Prediction Models for Venous Thromboembolism

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Venous thromboembolism (VTE) is a significant cause of mortality in patients with lung cancer. Despite the availability of a wide range of anticoagulants to help prevent thrombosis, thromboprophylaxis in ambulatory patients is a challenge due to its associated risk of haemorrhage. As a result, anticoagulation is only recommended in patients with a relatively high risk of VTE. Efforts have been made to develop predictive models for VTE risk assessment in cancer patients, but the availability of a reliable predictive model for ambulate patients with lung cancer is unclear.

Keywords: venous thromboembolism ; lung cancer ; thromboprophylaxis ; anticoagulant ; risk prediction ; risk assessment ; risk model ; prediction rules ; risk factors

1. Background and Introduction

Cancer is a major risk factor for venous thromboembolism (VTE), which includes deep vein thrombosis and pulmonary embolism. VTE has an annual incidence of around 0.5% in cancer patients compared to around 0.1% in the general population [1]. The incidence of VTE in patients with cancer varies with cancer type, stage, and aggressiveness [2]. Among all cancer types, lung cancer has the second highest risk of VTE [3]. In cohort studies, the incidence of VTE in patients with lung cancer receiving chemotherapy was variously reported as 16.8% at three months and 14.1% at six months after the start of chemotherapy [4], and 13.9% after a median follow-up period of 12 months [5]. Having a VTE is a significant predictor of death within 2 years in patients with primary lung cancer, with hazard ratios (HRs) 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 [6]. This matter highlights the importance of the identification of patients at risk of developing VTE so that therapeutic or preventive measures are implemented in a timely manner.

Thromboprophylaxis is suggested in hospitalised patients with lung cancer and those undergoing surgery, but the use of primary prevention of VTE in ambulatory patients with lung cancer is still debatable [7]. Choice of the anticoagulation therapy is particularly challenging in patients undergoing antineoplastic chemotherapy. On one hand, these patients are at risk of VTE over the course of therapy and beyond. On the other hand, anticoagulation is associated with a high bleeding risk, which could be life-threatening [8]. Low-molecular-weight heparins (LMWH) can reduce the risk of VTE, but current practice guidelines do not recommend their routine use, while direct-acting oral anticoagulants (DOACs) are an interesting alternative to LMWH in cancer patients [9][10][11]. Recent studies have confirmed their efficacy and safety in these patients [12]. Scientific societies such as the National Comprehensive Cancer Network (NCCN), the International Society on Thrombosis and Haemostasis (ISTH), and more recently, the American Society of Clinical Oncology (ASCO) and The International Initiative on Thrombosis and Cancer (ITAC) have supported the use of DOACs [9][10][11]. Nevertheless, the use of DOACs in this scenario should be carefully weighed against the bleeding risk, as evidence for higher risks of bleeding has emerged in studies of the general cancer population [13] and in patients starting chemotherapy [14]. As a result, it is recommended that anticoagulation is only offered to patients with a high risk of VTE, and for this we need to have robust and reliable risk assessment tools [15]. This requires a thorough understanding of the VTE risk factors and clinical prediction models to identify high-risk patients.

Clinical prediction models are epidemiological/statistical tools, which use a small number of parameters (related to the individual, or the disease, or the treatment) to estimate a likelihood in which a specific outcome (e.g., VTE) could happen. Prediction models can help clinicians better understand the individual patient's conditions or risks, so they are able to devise a personalised treatment regimen for them [16]. In 2008, Khorana et al. established a predictive model to assess individual risk of VTE in ambulatory cancer patients receiving chemotherapy [11]. With this model, patients are assigned to one of three risk groups: low (score = 0), intermediate (score = 1–2) and high risk (score ≥ 3) [17]. Using this model, patients with lung cancer are stratified as either intermediate or high risk of developing VTE [17]. The pooled data from 45 studies including various types of cancer showed that only 23.4% (95% CI: 18.4–29.4%) of the patients who developed VTE in the first six months had been classified as being at high risk according to the Khorana score [18]. This poor

performance led to the development of several modifications for the Khorana score over the years, including the Vienna Modification [19], PROTECHT [20], CONKO [21], and COPASS-CAT [22], with varying degrees of predictive ability. In this article, we have reviewed the risk factors for VTE in ambulatory patients with lung cancer, discussed some main risk assessment models for VTE in this group of patients, and reflected upon advantages and disadvantages of the models. We have also explored literature gaps and provided suggestions for further research.

2. VTE Risk Factors in Ambulatory Patients with Lung Cancer

Risk factors for VTE are grouped into three categories: patient-related, cancer-related, and biomarkers [1]. Regarding the patient-related risk factors for VTE, co-morbidities such as atrial fibrillation, chronic kidney disease [23], cardiovascular conditions, and overweight or obesity [24] increase the risk of VTE. Smoking [25] and recent hospitalisation [23][24] also raise the risk of VTE. It is believed that the Asian race has a lower risk than other races [26]. Factor V Leiden and prothrombin 20210A mutations are relatively common in Caucasians whereas they are very rare in Asians [27][28]. These mutations have been identified as additional risk factors for VTE in cancer patients [3]. Cancer patients carrying Factor V Leiden mutation or prothrombin 20210A mutation had a 12.1-fold (95% CI 1.6–88.1) and2.3-fold (95% CI 1.6–3.3) higher risk of VTE, respectively [3].

Similar to variations in the observed VTE risk among other types of cancer [3], some subtypes of lung cancer have higher risks of VTE compared to others; for example, lung adenocarcinoma had a higher risk of VTE occurrence than squamous cell carcinoma [6]. However, within the NSCLC group, the association of oncogene mutations with the risk of VTE is debatable. A systematic review by Liu et al. of 20 retrospective studies showed that anaplastic lymphoma kinase (ALK) mutation has a higher risk of VTE than epidermal growth factor receptor (EGFR) mutation [29], while another systematic review by Alexander et al. reported that EGFR mutation was the strongest risk factor for VTE in patients with lung cancer [30]. Several studies showed patients with an ALK mutation had a higher VTE risk than those without [31], with a hazard ratio of 2.47 (95% CI 1.04–5.90) for VTE in a median follow-up period of 7.5 months (95% CI 3.1–15.4 months) [32] or increasing the risk of VTE by 3 to 5 times over a median follow-up period of 22 months comparing to the general NSCLC population [33]. One possible reason is the expression of tissue factor (TF) gene was elevated in around 41.7% of ALK-positive, but only 11.5% of ALK-negative tissue in patients with lung cancer ($p = 0.015$) [34]. On the other hand, the prospective interventional studies using ALK inhibitor found a lower incidence of VTE than that in retrospective studies, which may be due to reduced use of chemotherapy [35].

Cancer treatment is a strong risk factor for VTE, and commonly used chemotherapy drugs can increase the risk of this clinical condition [25][26][36]. For example, gemcitabine-based chemotherapy increases the risk of VTE, with a reported odds ratio of 3.37 (95% CI 1.09–10.39) [23]. In addition, VTE was more likely to occur within the first six months of the commencement of standard chemotherapy [24]. In terms of the mechanisms involved, they are probably related to vascular endothelial damage caused by chemotherapy, especially in patients who receive the medications through central venous catheterisation over a long period [25][26][36].

3. Risk Prediction Models for VTE in Patients with Cancer

Risk prediction models, also referred to as risk assessment tools or clinical prediction rules, are prognostic models, which use predictors to estimate the probability for individuals to develop a condition in the future [37]. This review covers the particulars of some available VTE risk prediction models which have been developed and/or validated in ambulatory patients with lung cancer. A summary of the main features can be found in **Table 1**.

Table 1. Models for predicting VT E in ambulatory patients with lung cancer [17][20][21][22][23][24][25][38][39][40][41][42][43].

Name of Model (Author, Year)	Cancer Type for Model Derivation	Predictors	Score	High Risk	Validated By First Author, Year	Cancer Type for Model Validation
Khorana Score (Khorana, 2008) [17]	various	Cancer tissue: • Very high-risk site (stomach, pancreas)	2	Score ≥ 3 #	Alexander 2019 [38]	NSCLC
		• High-risk site (lung, lymphoma, gynaecologic, bladder, testicular)	1		van Es 2020 [41]	Various (lung cancer 58%)
PROTECHT (Verso 2012) [20]	various	Platelet count ≥ 350 × 10^9/L	1	Score ≥ 3	Vathiotis 2018 [39]	Lung adenocarcinoma
		Haemoglobin < 100 g/L and/or use of ESA	1		Kuderer 2018 [25]	Lung cancer (84% NSCLC)
		Leukocyte count >11 × 10^9/L	1		Rupa-Matysek 2018 [23]	Lung cancer (97/118 NSCLC)
		BMI ≥ 35 kg/m^2	1		Mansfield 2016 [40]	Lung cancer (87.1% NSCLC)
CONKO (Pelzer 2013) [21]	various	As Khorana Score, but		Score ≥ 3	Alexander 2019 [38]	NSCLC
		adds gemcitabine chemotherapy, and	1		Rupa-Matysek 2018 [23]	Lung cancer (NSCLC 97/118)
		platinum chemotherapy	1			
COMPASS-CAT (Gerotziafas 2017) [22]	Various (13% lung cancer)	As Khorana Score, but s		Score ≥ 7	Alexander 2019 [38]	NSCLC
		removes BMI ≥ 35 kg/m^2, and			Rupa-Matysek 2018 [23]	Lung cancer (NSCLC 97/118)
		adds ECOG PS ≥ 2	1			
		Anthracycline treatment	6		Spyropoulos 2020 [43]	Various (29.05% lung cancer)
		Time since cancer diagnosis ≤ 6 months	4			
		Central venous catheter	3			
		Advanced stage of cancer	2			
		Cardiovascular risk factors present	5		Syrigos 2018 [24]	Lung adenocarcinoma
		Hospitalisation for acute medical Illness	2	Score ≥ 11	Rupa-Matysek 2018 [23]	Lung cancer (97/118 NSCLC)
		A history of VTE	1			
		Platelet count ≥ 350 × 10^9/L	2			

Name of Model (Author, Year)	Cancer Type for Model Derivation	Predictors	Score	High Risk	Validated By First Author, Year	Cancer Type for Model Validation
ROADMAP-CAT (Syrigos 2018) [24]	Lung adenocarcinoma	Procoag-PPL < 44 s, and MRI < 125 nM/min	1 †	score = 1		
HS D-dimer (Ferroni 2012) [42]	Lung cancer	Khorana Score intermediate group adds high-sensitive D-Dimer		Khorana Score 1–2 and HS D-dimer ≥ 1500 ng/mL		
Model 1 (Alexander 2019) [38]	NSCLC	Baseline fibrinogen ≥ 4.0 g/L and baselie D-dimer ≥ 0.5 mg/L	1	Score ≥ 1	Underway ACTRN12618000811202 [38]	NSCLC
		Baseline D-dimer ≥ 1.5 mg/L	1			
		Month-1 D-dimer ≥ 1.5 mg/L	1			

[#] Score ≥ 2 was used to stratify high-risk patients in the CASINI clinical trial of primary thromboprophylaxis and has been incorporated into ASCO Guideline. [†] binary scoring: score = 1 if Procoag-PPL < 44 s and MRI < 125 nM/min; score = 0 if Procoag-PPL > 44 s or MRI >125 nM/min. VTE: venous thromboembolism; ESA: erythropoiesis stimulating agents; BMI: body mass index; NSCLC: non-small cell lung cancer; ECOG PS: Eastern Cooperative Oncology Group performance status; Procoag-PPL: procoagulant phospholipid-dependent clotting time; MRI: mean rate index of thrombin generation; HS: high-sensitive.

4. Risk of Bias in VTE Risk Model Development and Validation Studies

We used the Prediction model Risk Of Bias ASessment Tool (PROBAST) [44] to identify potential biases in the development or validation of current VTE risk models. The first issue is the small sample size of many studies. As a rule of thumb, for risk model development studies, events per variable (EPV) should not be less than 10, while for risk model validation studies, there should be more than 100 participants with the occurrence of the outcome, in this case, VTE [45]. Secondly, dichotomisation of continuous predictors, such as white cell count, platelet count, BMI, D-dimer and fibrinogen, occurs in almost all models, which may lead to loss of linear information [45]. In addition, univariable analysis is a popular approach for predictor selection; however, this may miss some important predictors that are confounded by other predictors [45]. Furthermore, internal validation is necessary for directing an adjustment to build a robust risk prediction model, but in the VTE risk model development studies in ambulatory patients with lung cancer, internal validation was overlooked [45].

Model overfitting in risk model development could arise from issues such as small EPV, dichotomisation of continuous predictors, selecting predictors solely based on univariable analysis, or lack of internal validation with bootstrapping or cross-validation in the development studies. A lack of calibration is the next problem in both risk model development and validation. Calibration indicates the accuracy of a risk model by showing agreement between the expected number of events based on the risk model and the observed number of events [46]. Calibration is indispensable in the external validation of prognostic risk models, and calibration plots are even suggested at more than one time point for those models with competing risks [47]. Last but not least, there is use of a derived clinical score in risk models that does not reflect the actual weight of a predictor from the multivariable analysis in VTE risk model development [38]. The logistic regression equation is the actual expression of the risk model developed from the data [23].

Validation of VTE risk models should include patients receiving all currently approved medications, including anticoagulation therapies in this context. Ideally, a VTE risk model to be used in cancer patients should also provide some hint as to the most suitable medication to be used [48]. To address the growing clinical complexity, use of novel technologies, such as information-technology-powered decision support systems and Artificial Intelligence (AI) algorithms might be helpful both in the development and the validation phases. In this regard, preliminary studies have recently provided promising results [48][49].

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