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Review Article

A systematic review of biomarkers for the prediction of thromboembolism in lung cancer — Results, practical issues and proposed strategies for future risk prediction models

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ABSTRACT

Introduction: This review aimed to identify candidate biomarkers for the prediction of thromboembolism (TE) in lung cancer.
Materials and methods: Systematic review of publications indexed in PubMed or EMBASE databases in the past 5 years (01/05/2011–01/05/2016) which evaluated baseline and/or longitudinal biomarker measurements as a predictor of subsequent TE (venous and arterial) in lung cancer patients.
Results: Of 1105 studies identified, 18 fulfilled predefined inclusion criteria: 6 prospective and 12 retrospective. The 18 studies included 11,262 patients and 36 unique biomarkers. The combined TE rate was 7% (741/10,854), increasing to 11% (294/2612) within prospective studies. All biomarker measurements were baseline only, with no longitudinal assessment reported. The most frequently investigated biomarkers were tumour-related driver mutations, D-dimer, haemoglobin, white cell, and platelet count; as well as biomarker combinations previously used in risk prediction models, such as Khorana risk score. Biomarker thresholds rather than continuous variable analyses were generally applied, however thresholds were not consistent across studies. D-dimer and epidermal growth factor receptor mutation were the strongest and most reproducible predictors of TE.
Conclusion: An important limitation is the lack of prospective data across specific subpopulations of cancer, with correlative, and preferably longitudinal, biomarker assessments. This would provide insight into the pathophysiology, allow patient profiling, and the development of personalised decision-making tools that can be used real-time and throughout the course of the patients' journey, for targeted, risk-adaptive preventative strategies.

Contents

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1. Introduction

As a commonly diagnosed and well established thrombogenic cancer, lung cancer is a major contributor to cancer associated thromboembolism (TE) [1,2]. TE is a major complication and an important contributor to morbidity and mortality, however the risk is dynamic and heterogeneous. Various thrombogenic biomarkers have been utilised to predict risk in various populations, with discordant success.

The pathophysiology is complex and involves the interaction between the tumour (oncogenes and proteins), intracellular signalling pathways, coagulation system and the anticancer treatment [3–5]. As a consequence, the overall TE risk is heterogeneous even within lung cancer populations and moreover, is dynamic over the individual patient's journey. As such, a generic broad application of thromboprophylaxis particularly given the potential concomitant bleeding risks, is not appropriate, as reflected by low utilisation of preventative therapy outside of hospitalisation and/or surgery [6,7].

Clinicians are looking for simple, practical and relevant methods to risk stratify patients, real time in the clinic and enable a personalised targeted approach to TP. Despite the existence of validated risk assessment models for the prediction of cancer associated TE, [8,9] they have not resulted in decision-making algorithms for prophylactic therapy among patient groups. A major limitation has been the substantial population heterogeneity within the derivation and validation cohorts, with TE rates across included cancer populations ranging from <1% to 40%, [10,11] and resultant poor sensitivity and potency of biomarkers. Moreover studies have not measured longitudinal change over time, or considered competing factors, which results in an overall underestimation of the true effect for high TE risk patients during high risk periods.

The conventional Khorana risk score for the prediction of TE among cancer patients receiving ambulatory chemotherapy considers site of cancer, body mass index (≥35 kg/m^2), haemoglobin level (<100 g/L), platelet count (≥350 × 10^9) and white cell count (≥11 × 10^9) [8]. The model is simple and contains parameters that can be measured real time and in routine diagnostic laboratories. However, these clinical and non-specific laboratory markers achieve only modest sensitivity and specificity, which is paramount in risk-prediction tools. Adaptations to improve performance have included additional biomarkers p-selectin and D-dimer [9], and weighting for patients receiving chemotherapy regimens associated with the highest rates of TE (cisplatin, carboplatin or gemcitabine) [12]. Within these models, lung cancer with no additional risk factors, already achieves an intermediate TE risk score. Moreover, the cited "thrombogenic" chemotherapy agents are those commonly used for the treatment of lung cancer, and biomarkers such as D-dimer are regularly elevated in patients with lung cancer [13–15]. As such, the current models lack stratification power, and would suggest that all lung cancer patients warrant consideration of thromboprophylaxis, for the entirety of their treatment. The FRAGMATIC study assessed this approach in a multi-centre, randomised controlled trial comparing standard treatment plus low molecular weight heparin (LMWH) versus standard treatment alone in >2000 patients with newly diagnosed lung cancer [16]. Non-targeted LMWH prophylaxis reduced the risk of TE by 40% in the entire cohort (hazard ratio 0.57, p = 0.001). A more targeted strategy would have potentially resulted in a greater risk reduction in patients identified at intermediate to high TE risk, while avoiding unnecessary intervention in those with the lowest risk. Importantly, supportive treatments should focus on outcomes such as improved morbidity, quality of life, decreased health resource utilisation, rather than lack of survival benefit. But this result (hazard ratio for 1 year survival 1.01, p = 0.814) in the FRAGMATIC study has likely contributed to lack of global uptake for primary TE prophylaxis in lung cancer patients [16].

This systematic review was undertaken to identify candidate biomarkers in patients with lung cancer and propose future strategies for the development of a dynamic TE risk prediction tool, which contributes to appropriate real-time decision-making algorithms.

2. Methods

2.1. Search strategy

Papers indexed in PubMed (including MEDLINE via NCBI) and EMBASE (via OVID) were systematically searched for the most recent 5-year period (01/05/2011–01/05/2016). Reference lists of retrieved articles were reviewed for additional citations. Broadly, the search strategy combined the following key search terms: thromboembolism/deep vein thrombosis/pulmonary embolism, AND biomarker/risk factor, AND lung cancer; full search strategy available as Supplementary material.

2.2. Inclusion criteria

Studies included in the analysis were required to report i) data analyses on a defined lung cancer population as entire cohort or stratified subset of mixed cohort; ii) at least one biomarker either as single baseline or longitudinal measurements, as a predictor of risk for TE; iii) a measure of association (or ability to calculate) between biomarker and TE. Patients could receive any or no anti-cancer treatment and any or no thromboprophylaxis. TE was defined as any venous thromboembolism (VTE) or arterial thromboembolism (ATE) including but not limited to deep vein thrombosis (DVT), pulmonary embolism (PE), cerebral vascular accident (CVA) or acute myocardial infarction (AMI).

2.3. Data collection and analysis

Two independent authors assessed study inclusion and quality. Data was extracted by author one and then reviewed and validated by author two. Principal summary measures extracted were biomarker levels, TE rates, and TE risk (hazard ratio (HR), odds ratio (OR)). Where appropriate, data was pooled using a random effects model in Review Manager 5.3 software [17]. Risk of bias assessments was conducted using the Newcastle-Ottawa Scale (NOS) [18], a validated tool for non-randomised studies [19]. Within the NOS a total of 4 points can be allocated for selection methods, 2 points for comparability of cohorts or cases and controls, and 3 points for outcomes or exposures [18].

3. Results

The search strategy identified 1105 studies of which 18 (6 prospective and 12 retrospective) fulfilled predefined inclusion criteria and were included in the final review, Fig. 1. The 18 studies included 11,262 patients and 36 unique biomarkers. All studies investigated venous events (deep vein thrombosis (DVT) and/or pulmonary embolism (PE)), with no study including arterial thrombotic events. Anticancer treatments varied: chemotherapy (5 studies); surgery (2 studies); any chemotherapy, radiotherapy, surgery or biologic therapy (5 studies); and treatment not specified (6 studies).