The Prognostic Influence of Venous Thromboembolism in Non-Small Cell Lung Cancer: A Meta-Analysis and Systematic Review

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Research

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Abstract

**Background:** Patients with non-small cell lung cancer (NSCLC) have a significantly higher risk of developing venous thromboembolism (VTE), a condition that significantly influences the prognosis of these patients. However, the impact of VTE on the survival of NSCLC patients remains unclear. We aim to evaluate the impact of VTE on the mortality of patients with NSCLC.

**Methods:** We systematically reviewed all indexed studies examining the prognosis of NSCLC patients with VTE. Web of Science, EMBASE, PubMed, and the Cochrane Library were searched through December 31, 2019 to identify relevant studies. Fixed- or random-effects models were chosen based on heterogeneity.

**Results:** Twelve articles with 6480 patients were included in this analysis. The heterogeneity of these studies was significant ($I^2=81\%$, $P<0.01$). The overall survival (OS) of NSCLC patients with VTE was shorter compared to patients without VTE (HR=1.71, 95% CI [1.39–2.10], $P<0.01$). Two small groups of SCLC patients were excluded and the remaining patients were divided into the Asian and non-Asian groups. The Asian group showed low heterogeneity ($I^2=35\%$, $P=0.20$), in which NSCLC patients with VTE also had shorter OS (HR=1.49, 95% CI [1.19–1.88], $P<0.01$).

**Conclusions:** VTE is significantly associated with a shorter OS of NSCLC patients, especially in Asian patients. Proper prevention and management of VTE is the key to improving the survival of patients with NSCLC.

Introduction

The association between cancer and venous thromboembolism (VTE) was first identified in 1865 [1]. VTE is a medical condition that includes deep vein thrombosis (DVT), pulmonary embolism (PE), and Trousseau syndrome (migratory thrombophlebitis). Approximately 20% of VTE cases occur in cancer patients [2, 3]. Moreover, cancer-associated VTE is more aggressive and usually associated with worse prognosis [4].

Lung cancer is one of the most common cancers worldwide with a 5-year survival rate of only 19% [5, 6]. Non-small cell lung cancer (NSCLC) accounts for 80–85% of the lung cancer cases [7]. The incidence of VTE in NSCLC patients is 7.3–13.6% [8, 9]. VTE in cancer patients, including NSCLC patients, may lead to devastating consequences, including thrombotic events, treatment-related bleeding, delay in chemotherapy, and drug interactions [10].

Cancer patients with VTE have up to three times higher risk of one-year mortality compared to those at the same stage of the disease but without thrombosis [4, 11]. Specifically, lung cancer patients with DVT have a 1.29-fold higher risk of mortality compared to those without thrombotic events (95% CI: 1.12–1.48) [12]. Most large cohort studies investigated the general population with cancer rather than NSCLC patients. The prognostic influence of VTE can only be evaluated through subgroup analysis. However, previous studies mainly focused on more specific subgroups, such as lung cancer patients with PE [13], patients with early-staged or resectable NSCLC[14], and lung cancer patients with preventive anticoagulation [15]. Many oncologists pay attention to the treatment of the tumor itself, lack of awareness of VTE, meanwhile, the treatment strategies of NSCLC have been emerging in recent years, there is need to evaluate and update the understanding of the prognostics of NSCLC with VTE. Therefore, a meta-analysis was performed in this study to investigate the impact of VTE on the survival of NSCLC patients by comparing the overall survival (OS) between NSCLC patients with and without VTE. We further discussed the importance of VTE management and prevention in improving the prognosis of NSCLC patients.

Methods

**Literature search**

A comprehensive systematic search was performed in four major databases (Web of Science, EMBASE, PubMed, and Cochrane Library) on December 31, 2019. The following terms were used: ["non-small cell lung cancer" OR "NSCLC"] AND ["venous thromboembolism" OR "VTE" OR "deep vein thrombosis" OR "DVT" OR "pulmonary thromboembolism" OR "PE"]. We reviewed the reference lists of included studies for additional screening.

**Study selection**

The inclusion criteria for screening studies were: (1) study population was NSCLC patients complicated with VTE; (2) the control group was NSCLC patients without VTE; (3) endpoints included OS or progression-free survival (PFS); (4) a Newcastle-Ottawa Scale (NOS) score of > 5 points.

Studies were excluded if (1) there was no control group or the control group was not non-VTE NSCLC patients; (2) the endpoint was not PFS or OS; (3) not published in English; (4) published in the format of review articles, short survey, case report, meeting reports, or grey literature; (5) repeated previous findings; (6) only reported non-clinical results.

**Date extraction and literature evaluation**

Two investigators (YB and XM) independently reviewed the titles and abstracts of the articles and then selected potentially relevant studies based on the inclusion/exclusion criteria. Data were extracted using a standardized form and categorized as follows: name of the first author, year of publication, research type, number of eligible patients, classification of NSCLC, pathological typing of NSCLC, age, sex, and endpoints. Finally, the extracted data were cross-checked and any discrepancies were discussed with a third investigator. Each included article was evaluated for the risk of bias using a modified version of the NOS. Only high-quality articles with a score of greater than 5 were selected.

**Statistical analysis**
RevMan 5.3 (The Cochrane Collaboration, London, UK) was used for analysis. The heterogeneity was evaluated by the Q test and the $I^2$ test metric [16]. Heterogeneity was considered to be present when $p < 0.1$ and $I^2 > 50\%$. A random-effects model was then selected to calculate pooled hazard ratio (HR) and 95% confidence interval (CI) with a forest plot. When heterogeneity was not present, a fixed-effects model was used to estimate pooled HR and 95% CI. Kaplan-Meier survival curves were read by Engauge Digitizer (version 12.0) to obtain HR and 95% CI [17]. Publication bias and sensitivity analysis were performed using STATA 15.0 (StataCorp LLC, College Station, USA).

**Results**

**Search result**

Of the 5,096 studies identified by the search strategy, 2,574 remained after eliminating duplicates. Of these, 2,550 were excluded after screening the titles and abstracts, leaving 24 articles for full-text review. Twelve articles were further excluded after full-text screening following the inclusion/exclusion criteria. Finally, twelve articles were included in the analysis. The screening process was summarized in Fig. 1.

**Characteristics of included studies**

Of the 12 articles, two included a small group of patients with small-cell lung cancer (SCLC) [18][19], whereas the rest only recruited NSCLC patients [9, 14, 20–27]. All studies compared the OS between NSCLC patients with and without VTE. Four of them were prospective observational cohort studies [14, 20, 22, 27] and the remaining eight were retrospective studies [9, 18, 19, 21, 23–26]. All included articles were of high quality (Table 1).
<table>
<thead>
<tr>
<th>Study</th>
<th>Year of publication</th>
<th>Country</th>
<th>Study type</th>
<th>Group</th>
<th>Number of patients</th>
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<th>Age (years)</th>
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Abbreviations: VTE, venous thromboembolism; M, male; F, female; PE, pulmonary embolism; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; LCNEC, large cell neuroendocrine carcinoma.
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Abbreviations: VTE, venous thromboembolism; M, male; F, female; PE, pulmonary embolism; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; LCNEC, large cell neuroendocrine carcinoma.

Comparison of OS between NSCLC patients with and without VTE

Twelve studies explored the relationship between VTE and OS in NSCLC patients [9, 14, 26, 27, 18–25]. Significant heterogeneity was present in the analysis of OS between VTE and non-VTE NSCLC patients ($I^2 = 81\%, p < 0.01$). Therefore, pooled HR was calculated by a random-effects model. The analysis showed that NSCLC patients with VTE had significantly short OS compared to those without VTE (HR = 1.71, 95% CI [1.39–2.10], $p < 0.01$) (Fig. 2).

Comparison of OS between NSCLC patients with and without VTE in different subgroups

As the heterogeneity was high, we further conducted a subgroup analysis. Firstly, we excluded two studies with a small number of SCLC patients [18, 19]. The remaining ten studies [9, 14, 20–27] were divided into two subgroups according to the race of the study population. Studies in the first subgroup ($n = 4$) compared the OS between Asian NSCLC patients with and without VTE, whereas studies in the second group ($n = 6$) compared the OS between non-Asian patients with and without VTE. The first subgroup was homogeneous ($I^2 = 35\%, p = 0.20$), while the non-Asian subgroup showed significant heterogeneity ($I^2 = 74\%, p < 0.01$). Therefore, a random-effects model was used to evaluate the pooled effect of OS in NSCLC patients (Fig. 3). The meta-analysis demonstrated...
that NSCLC patients with VTE had shorter OS compared to those without VTE (Asian group: HR = 1.49, 95% CI [1.19–1.88], \( p < 0.01 \); non-Asian group: HR = 1.52, 95% CI [1.37–1.68], \( p < 0.01 \); Total population: HR = 1.51, 95% CI [1.38–1.66], \( p < 0.01 \)) (Fig. 3).

**Publication bias and sensitivity analysis**

The Begg’s funnel plot (\( p = 0.381 \)) and Egger’s test (\( p = 0.149 \)) showed no publication bias (Fig. 4). Additionally, pooled HR was not significantly changed after removing individual studies. Therefore, our results were stable and reliable.

**Discussion**

VTE is a common and life-threatening condition that occurs in cancer patients [1][2]. Lung cancer is the leading cause of cancer-related death worldwide [6] and the incidence rate of VTE reaches 14% in lung cancer patients [28]. VTE leads to a higher risk of death, higher cost of treatment, and lower quality of life in NSCLC patients [18, 29, 30]. Factors related to the formation of VTE include individual factors and tumor-related factors. A large prospective study showed that older patients had a 10-fold higher incidence of VTE relative to young patients [31]. Meanwhile, different gender can also be a risk factor for VTE [32, 33]. Additionally, a large retrospective study reported that [33] the highest rate of VTE (about 5%) was observed in African American patients, while the lowest rate (3%) was found in Asian/Pacific Islander patients. Surgery and chemotherapy have been shown to increase the risk of VTE as well. Cancer patients have a six- to seven-fold higher risk of developing chemotherapy-associated thrombosis [34]. Chemotherapy-related VTE was first identified in patients treated with cisplatin, a platinum-based drug that has been widely used in many cancers [35]. Other drugs such as tamoxifen, L-asparaginase, lenalidomide, immunosuppressive and cytotoxic drugs have also been reported to increase the risk of VTE [36]. Recent evidence has indicated that some oncogenic driver mutations in NSCLC are related to VTE, such as anaplastic lymphoma kinase (ALK) [25] and ROS-1[37].

In this meta-analysis, 12 articles were included, involving 6,360 NSCLC and 120 SCLC patients. SCLC is a type of lung cancer with completely different pathological features and biological behavior, as well as different treatment strategies. We first performed a heterogeneity test based on the above-mentioned VTE-related factors and found that the heterogeneity of this meta-analysis was high (\( I^2 = 81\% \), \( P < 0.01 \)). The heterogeneity still existed after excluding the studies with SCLC patients. Also, there was still some heterogeneity in the Asian and non-Asian subgroups (data not shown). However, when studies with SCLC patients were removed, low heterogeneity was observed in the Asian subgroup. Since most of the studies included patients treated with chemotherapy, radiotherapy, and surgical treatment, we did not categorize them according to therapeutic regimens. Because of the high heterogeneity of the included studies, we used random-effects models for the analysis.

Our results showed that the OS of NSCLC patients with VTE was significantly shorter compared to those without VTE (HR = 1.71, 95% CI [1.39–2.10], \( P < 0.01 \)). We deleted studies by Lee et al. [19] and Kourelis et al.[18], which included patients with SCLC. The remaining studies were divided into two subgroups: Asian and non-Asian. The heterogeneity of the Asian subgroup significantly decreased (\( I^2 = 35\% , P = 0.20 \)). Both subgroups showed that NSCLC patients with VTE had shorter OS than those without VTE. The sensitivity analysis showed that studies contributing to the heterogeneity did not significantly affect the pooled results, suggesting that our results were statistically robust.

A cohort study compared the survival of cancer patients with or without VTE and observed a higher mortality rate in those who experienced VTE (OR = 2.20, 95% CI [2.05–2.40]). The mortality ratio of patients who were diagnosed with cancer within one year after the diagnosis of VTE was 1.30 times (95% CI: 1.18–1.42) higher relative to those without VTE [4]. Therefore, it is certain that VTE exerts a negative influence on the prognosis of cancer patients. A review involving 412,008 patients showed that 2.5% of them developed VTE and had a higher mortality compared to those without thrombotic events (HR = 1.38; 95% CI [1.28–1.49]). Lung cancer patients had a 1.29-fold greater risk of mortality (95% CI [1.12–1.48]) when complicated with VTE [12], which was slightly lower than our results. It has also been shown that lung cancer patients with PE had significantly shorter survival compared to the control group (243.5 vs. 327 days, \( p = 0.01 \)), and a more significant difference was found in patients who were simultaneously diagnosed with PE and lung cancer [13].

Lung cancer is a very heterogeneous type of tumor disease, at a cellular and histological level[38]. The treatment strategies and prognostic outcomes of different lung cancer pathological types are very different. Lung cancer patients in a hypercoagulable state are related to the primary disease. The understanding of lung cancer heterogeneity is crucial to the awareness of the VTE implications and future developments regarding this field. For risk assessment of lung cancer patients with VTE, more targeted risk prediction models based on the pathological types should be explored, and corresponding molecular biomarkers should also be investigated.

However, our study has some limitations. First, we only reviewed English articles, which may lead to language bias. Second, data were extracted from the forms and converted to HR values, which may not accurately describe the original results. However, despite limitations, the study provides a clear understanding of management of NSCLC with VTE in clinical practice.

**Conclusions**

In summary, our meta-analysis showed that VTE had a significantly negative impact on the prognosis of NSCLC patients, especially Asian patients (HR for OS = 1.49; 95% CI = 1.19–1.88). At present, multidisciplinary teams, including clinicians, nurses, and pharmacists, are increasingly involved in the overall management of cancer patients with VTE. It is of great importance to furtherly identify risk factors including pathological types, molecular heterogeneity, biomarkers, and therapeutic regimens for lung cancer with VTE for future investigations.

**Abbreviations**

NSCLC
Declarations

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All data used for the systematic review and meta-analysis is present in the main manuscript in the Table.

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References


