exclusion criteria

1. Experimental studies in which patients have been diagnosed of VTE and were on anti-VTE treatment.
2. Studies with a high risk of bias.

Sources of information and search strategy

A methodologist (MN) devised, tested, and refined the search strategy. The search strategy comprised MeSH terms and free terms. A PubMed pilot search was carried out to ascertain the face sensitivity of the search technique. The search terms were adapted to the syntax and subject headings of the other databases including MEDLINE, Academic Search Complete, and CINAHL (Appendix Table A1). Additional research was undertaken on the list of references of relevant publications to find relevant studies. We searched databases from onset to June 2022.

Study selection

The results of the literature search were exported to a citation manager to aid data management namely de-duplicate elimination and selection of articles for inclusion. Selection was pursued as per the outline eligibility criteria. The full-text versions of articles that meet the criteria were downloaded. Finally, the selected articles were published between 2012 and 2022.

Procedures for data screening and extraction

MN undertook title and abstract screening. NT and MN independently performed full-text screenings. Data were extracted by NM and verified by a research assistant (MU), with any inconsistencies resolved by MN. The PRISMA diagram was used to display the details of the flow of studies throughout the selection process.

Data items

Risk estimates such as odds ratio (OR), correlation coefficient, standardized mean difference, and the number of eligible studies per factor constituted the primary data. For ease of comparison, all estimates were converted to OR. The stability index, Rw, and critical risk point constituted were calculated from the primary outcome. Study design, sample size, sampling procedure, method of evaluation, age, race, type of lung cancer, setting, and country formed the secondary outcomes.

Quality appraisal/risk of bias assessment

To ensure that stakeholders and consumers of health information exercise their best judgment when interpreting the study's findings, we evaluated the quality of the included studies. For quality assessment, the mixed methods appraisal tool Version 2011 was used.[30] The risk was classified as low for a quality score 80% to 100%, medium for a quality score 40% to 60%, and high for a score less than 40%.[31]

Summary measures

The Rw and critical risk point constitute the summary measures. Rw was computed for each risk factor to highlight their putative clinical significance. The critical risk point for preemptive action will be estimated per Nweke et al.[32]

Data synthesis and analysis

To meet the review objectives, we adopted an evidence-based approach first described by Nweke et al.[30] Where applicable, the approaches described by Borenstein et al[33] and Lenhard and Lenhard[34] were used to estimate ORs from other effect sizes. Using the random effects model, the pooled OR was computed per risk factor. The Nweke (N)-factor otherwise known as Rw, which is a function of the effect size (OR) and Ri (also known as risk recurrence), was used to weigh individual risk factors. Based on N-factor (Rw), risk factors were weighted and ranked into upper, intermediate, and lower quartiles.[32] Level-1 or high-risk factors occupy the upper quartile, level-2 or medium-risk factors occupy the intermediate quartile, and level-3 or low- risk factors occupy the lower quartile. Preemptive interventions are usually reserved for the high-risk group, hence, the critical risk point lies within the upper quartile. Again, such point must be one that highlights the polygenic nature of VTE. Based on the distribution of Rw across risk factors, the critical point was calculated as the upper third of the upper quartile class.[32]

Assessment of heterogeneity

Measures of heterogeneity (study characteristics) were categorized by publication and presented narratively in an evidence table (Table 1). The heterogeneity measure I^2 was determined and I^2 values were interpreted following the Cochrane Collaboration Handbook for Systematic Reviews.[35] Low heterogeneity was indicated by a score of 0% to 40%, moderate heterogeneity by a score of 30% to 60%, substantial heterogeneity by a score of 50% to 90%, and considerable heterogeneity by a score of 75% to 100%. Egger test was used to assess publication bias. Comprehensive meta-analysis Version 3 was used for statistical processes.

Results

Study selection and characteristics

We identified 4975 records. After de-duplication and title and abstract screening, we excluded 4936 irrelevant records, leaving 132 records for full-text review. Of the 132 full texts, 102 publications were excluded. Reasons for exclusion were (1) studies that did not meet our requirement in terms of study design (eg, case reports) and (2) studies that examined level of risk of lung cancer-associated VTE but did not report the risk factors and corresponding risk estimate. Ultimately, our review included 29 articles involving 145 830 participants from nine countries (Figure 1). Twelve (41%) of the studies were conducted in China, five (17%) in the USA, 3 (10%) in Korea, and two (7%) in Japan. Over 50% of the studies reported VTE in patients with non-small cell lung cancer (Table 1). To be included in the meta-analysis, at least three studies provided reports on the association of VTE and a given risk factor/biomarker in lung cancer patients.

Risk factors and risk stratification

Following the meta-analyses, ten risk factors/biomarkers emerged as the most important determinants of lung cancer-associated VTE and we classified them into three levels based on Rw), a measure of clinical significance, which is the product of risk stability and summary effect size otherwise known as risk estimate. Level-1 risk factors/biomarkers occupy the upper quartile and include D-dimer (OR = 5.50; Rw = 5.00) and albumin (OR = 2.23; Rw = 1.79). The D-dimer was the most stable/reliable biomarker for the prediction of lung cancer-associated VTE (Ri = 0.91), followed by albumin (Ri = 0.80). Level-2 risk factors/biomarkers include leukocyte (OR = 2.48; Rw = 1.77), histological features (OR = 1.69; Rw = 1.27), and age (OR = 1.56; Rw = 0.99). Of the level-2 risk factors/biomarkers, histological features (Ri = 0.75) and leukocyte (Ri = 0.71) were the most stable. Level-3 risk factors/biomarkers include hemoglobin (OR = 1.85; Rw = 0.92), BMI (OR = 1.48; Rw = 0.74), and serum carcinoembryonic antigen (OR = 1.69; Rw = 0.67). Throughout the study, we recorded no publication bias except for histology (Egger $t = 2.580$; $P = 0.027$) and BMI (Egger $t = 2.807$; $P = .031$). The critical point for the detection of lung cancer-associated VTE lies within the upper quarter. Based on the distribution of Rw across risk factors, the critical point was calculated as the upper third (4.5) of the upper quartile class. Hence, a cumulative Rw of $\geqslant 4.5$ may possess the highest diagnostic accuracy for lung cancer-associated VTE and could mark the critical point at which preemptive interventions should be instituted (Table 2).

To substantiate cost-effectiveness, we sourced the investigative cost of the selected biomarkers from three LMICs namely Nigeria, Ghana, and India, and calculated the average cost. We

Table 1. Characteristics of the studies included in the review.

AUTHORS	DESIGN	LUNG CANCER TYPE	VTE TYPE	SAMPLE SIZE	COUNTRY
Zhang et al[13]	Meta-analysis	NSCLC	VTE	13436	Global review
Kadlec et al[20]	Prospective	NSCLC/SCLC	VTE	950	Czech Republic
Zhang et al[36]	Prospective	NSCLC	VTE	673	China
Lee et al[37]	Prospective	NSCLC	VTE	1998	Korea
Wang et al[38]	Prospective	NSCLC	VTE	183	China
Chiari et al[39]	Prospective	NSCLC	VTE	94	Italy
Dou et al[40]	Prospective	NSCLC	VTE	378	China
Junjun et al[41]	Prospective	NR	PE	106	China
Zhang et al[42]	Prospective	NR	VTE	952	China
Li et al[43]	Prospective	NSCLC	VTE	629	USA
Cui et al[44]	Prospective	Mixed	VTE	339	China
Khorana et al[45]	Prospective	NSCLC	VTE	2299	USA
Zhu & Liu et al[46]	Retrospective	NR	DVT	2053	China
Lee et al[47]	Retrospective	SCLC	VTE	277	Korea
Chew et al[48]	Retrospective	NSCLC	VTE	91933	USA
Blom et al[49]	Retrospective	NR	VTE	537	Netherlands
Dou et al[50]	Retrospective	NSCLC	VTE	605	China
Hill et al[51]	Retrospective	NSCLC	VTE	1587	USA
Hiraide et al[52]	Retrospective	Mixed	VTE	682	Japan
Liu et al[12]	Retrospective	Mixed	VTE	283	China
Shen et al[53]	Retrospective	NSCLC	VTE	1560	China
Takemoto et al[54]	Retrospective	NR	DVT	944	Singapore
Thomas et al[55]	Retrospective	NR	VTE	14308	USA
Yang et al[56]	Retrospective	NR	VTE	1001	China
Cui et al[57]	Retrospective	Mixed	PE	100	China
Go et al[58]	Retrospective	NSCLC	VTE	998	Korea
Tsubata et al[59]	Retrospective	NR	VTE	1008	Japan
Zer et al[60]	Retrospective	NSCLC	VTE	98	Israel
Li et al[61]	Systematic review	Mixed	VTE	5819	18 of 19 are in Asia mostly in China

Abbreviations: DVT, deep vein thrombosis; NR, not reported; NSCLC, non-small cell lung cancer; PE, pulmonary embolism; SCLC, small cell lung cancer; VTE, venous thromboembolism.

defined a biomarker (test) as cost-effective if the cost of investigation falls within the average ($15.6). From Table 3, all the biomarkers (test) were within the average cost except D-dimer and histology.

Examining the preexisting risk assessment tools in the light of our study findings, we identified two major flaws namely low model predictive power and cost-ineffectiveness vis-à-vis resource-constrained LMICs where an average person lives below poverty line. Risk assessment tools with low predictive power (Rw) include the Khorana score and PROTECHT score, while the cost-ineffective tools include the Vienna (CATS) score, COMPASS-CAT Score, and Tic-ONCO score and their procedural cost may not be afforded by patients in LMICs (Table 4).

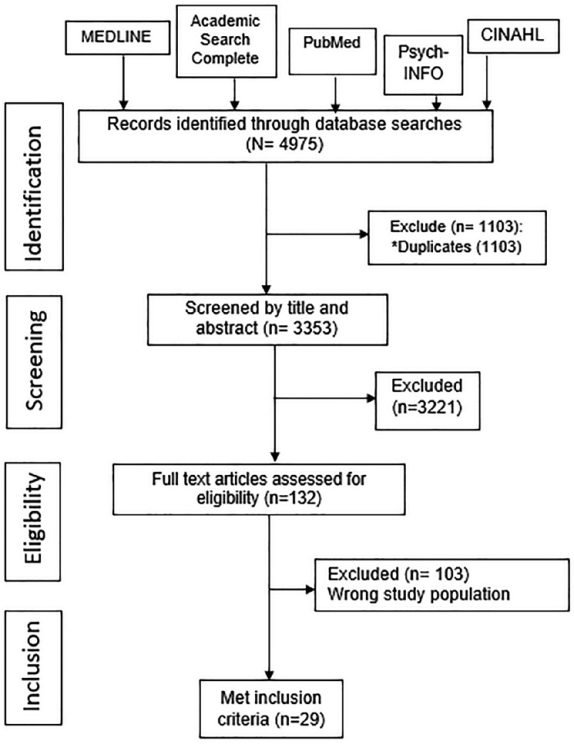

Figure 1. PRISMA flow diagram of the systematic review on stratification of risk factors of cancer-associated venous thromboembolism in patients with lung cancer (2012-2022).

*Exclusion

Discussion

A close observation of several risk assessment models for VTE in cancer patients shows two major challenges namely inclusion of unreliable biomarkers and the high cost of investigation of model biomarkers vis-à-vis as defined by the affordability in LMICs. With the identification of reliable and clinically relevant biomarkers, and cost-effective model namely albumin-leukocyte-hemoglobin-age-BMI model (ALHAB), we expect a further reduction in the false negative and false positive rates previously reported with existing models. Similarly, identifying several possible combinations of biomarkers that meet the critical point allows for the individuality of person and cost-effectiveness, especially in LMICs where an average person may scarcely afford the high cost of investigation of biomarker inclusive in some of the preexisting models. The outcome of the study may necessitate recalibration of several of the preexisting models, although further studies are required to validate the study outcome. An accurate diagnosis of VTE is important due to the morbidity and mortality associated with missed diagnoses and the potential side effects, patient inconvenience, and resource implications of anticoagulant treatment given for VTE.[70] Furthermore, this review provides an exhaustive list of relevant risk factors/biomarkers ranked in their order of importance in predicting VTE and fitted a cost-effective model for LMICs.

Our study reveals D-dimer as a significant predictor of thromboembolism in lung cancer patients. This is consistent with the previous meta-analysis[61] which stated that the odds for VTE among lung cancer patients were four times high in individuals with high D-dimer (>653 μg/L) compared with those with lower D-dimer values (⩽653μg/L). Many previous studies have shown that the D-dimer test is highly sensitive (>95%) in early detection of venous thrombosis embolism usually with a cut-off value of 500 μg/L, which reasonably rules out acute VTE.[71] By implication, patients with high D-dimer levels on presentation should be subjected to a more intense diagnostic approach probably using the Doppler ultrasound.[71] Of all the biomarkers sampled in our study, D-dimer is the most significant and reliable predictor of VTE in lung cancer patients with a high cumulative Rw of 5.0 and a near-perfect stability index of 0.9. In collaboration with previous studies, D-dimer is unequivocally a highly sensitive myeloma-specific and generic biomarker for the detection of cancer-associated thromboembolism.[71-73] This is in keeping with the American Society of Hematology 2018 guidelines for the management of VTE[70] which recommends D-dimer as the initial test reduces the need for diagnostic imaging. Despite its predictive potential, D-dimer is often excluded from notable risk assessment tools[23,24,74-76] except the Vienna (CATS) score.[74] In high-income countries, this exclusion may be unjustifiable especially as these tools often present with one of the cardinal flaws namely lesser predictive power than required. The high investigative cost disfavors its inclusion models targeted for the LMICs. Its low specificity of D-dimer as an index of VTE,[77] differences in analytic techniques and cut-off values, and other factors (age, pregnancy, and malignancy) affecting D-dimer level and the polygenic nature of VTE all constitute a limitation to a sole D-dimer model.[78]

Our study shows that albumin was a significant marker of VTE in lung cancer patients possessing a cumulative Rw of approximately 1.79 and an Ri of 0.8. By implication, lung cancer patients with low serum albumin (<35 g/L) possess 2.2 odds of having VTE compared with those with higher values (>35 g/L). This is in keeping with the fact that reduced serum albumin is reportedly a marker of global health decline and poor prognosis.[11] Of the risk factors/biomarkers of lung cancer-associated VTE, albumin is second only to D-dimer in terms of both predictive capacity and risk stability. This is arguably the most important finding of this study as it highlights the neglect of the predictive potential of serum albumin in the prediction of cancer-associated VTE, substantiated by the facts that none of the well-known risk assessment tools has it in its model despite being cost-effective.[23,24,74-76] The exact reason for this is not known; however, we observed that most of the albumin were recent studies from China, a middle-income Asian country, thus suggesting albumin as an emerging risk factor of VTE. Although our study is the first meta-analysis on the predictive role of serum albumin in the detection of lung cancer-associated thromboembolism, it has been demonstrated that the predictive potential of D-dimer ratio could be improved by the addition of albumin in patients with advanced gastric cancer.[79]

Table 2. Risk factors/biomarkers of VTE among lung cancer patients.

FACTORS	REFERENCE CATEGORY	RISK STABILITY INDEX (RI)	OR	95% CI	*P* VALUE	I^2	EGGERS' TEST *T*-VALUE	*P* VALUE	RISK WEIGHT (RW)	RISK CATEGORY
Sex*	Female	0.33	1.448	1.048-2.001	.025	58.744	1.7087	.377	0.483	Level 3
Smoking	—	0.50	1.561	0.71-3.460	.272	79.25	1.180	.359	0.781	NSF
AST	—	0.33	1.146	0.395-3.328	.802	77.289	0.892	.536	0.382	NSF
ALT	—	0.33	1.077	0.349-3.327	.897	80.027	0.243	.848	0.359	NSF
Albumin*	<35 g/L	0.80	2.232	1.044-4.774	<.001	78.172	0.4684	.672	1.786	Level 1
Serum* carcinoembryonic antigen	>8 ng/mL	0.40	1.686	1.104-2.575	.016	37.756	1.0149	.385	0.674	Level 3
Age*	<60 years	0.64	1.557	1.254-1.933	<.001	79.241	2.214	.0541	0.991	Level 2
D-dimer*	>625 μg/L	0.91	5.510	2.586-11.742	<.001	91.493	0.3567	.730	5.00	Level 1
Hemoglobin*	⩽10 g/dL	0.50	1.845	1.328-2.556	<.001	28.909	1.6342	.178	0.923	Level 3
BMI*	⩾30 kg/m^2	0.50	1.483	1.142-1.925	.003	51.090	2.8070	.031	0.742	Level 3
Leukocyte*	⩾11×10^9/L	0.71	2.482	1.921-3.202	<.001	0.000	0.8540	.432	1.773	Level 2
Histology*	Adenocarcinoma	0.75	1.690	1.206-2.369	.002	77.680	2.580	.027	1.268	Level 2
Platelet*	⩾300×10^9/L	0.33	1.830	1.183-2.881	.007	69.50	0.4649	.666	0.61	Level 3

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; NSF, not a significant factor; OR, odds ratio; VTE, venous thromboembolism.
Level 1: risk weight in the upper quartile (Rw⩾1.78).
Level 2: risk weight in the interquartile range (Rw=0.96-0.77).
Level 3: risk weight in the lower quartile (Rw⩾0.66-0.76).
*Factors significant at $\alpha=0.05$.

Table 3. Cost of investigation of biomarkers in selected LMICs.

BIOMARKER (TEST)	NIGERIA (₦)[1]	GHANA (GHC)	INDIA (RS)	AVERAGE COST IN DOLLARS AS AT MARCH 18, 2023
Albumin[a]	1700[62]	70[63,a]	300[64]	4.36
Serum[a] carcinoembryonic antigen	5500[62]	182[65]	670[66]	11.69
D-dimer[a]	21 500[62]	—	1150[67]	30.72
Hemoglobin[a,b]	2300[62]	40[63]	130[68]	3.30
Leukocyte[a,b]	3000[62]	40[63]	130[68]	3.81
Histology[a]	24 700[62]	750[63]	3375[69]	52.13
Platelet[a,b]	1700[62]	40[63]	130[68]	2.86
Average	6400	1122	5885	15.55

Abbreviation: LMICs, low- and middle-income countries.
[a]Component of liver function test.
[b]Component of full blood count.

In this maiden meta-analysis, leukocyte with a cumulative Rw of approximately 1.8 and stability index of 0.8 was a significant biomarker that could be employed in the early detection of VTE in lung cancer patients. This implies that individuals with elevated leukocyte ⩾10.5×10^9/L had approximately possessed 2.5-fold higher odds for lung cancer-associated VTE. Furthermore, this justifies its inclusion in most of the well-known risk assessment tools.[23,74,76] However, our

Table 4. Examining the flaws in preexisting and notable risk assessment tools for predicting lung cancer-associated VTE.

RISK ASSESSMENT TOOL	RELEVANT BIOMARKER	FLAWS	IMPLICATION OF FLAWS
Khorana score	Platelet count, hemoglobin concentration, leukocyte and body mass index	Biomarkers are mainly of level 3 and cumulative risk weight does not meet the critical point	Suboptimal predictive power Suboptimal cost-effectiveness
Vienna (CATS) score	Platelet count, hemoglobin concentration, leukocyte and body mass index, D-dimer, soluble P-selectin	Although risk weight met the critical point, the inclusion of unproven/unreliable biomarker P-selectin may be unnecessary	Not cost-effective
PROTECHT score	Platelet count, hemoglobin concentration, leukocyte and body mass index, and cisplatin/carboplatin-based chemotherapy or gemcitabine	Biomarkers are mainly of level 3 and cumulative risk weight did not meet the critical point. More studies on the association of cisplatin/carboplatin-based chemotherapy or gemcitabine and lung cancer-associated VTE.	Suboptimal predictive power Suboptimal cost-effectiveness
ONKOTEV Score	Khorana score >2, personal history of VTE, metastatic disease, vascular/lymphatic macroscopic compression	Although risk weight meets the critical point, both personal history of VTE and vascular/lymphatic macroscopic compression are currently unproven biomarkers. Hence, more studies are required on their association with lung cancer-associated VTE.	Not cost-effective
COMPASS-CAT Score	Anthracycline/anti-hormonal therapy, time since cancer diagnosis, central venous catheter, stage of cancer, presence of cardiovascular risk, platelet count, recent hospitalization for acute medical illness, personal history of VTE	Many of the risk factors/biomarkers are systematically unproven	Not cost-effective
Tic-ONCO score	Genetic risk score, hemoglobin concentration, leukocyte and body mass index	Met the criteria but cost-ineffective	Not cost-effective

Abbreviation: VTE, venous thromboembolism

study revealed that leukocyte is a level-2 biomarker with cumulative Rw and stability index of approximately 1.8 and 0.7, respectively. Its stability and minimal cost of investigation make it a biomarker of choice in predictive models for cancer-associated VTE.

The result showed that histological type is a significant determinant of the risk for VTE among lung cancer patients. Specifically, lung cancer patients with adenocarcinoma type had approximately 2-fold higher odds for VTE compared with those with squamous type. This is consistent with a previous meta-analysis[16] in which adenocarcinoma was confirmed to be a risk factor for thrombosis in lung cancer patients (OR = 2.2). Interestingly, histology type is a reliable predictor of lung cancer-associated VTE with an Ri of 0.75; however, it is not included in any of the well-known risk assessment tools.[23,24,74-76] It is possible that its relatively high investigative cost might disfavor it as a biomarker of choice especially when early detection is being sought.

In this study, both hemoglobin and platelets are significant predictors of lung cancer-associated VTE of the level-3 category. By implication, lung cancer patients with low hemoglobin levels (⩽10 g/dL) were twice as at risk of having VTE compared with those with higher hemoglobin levels (>10 g/dL). On contrary, lung cancer patients with high platelet count (⩾300×10^9/L) were twice as at risk of having VTE compared with those with lower platelet count (<300×10^9/L) The finding that hemoglobin was an important biomarker for the detection of VTE in lung cancer patients resonates well with most of the risk assessment models.[23,74,76] The fact that platelet was a significant predictor of lung cancer-associated VTE collaborates with earlier findings by Vitale et al[80] which showed platelet as an independent determinant of VTE in cancer patients and equally justifies its inclusion of in most of the well-known risk assessment models.[23,24,74,76]Although their investigative costs are relatively low, their poor to average stability index should be of concern to their utility especially when early detection is being pursued. Hence, risk assessment models using platelets should do so in combination with the very powerful biomarkers to improve model predictive power as measured by the cumulative Rw.

Our meta-analysis showed that sex and BMI were level-3 predictors of lung cancer VTE, with the risk of VTE being higher among females and the obese. BMI is a popular risk factor in well-known risk assessment models.[23,24,61] With just an average Ri, it should be used in combination with more

powerful biomarkers in the pursuit of early detection of VTE among lung cancer patients. Of all the risk factors/biomarkers, sex ranked least in terms of Rw and this may explain why it is missing in most risk assessment models. While one may be wary of including sex in a risk assessment model, it could add to the model's predictive power especially as no investigative cost is involved. Regarding age, in a previous review, Di et al[7] stated that age remained a controversial factor for the increased occurrence of VTE in lung cancer and an additional investigation was needed to clarify their association. However, our meta-analysis indicates that the risk of VTE in lung cancer patients was approximately 1.6 times higher at age <60 years. Although the Ri is just a little above average, the fact that no cost or instrumentation is required may improve its assimilation in risk assessment models.

The fact that there was substantial degree of heterogeneity regarding the risk estimates of seven of the twelve biomarkers analyzed in this study constitutes a limitation. Also, publication bias was reported regarding the risk estimates of two biomarkers. Although the included studies were of high quality, certain degree of caution must be exercised when interpreting the findings of this study. The use of discretional judgment in deciding the critical risk constitutes a limitation especially when employing the principle of this study to investigating health conditions other than VTE. However, the subjectivity is a trade-off between sensitivity and specificity, and suggests that the emerging model should be subjected to validation to determine the optimum critical point.

Conclusions

D-dimer is the most important predictor of lung cancer-associated thromboembolism, followed by serum albumin, leukocyte, histology type, age, hemoglobin, etc. A cumulative Rw of 4.5 is predictive of lung cancer-associated VTE and marks the critical point at which preemptive measures should be instituted with or without further testing with Doppler ultrasonography. An ideal risk assessment model should employ a prudent combination of risk factors/biomarkers to ensure high predictive power as well as cost-effectiveness. For LMICs, we recommend the ALHAB model.

Author Contributions

Theresa Nwagha and Martins Nweke conceived and designed the study. Searches were conducted by Nweke. Data selection and extraction were undertaken by trained research assistants. Nwagha and Nweke contributed to quality appraisal and both contributed to the drafting of articles, revised it critically for important intellectual content, and approved the version to be published.

ORCID iD

Martins Nweke https://orcid.org/0000-0002-9493-9443

REFERENCES

1. Abdol Razak NB, Jones G, Bhandari M, Berndt MC, Metharom P. Cancer-associated thrombosis: an overview of mechanisms, risk factors, and treatment. *Cancers (Basel)*. 2018;10:380.
2. Verso M, Agnelli G. New and old anticoagulants in cancer. *Thromb Res*. 2012;129:S101-S105.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68:7-30.
4. Park ER, Japuntich SJ, Rigotti NA, et al. A snapshot of smokers after lung and colorectal cancer diagnosis. *Cancer*. 2012;118:3153-3164.
5. Chen Y, Tsang YS, Chou X, Hu J, Xia Q. A lung cancer patient with deep vein thrombosis: a case report and literature review. *BMC Cancer*. 2019;19:285.
6. Suzuki T, Fujino S, Inaba S, et al. Venous thromboembolism in patients with lung cancer. *Clin Appl Thromb Hemost*. 2020;26:977910.
7. Di W, Xu H, Xue T, Ling C. Advances in the prediction and risk assessment of lung cancer-associated venous thromboembolism. *Cancer Manag Res*. 2021;13:8317-8327.
8. Rupa-Matysek J, Lembicz M, Rogowska EK, Gil L, Komarnicki M, Batura-Gabryel H. Evaluation of risk factors and assessment models for predicting venous thromboembolism in lung cancer patients. *Med Oncol*. 2018;35:63.
9. Weitz JI, Farjat AE, Ageno W, et al. Influence of body mass index on clinical outcomes in venous thromboembolism: insights from GARFIELD-VTE. *J Thromb Haemost*. 2021;19:3031-3043.
10. Roselli M, Riondino S, Mariotti S, La Farina F, Ferroni P, Guadagni F. Clinical models and biochemical predictors of VTE in lung cancer. *Cancer Metastasis Rev*. 2014;33:771-789.
11. Königsbrügge O, Lötsch F, Reitter EM, et al. Presence of varicose veins in cancer patients increases the risk for occurrence of venous thromboembolism. *J Thromb Haemost*. 2013;11:1993-2000.
12. Liu Y, Gu Y, Yi F, Cao B. Retrospective analysis of risk factors for venous thromboembolism in 283 patients with lung cancer during systemic therapy. *Zhongguo Fei Ai Za Zhi*. 2019;22:419-426.
13. Zhang Y, Yang Y, Chen W, et al. Hypertension associated with venous thromboembolism in patients with newly diagnosed lung cancer. *Sci Rep*. 2016;6:19603.
14. Walker AJ, Baldwin DR, Card TR, Powell HA, Hubbard RB, Grainge MJ. Risk of venous thromboembolism in people with lung cancer: a cohort study using linked UK healthcare data. *Br J Cancer*. 2016;115:115-121.
15. Corrales-Rodriguez L, Soulières D, Weng X, Tehfe M, Florescu M, Blais N. Mutations in NSCLC and their link with lung cancer-associated thrombosis: a case-control study. *Thromb Res*. 2014;133:48-51.
16. Zhang M, Wu S, Hu C. Do lung cancer patients require routine anticoagulation treatment? A meta-analysis. *J Int Med Res*. 2020;48:896919.
17. Dickmann B, Ahlbrecht J, Ay C, et al. Regional lymph node metastases are a strong risk factor for venous thromboembolism: results from the Vienna Cancer and Thrombosis Study. *Haematologica*. 2013;98:1309-1314.
18. Ahlbrecht J, Dickmann B, Ay C, et al. Tumor grade is associated with venous thromboembolism in patients with cancer: results from the Vienna Cancer and Thrombosis Study. *J Clin Oncol*. 2012;30:3870-3875.
19. Gong CY, Li ZW, Zhou DX, et al. [Risk factors of lung cancer complicated with symptomatic venous thromboembolism]. *Zhonghua Jie He He Hu Xi Za Zhi*. 2016;39:454-458.
20. Kadlec B, Skrickova J, Merta Z, Dusek L, Jarkovsky J. The incidence and predictors of thromboembolic events in patients with lung cancer. *Scientificworldjournal*. 2014;2014:125706.
21. Anghel L, Sascău R, Radu R, Stătescu C. From classical laboratory parameters to novel biomarkers for the diagnosis of venous thrombosis. *Int J Mol Sci*. 2020;21:1920.
22. Khorana AA, Francis CW, Culakova E, Lyman GH. Risk factors for chemotherapy-associated venous thromboembolism in a prospective observational study. *Cancer*. 2005;104:2822-2829.
23. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood*. 2008;111:4902-4907.
24. Ay C, Simanek R, Vormittag R, et al. High plasma levels of soluble P-selectin are predictive of venous thromboembolism in cancer patients: results from the Vienna Cancer and Thrombosis Study (CATS). *Blood*. 2008;112:2703-2708.
25. Pelzer U, Opitz B, Deutschinoff G, et al. Efficacy of prophylactic low-molecular weight heparin for ambulatory patients with advanced pancreatic cancer: outcomes from the CONKO-004 trial. *J Clin Oncol*. 2015;33:2028-2034.
26. Gerotziafas GT, Taher A, Abdel-Razeq H, et al. A predictive score for thrombosis associated with breast, colorectal, lung, or ovarian cancer: the prospective COMPASS-Cancer-Associated Thrombosis Study. *Oncologist*. 2017;22:1222-1231.
27. Mansfield AS, Tafur AJ, Wang CE, Kourelis TV, Wysokinska EM, Yang P. Predictors of active cancer thromboembolic outcomes: validation of the Khorana score among patients with lung cancer. *J Thromb Haemost*. 2016;14:17738.

28. Overvad TF, Ording AG, Nielsen PB, et al. Validation of the Khorana score for predicting venous thromboembolism in 40 218 patients with cancer initiating chemotherapy. *Blood Adv*. 2022;6:2967-2976.
29. Mulder FI, Candeloro M, Kamphuisen PW, et al. The Khorana score for prediction of venous thromboembolism in cancer patients: a systematic review and meta-analysis. *Haematologica*. 2019;104:1277-1287.
30. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*. 2015;350:g7647.
31. Nweke M, Mshunqane N, Govender N, Akinpelu AO, Ukwuoma M. Impact of HIV-associated cognitive impairment on functional independence, frailty and quality of life in the modern era: a meta-analysis. *Scientifc Reports*. 2022;12:6470.
32. Nweke M, Ukwuoma M, Adiuku-Brown AC, Ugwu P, Nseka E. Characterization and stratification of the correlates of postpartum depression in sub-Saharan Africa: a systematic review with meta-analysis. *Womens Health*. 2022;18:118773.
33. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Converting among effect sizes. *Introduction Meta-anal*. 2009:45-49.
34. Lenhard W, Lenhard A. Calculation of effect sizes: psyhometrica, Bibergau (Germany); 2015. http://www.psychometrica.de/effect_size.htlm. Accessed May 29, 2022.
35. Higgins JPT, Thomas J, Chandler J, et al, eds. *Cochrane handbook for systematic reviews of interventions version 6.3*; Cochrane; 2022. Updated 2022. www .training.cochrane.org/handbook.
36. Zhang Y, Yang Y, Chen W, et al. Prevalence and associations of VTE in patients with newly diagnosed lung cancer. *Chest*. 2014;146:650–658. doi: 10.1378/chest.13-2379
37. Lee YG, Kim I, Lee E, et al. Risk factors and prognostic impact of venous thromboembolism in Asian patients with non-small cell lung cancer. *Thromb Haemost*. 2014;111:1112–1120. doi: 10.1160/TH13-11-0956
38. Wang Y, Midthun DE, Wampfler JA, et al. Trends in the proportion of patients with lung cancer meeting screening criteria. *JAMA*. 2015;313:853–855. doi: 10.1001/jama.2015.413
39. Chiari R, Ricciuti B, Landi L, et al. ROS1-rearranged non-small-cell lung cancer is associated with a high rate of venous thromboembolism: analysis from a Phase II, prospective, multicenter, two-arms trial (METROS). *Clin Lung Cancer*. 2020 ;21:15–20. doi: 10.1016/j.cllc.2019.06.012
40. Dou F, Zhang Y, Yi J, et al. Association of ALK rearrangement and risk of venous thromboembolism in patients with non-small cell lung cancer: a prospective cohort study. *Thromb Res*. 2020;186:36–41. doi: 10.1016/j.thromres.2019.12.009
41. Junjun L, Pei W, Ying Y, Kui S. Prognosis and risk factors in older patients with lung cancer and pulmonary embolism: a propensity score matching analysis. *Sci Rep*. 2020;10:1272. doi: 10.1038/s41598-020-58345-4
42. Zhang Y, Shi Z, Yi J, et al. Correlation between clinicopathological characteristics of lung adenocarcinoma and the risk of venous thromboembolism. *Thorac Cancer*. 2022;13:247–256. doi: 10.1111/1759-7714.14260
43. Li R, Hermann G, Baldini E, et al. Advanced nodal stage predicts venous thromboembolism in patients with locally advanced non-small cell lung cancer. *Lung Cancer*. 2016;96:41–47. doi: 10.1016/j.lungcan.2016.03.004
44. Cui S, Li H, Tian B, Song C, Hu B. [Risk factors associated with venous thromboembolism after lung cancer surgery: a single-center study]. *Zhongguo Fei Ai Za Zhi*. 2018;21:753–760. doi: 10.3779/j.issn.1009-3419.2018.10.04
45. Khorana L, Rosenblatt L, Pisupati R, et al. RISK OF venous thromboembolism in patients on first line therapy for advanced non-small cell lung cancer: a comparison of immune checkpoint inhibitors and chemotherapy regimens. *J Am Coll Cardiol Cardiovasc Intv*. 2022;79: 1953.
46. Zhu R, Liu J. Venous thromboembolism in lung cancer with clinical analysis of 89 cases. *Eur Respir J*. 2012;40:3887.
47. Lee YG, Lee E, Kim I, et al. Cisplatin-based chemotherapy is a strong risk factor for thromboembolic events in small-cell lung cancer. *Cancer Res Treat*. 2015;47:670–675. doi: 10.4143/crt.2014.045, PMID 25672586.
48. Chew HK, Davies AM, Wun T, Harvey D, Zhou H, White RH. The incidence of venous thromboembolism among patients with primary lung cancer. *J Thromb Haemost*. 2008;6:601–608. doi: 10.1111/j.1538-7836.2008.02908.x
49. Blom JW, Osanto S, Rosendaal FR. The risk of a venous thrombotic event in lung cancer patients: higher risk for adenocarcinoma than squamous cell carcinoma. *J Thromb Haemost*. 2004;2:1760–1765. doi: 10.1111/j.1538-7836.2004.00928.x
50. Dou F, Li H, Zhu M, et al. Association between oncogenic status and risk of venous thromboembolism in patients with non-small cell lung cancer. *Respir Res*. 2018;19:88. doi: 10.1186/s12931-018-0791-2
51. Hill H, Robinson M, Lu L, et al. Venous thromboembolism incidence and risk factors in non-small cell lung cancer patients receiving first-line systemic therapy. *Thromb Res*. 2021;208:71–78. doi: 10.1016/j.thromres.2021.10.014
52. Hiraide M, Shiga T, Minowa Y, et al. Identification of risk factors for venous thromboembolism and evaluation of Khorana venous thromboembolism risk assessment in Japanese lung cancer patients. *J Cardiol*. 2020;75:110–114. doi: 10.1016/j.jjcc.2019.06.013
53. Shen Q, Dong X, Tang X, Zhou J. Risk factors and prognosis value of venous thromboembolism in patients with advanced non-small cell lung cancer: a case-control study. *J Thorac Dis*. 2017;9:5068–5074. doi: 10.21037/jtd.2017.11.116
54. Takemoto T, Soh J, Ohara S, et al. The prevalence and risk factors associated with preoperative deep venous thrombosis in lung cancer surgery. *Surg Today*. 2021;51:1480–1487. doi: 10.1007/s00595-021-02243-3
55. Thomas DC, Arnold BN, Hoag JR, et al. Timing and risk factors associated with venous thromboembolism after lung cancer resection. *Ann Thorac Surg*. 2018;105:1469–1475. doi: 10.1016/j.athoracsur.2018.01.072
56. Yang Y, Zhou Z, Niu XM, et al. Clinical analysis of postoperative venous thromboembolism risk factors in lung cancer patients. *J Surg Oncol*. 2012;106:736–741. doi: 10.1002/jso.23190
57. Cui YQ, Tan XM, Liu B, et al. Analysis on risk factors of lung cancer complicated with pulmonary embolism. *Clin Respir J*. 2021;15:65–73. doi: 10.1111/crj.13270
58. Go SI, Lee A, Lee US, et al. Clinical significance of the neutrophil-lymphocyte ratio in venous thromboembolism patients with lung cancer. *Lung Cancer*. 2014;84:79–85. doi: 10.1016/j.lungcan.2014.01.014
59. Tsubata Y, Hotta T, Hamai K, et al. A new risk-assessment tool for venous thromboembolism in advanced lung cancer: a prospective, observational study. *J Hematol Oncol*. 2022;15:40. doi: 10.1186/s13045-022-01259-7
60. Zer A, Moskovitz M, Hwang DM, et al. ALK-rearranged non-small-cell lung cancer is associated with a high rate of venous thromboembolism. *Clin Lung Cancer*. 2017;18:156–161. doi: 10.1016/j.cllc.2016.10.007
61. Li J, Yan S, Zhang X, et al. Circulating D-Dimers increase the risk of mortality and venous thromboembolism in patients with lung cancer: a systematic analysis combined with external validation. *Front Med (Lausanne)*. 2022;9:853941.
62. Synlab Nigeria. All test. https://www.synlab.com.ng/all-tests/?search
63. Wiafe E, Mensah KB, Appiah KAA, et al. The direct cost incurred by patients and caregivers in diagnosing and managing prostate cancer in Ghana. *BMC Health Serv Res*. 2022;22:1105.
64. Kedar Health. Lab test: anaemia assessment, https://kedarhealth.com/products/lab-test-anaemia-assessment
65. Kedar Health. Lab test: tumor cancer markers assessment, https://kedarhealth.com/products/lab-test-tumor-cancer-markers-assessment?_pos=1&_psq=CEA&_ss=e&_v=1.0&variant=40371439567003
66. Merilab. Albumin test: price, purpose & normal values [2023], https://bookmerilab.com/tests/blood-tests/albumin-test/
67. Lal Path Labs. What is carcinoembryonic antigen test (CEA)? https://www.lalpathlabs.com/blog/what-is-carcinoembryonic-antigen/ (accessed 18 March 2023).
68. Medifee. D-Dimer test cost, https://www.medifee.com/tests/d-dimer-test-cost
69. Labs Advisor. Get histopathology-biopsy-large cost in India: up to 0% discount, multiple lab options, https://www.labsadvisor.com/cost-of-histopathology-biopsy-large-in-india accessed 18th March 18, 2023
70. Lim W, Le Gal G, Bates SM, et al. American society of hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism. *Blood Adv*. 2018;2:3226-3256.
71. Pulivarthi S, Gurram MK. Effectiveness of D-Dimer as a screening test for venous thromboembolism: an update. *N Am J Med Sci*. 2014;6:491-499.
72. Chen C, Li J, Li J, et al. Application of an elevated plasma D-Dimer cut-off value improves prognosis prediction of advanced non-small cell lung cancer. *Ann Transl Med*. 2020;8:1153.
73. Koch V, Biener M, Müller-Hennessen M, et al. Diagnostic performance of D-dimer in predicting venous thromboembolism and acute aortic dissection. *Eur Heart J Acute Cardiovasc Care*. 2020;10:559-566.
74. Thaler J, Ay C, Pabinger I. Venous thromboembolism in cancer patients: risk scores and recent randomised controlled trials. *Thromb Haemost*. 2012;108:1042-1048.
75. Cella CA, Di Minno G, Carlomagno C, et al. Preventing venous thromboembolism in ambulatory cancer patients: the ONKOTEV study. *Oncologist*. 2017;22:601-608.
76. Muñoz Martín AJ, Ortega I, Font C, et al. Multivariable clinical-genetic risk model for predicting venous thromboembolic events in patients with cancer. *Br J Cancer*. 2018;118:1056-1061.
77. Bounameaux H, Perrier A, Righini M. Diagnosis of venous thromboembolism: an update. *Vasc Med*. 2010;15:399-406.
78. Kabrhel C, Mark Courtney D, Camargo CA Jr, et al. Factors associated with positive D-Dimer results in patients evaluated for pulmonary embolism. *Acad Emerg Med*. 2010;17:589-597.
79. Zhang L, Wang Z, Xiao J, et al. Prognostic value of albumin to D-Dimer ratio in advanced gastric cancer. *J Oncol*. 2021;2021:973743.
80. Vitale C, D'Amato M, Calabrò P, Stanziola AA, Mormile M, Molino A. Venous thromboembolism and lung cancer: a review. *Multidiscip Respir Med*. 2015;10:28.

Appendix 1

Table A1. Search strategy.

SEARCH TERMS	DATABASE	FILTER	DATE OF SEARCH	NO. OF ARTICLES RETRIEVED
((Lung cancer or lung cancers) AND (venous thromboembolism or deep vein thrombosis or pulmonary embolism)) AND (Risk or risk factors or factors associated or predictive of predicted or predictor)	PubMed	None	May 30, 2022	1 101
((lung cancer or lung neoplasms or lung tumor or lung adenocarcinoma [All Text]) AND (venous thromboembolism or vte or deep venous thromboembolism or dvt[All Text]) AND (risk factors or contributing factors or predisposing factors or risk or factors associated or predictive of predicted or predictor[All Text]))	Academic Search Complete	None	June 01, 2022	2986
((lung cancer or lung neoplasms or lung tumor or lung adenocarcinoma [All Text]) AND (venous thromboembolism or vte or deep venous thromboembolism or dvt[All Text]) AND (risk factors or contributing factors or predisposing factors or risk or factors associated or predictive of predicted or predictor[All Text]))	CINAHL	None	June 01, 2022	117
((lung cancer or lung neoplasms or lung tumor or lung adenocarcinoma [All Text]) AND (venous thromboembolism or vte or deep venous thromboembolism or dvt[All Text]) AND (risk factors or contributing factors or predisposing factors or risk or factors associated or predictive of predicted or predictor[All Text]))	MEDLINE	None	June 01, 2022	766