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Risk factors and prognosis of pulmonary embolism in patients with lung cancer

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Abstract

Malignant tumors are often complicated with venous thrombosis and pulmonary embolism (PE), particularly in lung cancer. However, owing to the limited data regarding the clinical course about PE in lung cancer patients, the aim of this study is to analyze the risk factors and prognosis of patients with PE and lung cancer. We performed a retrospective case–control study, the clinical data of 90 patients in the First Affiliated Hospital of People's Liberation Army General Hospital between Jan 2010 and Jan 2015 were analyzed, including 30 lung cancer patients with PE (PE group), 60 lung cancer patients without PE (non-PE group), treated during the same period. Logistic regression analysis was applied to explore risk factors of PE. Patient survival was also compared with matched controls via a log-rank test. The multivariate analysis revealed that adenocarcinoma, stage III to IV, high D-dimer, and low PaO_2 were independent risk factors. The survival time in patients with PE was remarkably lower than that in patients without PE ($P < .0005$). Adenocarcinoma, stage III to IV, high D-dimer and low PaO_2 are important risk factors for lung cancer patients with PE. PE suggested a poor prognosis in lung cancer patients.

Abbreviations: CT = computed tomography, PE = pulmonary embolism, VTE = venous thromboembolism, WBC = white blood count.

Keywords: lung cancer, prognosis, pulmonary embolism, risk factor

1. Introduction

Cancer is a well-known cause of venous thromboembolism (VTE). Pulmonary embolism (PE) and deep vein thrombosis are both manifestations of VTE. Lung cancer is the most common malignancy coexisting in patients with VTE.[1] A large population-based, case–control study recently demonstrated that patients with hematologic malignancies had the highest risk of VTE, followed by patients with lung and gastrointestinal cancers.[2]

In China, lung cancer has the highest incidence, and it is the leading cause of mortality of all cancers. It has been estimated that lung cancer is the sixth most frequent malignancy responsible for PE.[3] PE is a well-known poor prognostic factor in cancer patients,[4] as the result of a direct relationship with fatality or an association with more aggressive tumor biology. However, there is very little information available pertaining to the relationship between PE and lung cancer. We performed the present retrospective case–control study to investigate the clinical course of lung cancer patients with PE and evaluate risk factors associated with the development of PE as well as the prognosis of PE in lung cancer patients.

2. Patients and methods

2.1. Patients

Institutional review board approval was obtained before conducting this study. Written informed consent was waived because this study was retrospective. Two groups of people were selected between Jan 2010 and Jan 2015 from the First Affiliated Hospital of People's Liberation Army General Hospital. The PE group was composed of 30 lung cancer patients with PE. The non-PE group was randomly selected among the patients who had lung cancer diagnosed without evidence of PE and were treated during the same time period, and patients with previous thromboembolic events were excluded. The non-PE group (n = 60) was matched (2:1) with the PE group based on gender, age (±5 years), and treatment modality (chemotherapy, radiotherapy, and epidermal growth factor receptor tyrosine kinase inhibitor therapy or no therapy).

The diagnosis of each patient was confirmed by clinical outcome, imaging diagnosis, and histological examinations. The diagnosis of PE was confirmed if the patient's clinical features were validated by imaging studies, including echocardiography, computed tomography (CT), magnetic resonance imaging, or ventilation/perfusion

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We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work; there is no professional or other personal interest of any nature or kind in any product, service, and/or company that could be construed as influencing the position presented in, or the review of the manuscript entitled. The paper is not based on a previous communication to a society or meeting. The paper has gained ethics committee approval.

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Table 1

Characteristics of patients in PE group and non-PE groups.

	PE group (n = 30)	Non-PE group (n = 60)	*P*
Age, y	67.4 ± 10.1	65.0 ± 11.5	.805
Gender (male/female)	20/10	40/20	1
Smoking history	21/9	48/12	.723
Comorbidities			
Diabetes	2 (6.7)	5 (8.3)	.834
Pulmonary tuberculosis	1 (3.0)	2 (3.0)	1.000
Hypertension	5 (16.7)	8 (13.3)	.743
Cardiovascular disease	3 (10.0)	8 (13.3)	.786
Chronic obstructive pulmonary disease	2 (6.6)	5 (8.3)	.641
Histologic types of lung cancer			
Adenocarcinoma	13 (43.3)	28 (46.7)	.876
Small-cell carcinoma	7 (23.3)	13 (21.6)	.892
Squamous cell carcinoma	8 (26.7)	15 (25.0)	.795
Non-small-cell carcinoma	2 (6.6)	4 (6.7)	.945
Stage of lung cancer			
I–II	3 (10.0)	15 (25.0)	.316
III–IV	27 (90.0)	45 (75.0)	.285
Laboratory data			
WBC, $\times 10^9$/L	8.6 ± 4.2	8.8 ± 3.7	.865
Hemoglobin, mg/dL	11.2 ± 4.5	12.1 ± 3.6	.853
Platelets, $\times 10^9$/L	275 ± 84	248 ± 96	.769
D-dimer, μg/L	865 ± 489	334 ± 179	.0001
PaO_2, mm Hg	58 ± 16	85 ± 13	.002

PE = pulmonary embolism, WBC = white blood count.

scan. On CT scan, PE was diagnosed as a sharply delineated pulmonary arterial filling defect present in at least 2 consecutive image sections and located centrally within the vessel or with acute angles at its interface with the vessel wall.[5] A diagnosis of PE was also made on the basis of the findings of a perfusion/ventilation scan fulfilling the criteria of high probability.[6] The medical records of the patients were reviewed for demographics, clinical characteristics, laboratory data, clinical course, and survival data. The laboratory data obtained included arterial blood gas analysis, D-dimer, white blood count (WBC), and platelet.

2.2. Statistical analysis

Statistical analysis was performed with SPSS software, version 15.0 for Windows (SPSS Inc., Chicago, IL). Results were given as percentages, mean and standard deviations, or median and ranges. Differences in clinicopathological parameters between patients with and without PE were determined by means of the χ^2 test. Variables with $P < .05$ in univariable analysis were included in the multivariable analysis. Multivariable stepwise logistic regression analysis was used to identify independent risk factors for PE. The hazard ratio and 95% confidence interval were calculated. Overall, survival curves were calculated using the Kaplan–Meier method. Comparisons between curves were carried out by the log-rank test. $P < .05$ was considered statistically significant.

3. Results

3.1. Demographics

Patients' characteristics are presented in Table 1. This study included 30 patients with PE group (male/female: 20/10) and 60 cases non-PE group (male/female: 40/20). The median age of the PE group was 68.5 years (34–81 years), and the median age of the non-PE group was 65.5 years (35–82 years). The smoking status and comorbid conditions did not differ between the PE and non-PE groups. Adenocarcinoma (43.3%, n = 13) was the most common histological type of PE group, followed by squamous cell carcinoma (26.7%, n = 8) and small-cell carcinoma (23.3%, n = 7). According to The TNM Classification of Malignant Tumors staging,[7] when PE was diagnosed, most of the lung cancer patients were in stages III and IV (90.0%, n = 27).

PE was the accompanying presentation of 3 (10.0%) patients admitted for establishing lung cancer diagnosis. Eight (26.7%) patients had PE established before the diagnosis of lung cancer. Nineteen (63.3%) patients had PE established after the diagnosis of lung cancer. The median time to the development of PE after lung cancer diagnosis was 3.5 months, ranging from 1 to 6.5 months.

3.2. Risk factors related to pulmonary embolism of all patients by multivariate analysis

Multivariable stepwise logistic regression analysis was used to identify independent risk factors for PE. The multivariate analysis revealed that adenocarcinoma, stage III to IV, high D-dimer, and low PaO_2 were independent risk factors associated with PE (Table 2). There was no significant difference in smoking history, comorbidities, WBC, hemoglobin, and platelets counts.

3.3. Clinical course and survival

The survival time of PE group was significantly shorter than in non-PE group ($P < .0005$, log-rank test; Fig. 1); median survival was 6.65 and 17.0 months, respectively. Twenty-seven of all (27/30, 90.0%) lung cancer patients with PE died during the follow-up, 1 patient was lost to the follow-up, and 2 patients were alive at the end of the follow-up. Five patients died of thromboembolic events: stroke, disseminated intravascular coagulopathy, and PE; the other 22 patients died of tumor progression. All patients in the PE group received unfractionated heparin intravenously or

Table 2

Risk factors for PE in patients with lung cancer by multivariate analysis.

Factor	OR	95% CI	*P* value
Adenocarcinoma	3.6	1.32–4.84	.018
III–IV	2.6	2.73–5.21	.029
D-dimer	3.1	1.79–4.32	.023
PaO_2	2.7	1.31–3.98	.014

CI = confidence interval, OR = odds ratio.

low-molecular-weight heparin subcutaneously, followed by an oral anticoagulant.

4. Discussion

PE is a blockage of an artery in the lungs by a substance that has traveled from elsewhere in the body through the bloodstream (embolism). The overall incidence rates of PE in cancer patients are higher than those in patients with other types of illness and increase rapidly over time. In the study by Sorensen et al,[1] the most common sites of cancer occurring concomitant with thromboembolic events are the lung, prostate, breast, colon, and rectum. The complex interactions between malignant tumor cells and procoagulant, fibrinolytic have also been associated with the progression of cancer. The coagulation system, which is activated in most cancer patients, has an important role in tumor biology.[8,9] It may make a substantial contribution to tumor angiogenesis and metastasis.

In our study, the most common histologic type was adenocarcinoma (43.3%); all of them were in advanced stage when PE was diagnosed. Previous studies reported that patients with adenocarcinoma of the lung had a higher risk of thromboembolic events.[10,11] The effects of mucin production on procoagulatory factor activation may trigger thromboembolic events.[12–14] Recently, Blom et al[11] demonstrated that the risk of VTE in lung cancer patients increased 20-fold compared to the general population and that patients with adenocarcinoma have a higher risk of VTE than patients with squamous cell carcinoma. D-dimer concentration may be determined by a blood test to help diagnose thrombosis. Since its introduction in the 1990s, it has become an important test performed in patients with suspected thrombotic disorders. Our study proved the value of the D-dimer test in the diagnosis of thromboembolic events of lung cancer patients. In addition, 70.0% of our lung cancer patients with PE had a smoking history. There are scarcely articles mentioning the relationship between cancer with PE and smoking.

In this report, the survival of lung cancer patients with PE was shorter than that of their matched patients. So far, the prognosis of PE in lung cancer patients has rarely been reported. Our results corroborate a previous report describing poor survival in cancer patients with thromboembolic events.[1] Most patients in the PE group had advanced stages of lung cancer, and the median survival was merely 6.65 months. When PE was diagnosed, most of the lung cancer patients were in stages III and IV. This may be another important factor contributing to the significant shorter survival time in PE group, so the conditions of those patients were worse already compared to their counterparts in non-PE group. The primary cause of death in the PE groups was lung cancer progression. Most of our patients received only supportive care after PE, pinpointing the important roles of PE in lung cancer patients such as affecting survival time and possible treatment strategies.

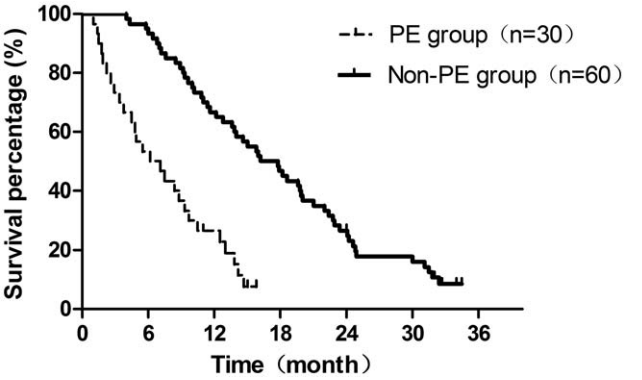

Figure 1. Survival curves for lung cancer patients with pulmonary embolism (PE) and without PE.

In conclusion, PE occurred more frequently in advanced stages of lung cancer, the most common histological type was adenocarcinoma, and D-dimer test was important. Survival time was significantly different between lung cancer patients with and without PE. PE suggested a poor prognosis. Owing to expected low PE incidence among patients with lung cancer, further studies are required to evaluate the prognostic significance of PE in lung cancer.

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