Original Article

Anaplastic lymphoma kinase rearrangement may increase the incidence of venous thromboembolism by increasing tissue factor expression in advanced lung adenocarcinoma

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Background: Patients with lung cancer are at an increased risk for venous thromboembolism (VTE). Approximately 8–15% of patients with advanced non-small-cell lung cancer (NSCLC) experience a VTE throughout the course of the disease. However, the incidence of VTE in different NSCLC molecular subtypes is rarely reported, although there are significant differences in clinical feature and prognosis. Tissue factor (TF) expressed in many solid tumors could trigger the downstream coagulation cascade and lead to thrombin generation and clot formation.

Methods: In the present study, retrospective data were obtained from electronic medical records at Henan Cancer Hospital in China between January 2015 and January 2017. Advanced lung adenocarcinoma patients with anaplastic lymphoma kinase (ALK) rearrangement, epidermal growth factor receptor (*EGFR*) mutation and both negative were included in the present study. The incidence of VTE of these patients was calculated. We then randomly selected ALK-rearrangement-positive and -negative lung adenocarcinoma tissues (n=29 and n=26, respectively) and detected TF protein expression via immunohistochemistry.

Results: At a median follow up of 2.5 years, 5.85% (n=30/513) patients with advanced lung adenocarcinoma experienced VTE. Compared to patients with *EGFR* mutation (n=11/218, 5.05%) or both negative (n=13/266, 4.89%), patients with ALK-rearrangement were more likely to develop VTE (n=6/29, 20.69%; P=0.006, P=0.004; respectively). In ALK-rearrangement-positive tissues, 41.67% (n=10/24) had a high TF protein expression; the incidence was significantly higher than the TF protein expression in ALK-negative tissues (11.54%, n=3/26, P=0.015).

Conclusions: ALK-rearrangement-positive NSCLC patients are more likely to develop VTE; this might be due to a higher TF expression in tumor tissues.

Keywords: Non-small cell lung cancer (NSCLC); venous thromboembolism; anaplastic lymphoma kinase; tissue factor

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Introduction

Patients with advanced lung cancer often experience venous thromboembolism (VTE), a condition that is associated with poor quality of life and decreased overall survival (1-3). The risk of VTE varies between cancers, and has been found to increase in the first several months after initial diagnosis (3,4). It is important to consider cancer tumor stage and treatment methods in the risk of VTE; for example, more advanced disease and the use of chemotherapy are associated with a greater risk of VTE (5).

Preclinical data suggest that oncogenes, such as estimated glomerular filtration rate (*EGFR*), *RAS*, and phosphatase and tensin homolog (*PTEN*), could induce the expression of genes controlling hemostasis (6-10); however, there are limited reports about the relationship between oncogene status and the risk of VTE. Additionally, the exact mechanism responsible for VTE development in cancer patients is still not fully understood.

In procoagulant activity, tissue factor (TF) plays an important role (10-12). Additionally, the expression of TF in tumor cells could be controlled by oncogenes (9). In tumor cells, TF is usually highly expressed, which can increase the onset of VTE (13).

The management of non-small cell lung cancer (NSCLC) has transformed from homogeneous disease treated mainly with chemotherapy to a condition classified by gene mutation status and treated with corresponding molecular target tyrosine kinase inhibitors (TKIs), that is, medicine with high response rates that can lead to prolonged progression-free survival (14,15). As a result, almost every diagnosis of advanced lung adenocarcinoma over the past decade has been detected with *EGFR* mutation and ALK-rearrangement status, which is generally treated with gefitinib and crizotinib, respectively, in China. We have found in clinical practice that patients with ALK rearrangement are more likely to develop VTE. And ALK-positive patients were significantly younger than EGFR-positive patients. Initial status of stage IV metastatic cancer was more frequently noted in EML4-ALK-positive patients, with initial brain metastasis frequently observed.

In the present study, we evaluated not only the relationship between ALK and the risk of VTE, but also the relationship between EGFR and the risk of VTE. We also exploratively examined TF protein expression to evaluate its association with specific gene status.

We present the following article in accordance with the MDAR reporting checklist (available at http://dx.doi.org/10.21037/atm-20-6619).

Methods

Study population

Patients diagnosed with advanced lung adenocarcinoma from January 2015 to January 2017 in Henan Cancer Hospital were included in the present study if they met the following inclusion criteria: (I) histopathology-confirmed lung adenocarcinoma; (II) TNM stages IIIB–IV; (III) identification of *EGFR* gene mutation status and ALK rearrangement status; and (IV) provided signed informed consent. All participants were followed up for a maximum of 3.5 years and a median of 2.5 years until they died. Both pulmonary embolism and deep venous thrombosis were included in VTE, and were confirmed by computed tomography venous angiogram and venous ultrasound, respectively. Patients confirmed with VTE within 1 month before advanced lung adenocarcinoma diagnosis were also included. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by Ethics Committee of Henan Cancer Hospital (No. 2019060). All the patients in the present study have signed informed consent.

Immunohistochemical (IHC) staining

IHC staining with anti-TF (Abcam) was performed on 24 ALK-rearrangement-positive tissue samples and 26 ALK rearrangement negative tissue samples. Briefly, standard avidin–biotin–peroxidase complex method was used for IHC staining, and tissue sections with a thickness of 5 μm were sectioned from these samples. A dry oven was used to incubate the sections at 60 ℃ for 1 hour. The sections were then deparaffinized and rehydrated in xylene and descending concentrations of graded ethanol; 5% hydrogen peroxide was used to block endogenous peroxidase activity for 10 minutes. For antigen retrieval, slides were boiled in 10% citrate buffer stock in distilled water (pH 6.0) for 10 minutes in a microwave oven; 5% normal goat serum was then used to block non-specific staining for 10 minutes. A 1:50 dilution of anti-TF was used to incubate the slides in a humidified chamber at 4 ℃ for 1 night, and the slides were then incubated with biotinylated goat anti-rabbit immunoglobulin at a concentration of 1:200 at room temperature for 45 minutes. We used an avidin-biotin-

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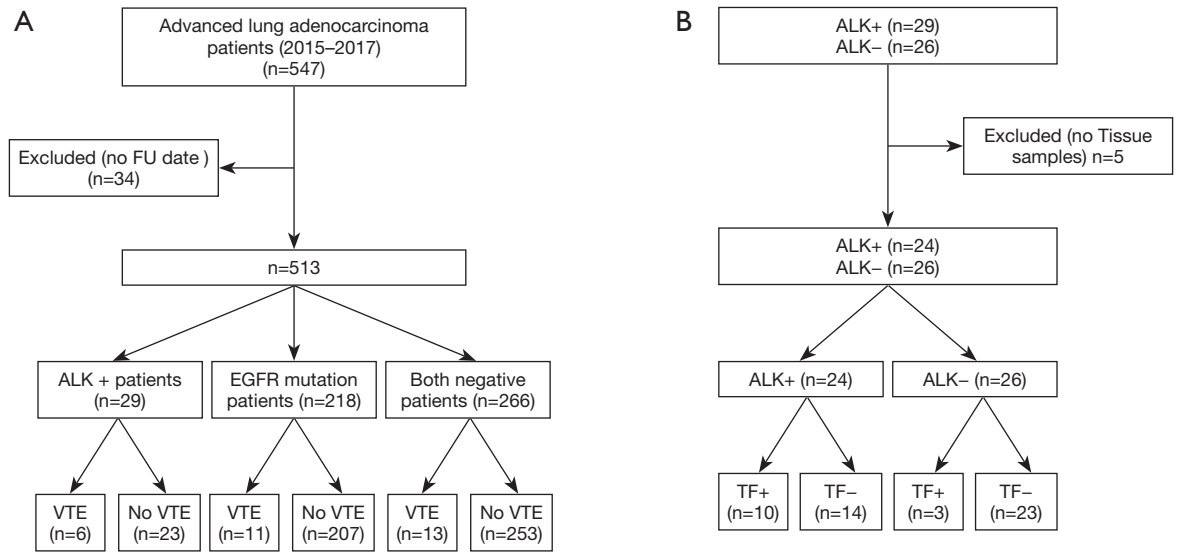

Figure 1 Study design and patient distribution. ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; FU, follow up; TF, tissue factor protein; VTE, venous thromboembolism.

peroxidase complex (Universal Elite ABC Kit, Vectastain) and diaminobenzidine tetrahydrochloride solution (HK153-5K, Biogenex) to develop immunostaining. Pancreatic cancer tissues were used as a positive control (known reactivity for the antibody).

An immunostaining score system was performed on the slides. Anti-TF-positive cell percentage was scored as 0, negative, <5%; 1, sporadic, 5–25%; 2, focal, 25–50%; and 3, diffuse, >50%. Anti-TF-positive staining intensity was scored as 0, negative; 1, weak; 2, moderate; and 3, strong. Both positive cell percentage and cell staining intensity were determined in a double-blinded manner. The total score was then defined as: staining index = positive cell percentage score × staining intensity score. A staining index ≤4 was considered as normal expression, and a staining index >4 was considered as high expression (16).

Statistical methods

Patients were separated into 2 or 3 subgroups based on clinical characteristics, such as smoking history, genotype status, and age. The percentage of VTE incidence was analyzed for patients in each of the aforementioned subgroups. The differences between patients with and without VTE were compared by χ^2 test or Fisher's exact test, as appropriate. Both statistical tests were 2 sided, and P<0.05 was considered statistically significant. All analyses were performed using SPSS version 20.0 (IBM).

Results

Patient characteristics

A total of 547 patients with newly diagnosed advanced lung adenocarcinoma were enrolled in the present study; 34 patients were excluded because of no follow-up data, and 513 patients were left. In the 513 patients, 5.85% (n=30/513) patients with advanced lung adenocarcinoma experienced VTE. Compared to patients with *EGFR* mutation (n=11/218, 5.05%) or both negative (n=13/266, 4.89%), patients with ALK-rearrangement were more likely to develop VTE (n=6/29, 20.69%; P=0.006, P=0.004; respectively) (*Figure 1A*). Baseline characteristics of the 513 patients included in the present study are listed in *Table 1*. The median age of the patients was 59 years, and 249 (48.5%) patients were male. There were 270 (52.6%) patients ≤60 years and 243 (47.4%) patients >60 years old. In total, 431(84%) patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–1, and 83 (16%) patients had an ECOG PS score of 2–4. Of the patients, 325 (63.5%) were non-smokers; 29 (5.7%) had ALK rearrangement, 218 (42.5%) had EGFR mutation, and 266 (51.9%) were negative for both.

Characteristics and TF protein expression

A total of 50 patients (n=24 with ALK rearrangement and n=26 randomly selected from an ALK-rearrangement-

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Table 1 Baseline demographic and clinical characteristics of the study population

Characteristic	All (n=513) (%)	No VTE (n=483) (%)	VTE (n=30) (%)	P value (χ^2-test)
Sex, n (%)				0.335
Male	249 (48.5)	237 (49.1)	12 (40.0)	
Female	264 (51.5)	246 (50.9)	18 (60.0)	
Age (years), median	59	60	58	0.230
≤60 years, n (%)	270 (52.6)	251 (52.0)	19 (63.3)	
>60 years, n (%)	243 (47.4)	232 (48.0)	11 (36.7)	
ECOG PS, n (%)				0.165
0–1	431 (84.0)	409 (84.7)	22 (73.3)	
2–4	83 (16.0)	74 (15.3)	8 (26.7)	
Smoking history, n (%)				0.119
Never	325 (63.4)	302 (62.5)	23 (76.7)	
Past/current smoker	188 (36.6)	181 (37.5)	7 (23.3)	
Genotype status, n (%)				0.018
ALK-rearrangement	29 (5.7)	23 (4.8)	6 (20.0)	
EGFR mutation	218 (42.5)	207 (42.9)	11 (36.7)	
Both negative	266 (51.9)	253 (52.4)	13 (43.3)	

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; VTE, venous thromboembolism; ECOG PS, Eastern Cooperative Oncology Group performance status.

negative cohort) were screened for TF protein expression with IHC; 5 ALK-rearrangement patients were excluded because of the absence of tissue samples (*Figure 1B*). Baseline characteristics of the 50 patients included in the present study are listed in *Table 2*. Of these patients, 28 (56%) were ≤60 years and 24 (48%) were male. Forty-three (86%) patients had an ECOG PS score of 0–1, and seven (14%) had an ECOG PS score of 2–4. There were 35 non-smokers (70%). In total, 24 (48%) patients had ALK rearrangement and 26 (52%) did not have ALK rearrangement. Seven of 50 (14%) patients had experienced a VTE event (*Table 2*). The median age of the 24 ALK rearrangement patients was 55; 16 in 24 were women; 3 in 24 had ECOG PS 2–4 and 18 in 24 never smoke.

Through IHC staining, differential cytoplasmic expressions of the TF protein were observed between patients with and without ALK rearrangement (*Figure 2*). The distribution of the TF protein expression according to sex (P=0.877), age (P=0.640), ECOG PS (P=0.527), and smoking history (P=0.778) was not statistically different. In patients with ALK rearrangement, 10 of 24 (76.9%) cases had highly expressed TF protein, and it was significantly higher (P=0.015) than that of patients who were ALK negative. The distribution of TF protein expression in the VTE group was similar to that of the ALK (P=0.013) (*Table 2*).

Summary of similar studies

Five studies related to ALK rearrangement and VTE are summarized in *Table 3*. Of these 5 studies, 3 also had a 6.6–24.7% VTE rate in an NSCLC population. The VTE rate in the ALK-rearrangement population ranged from 16.7% to 47.1% (17-19). The other 2 studies had a similar VTE rate with the 3 studies in ALK-rearrangement patients (17.1–41.8%) (20,21). In our current study, the VTE rate in the ALK-rearrangement patients was greater than that in the total 513 patients (20.7% *vs.* 5.8%, P=0.017). Then we merged our current study and another 3 studies with both VTE rate and VTE rate in ALK arrangement which I mentioned above. After merged, the VTE rate in ALK-rearrangement patients were much greater than that of NSCLC patients (7.8% *vs.* 26.3%, P<0.001).

Four prospective interventional studies are

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Table 2 Association between tissue factor (TF) protein expression and clinical characteristics

Characteristic	All (n=50) (%)	High TF (n=13) (%)	Normal TF (n=37) (%)	P value (χ^2-test)
Sex, n (%)				0.877
Male	24 (48.0)	6 (46.2)	18 (48.6)	
Female	26 (52.0)	7 (53.8)	19 (51.4)	
Age (years), n (%)				0.640
≤60	28 (56.0)	8 (61.5)	20 (54.1)	
>60	22 (44.0)	5 (38.5)	17 (45.9)	
ECOG PS, n (%)				0.527
0–1	43 (86.0)	10 (76.9)	33 (89.2)	
2–4	7 (14.0)	3 (23.1)	4 (10.8)	
Smoking history, n (%)				0.778
Never	35 (70.0)	10 (76.9)	25 (67.6)	
Past/current smoker	15 (30.0)	3 (23.1)	12 (32.4)	
ALK status, n (%)				0.015
Positive	24 (48.0)	10 (76.9)	14 (37.8)	
Negative	26 (52.0)	3 (23.1)	23 (62.2)	
VTE, n (%)				0.013
Yes	7 (14.0)	5 (38.5)	2 (5.4)	
No	43 (86.0)	8 (61.5)	35 (94.6)	

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; VTE, venous thromboembolism; ECOG PS, Eastern Cooperative Oncology Group performance status.

summarized in *Table 4*. All the patients in the four studies were ALK-rearrangement positive. And all of the patients in the 4 studies were treated with ALK inhibitors, including crizotinib (22), ceritinib (23), alectinib (24), and brigatinib (25). The VTE rate in these 4 studies ranged from 1.1% to 6.4%, and was significantly lower than that of the previously discussed 5 studies.

Discussion

In the present study, we found that patients with ALK-rearrangement advanced lung adenocarcinoma were at high risk for VTE throughout the course of the disease in Chinese population. The TF protein expression in ALK-rearrangement tumors was much higher than those without ALK-rearrangement, and TF protein expression was also much higher in patients with VTE than those without VTE.

Based on previous studies, cancer is significantly associated with an increased incidence of VTE (4–20%), and thromboembolism is a leading cause of death in cancer patients who had received outpatient chemotherapy (4,26-29). Since VTE is associated with poor quality of life and decreased overall survival, screening out high-risk groups for thrombosis appears especially impendency. Chew *et al.* suggested that approximately 3% of patients with lung cancer develop VTE within 2 years (1). However, another retrospective cohort analysis found that 14% of patients with lung cancer experienced VTE 3–12 months after chemotherapy initiation (2). In the 3 studies summarized in *Table 3*, the VTE rate in the NSCLC population ranged from 16.7–47.1%. In the present study, we found that the VTE incidence in advanced lung adenocarcinoma patients was 5.85% after a maximum of 3.5 years follow up in a Chinese population. The difference in the VTE incidence could be due to such differences as treatment modality, race, medical condition, and tumor stage.

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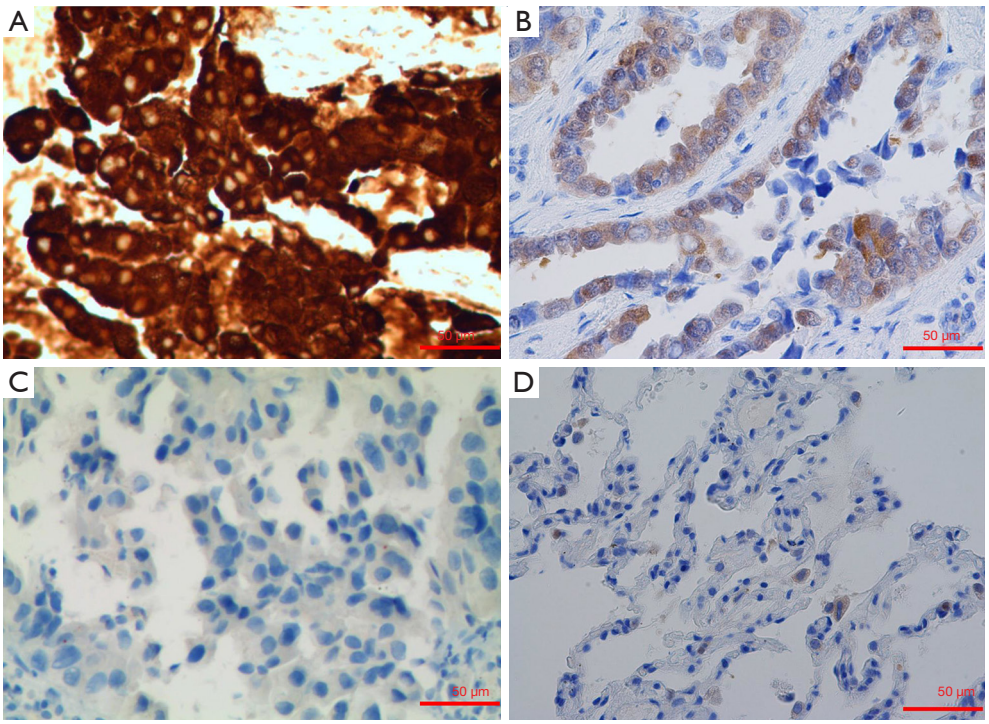

Figure 2 Standard avidin–biotin–peroxidase complex method was used for IHC staining on the selected tissue samples. Representative of anaplastic lymphoma kinase (ALK) (A) and tissue factor (TF) (B) protein expression in advanced lung adenocarcinoma tumor tissues detected by immunostaining with anti-ALK (D5F3) and anti-TF antibody, respectively. Negative expression detected by immunostaining with anti-ALK (D5F3) (C) and anti-TF antibody (D), respectively.

Table 3 Recent retrospective studies reporting venous thromboembolism (VTE) among patients with anaplastic lymphoma kinase (ALK)-rearrangement non-small-cell lung cancer

Study	Sample size (n)	VTE	VTE rate (%)	ALK+	VTE in ALK+	VTE rate in ALK+ (%)	P value (χ^2-test)	P_m
Verso *et al.* (17)	173	18	24.7	17	8	47.1	0.003	<0.001
Davidsson *et al.* (18)	293	53	18.1	48	13	27.1	0.242	
Lee *et al.* (19)	1,998	131	6.6	24	4	16.7	0.170	
Alexander *et al.* (20)	1,384	–	–	70	12	17.1	–	
Zer *et al.* (21)	–	–	–	55	23	41.8	–	
	–	–	–	43	12	27.9	–	
Current study	513	30	5.8	29	6	20.7	0.017	

P_m, P value in merged cohort.

In a further stratified study, ALK-rearrangement NSCLC was considered to be associated with a high rate of VTE in white patients (21). In the present study, we summarized 5 studies on ALK rearrangement and VTE. Of these 5 studies, 3 looked at the VTE rate in an NSCLC population, and the VTE rate in the ALK-rearrangement population (16.7–47.1%) was significantly higher than that in the overall population (6.6–24.7%) (17-19). The other 2 studies had a similar VTE rate as the 3 studies on ALK-rearrangement patients (17.1–41.8%) (20,21). However, to the best of our knowledge, the relationship between ALK rearrangement and VTE incidence in Chinese NSCLC

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Table 4 VTE rate in prospective interventional studies

Study	Drug	Sample size (n)	VTE	VTE rate (%)
Solomon *et al.* (22)	Crizotinib	171	11	6.4
Shaw *et al.* (23)	Ceritinib	130	–	<5.0
Shaw *et al.* (24)	Alectinib	87	1	1.1
Gettinger *et al.* (25)	Brigatinib	137	5	3.6

VTE, venous thromboembolism.

patients has never been reported. As a result, we performed a retrospective study and found that, in ALK-rearrangement advanced lung adenocarcinoma patients, the VTE incidence was significantly higher than that in patients with negative ALK-rearrangement Chinese population. After comparing the findings of the current study to those of the other 3 studies on the VTE rate in the overall population and VTE rate in the ALK-arrangement population, the VTE rate in the ALK-rearrangement patients was found to be much greater than that that of the overall NSCLC patients (26.3% *vs.* 7.8%, P<0.001). The strong association between ALK rearrangement and VTE can also be seen in *Table 4* (22-25). The VTE rate in prospective interventional studies was much lower than that in retrospective studies (1.1–6.4% *vs.* 17.1–47.1%), most likely because patients were treated with ALK inhibitors and the pathway to motivate VTE was blocked.

The exact mechanisms as to why ALK-rearrangement patients are more likely to experience VTE after cancer diagnosis are unknown; however, some theories have been proposed. As we know, TF plays an important role in the activity of procoagulant activity (11,12,30). Preclinical data have shown that oncogenes can induce TF expression by cancer cells (7,8); therefore, it is likely that ALK rearrangement could also increase TF expression, increasing the incidence of VTE. One of the proposed possible pathways is ALK-rearrangement-induced epithelial-mesenchymal transition (EMT) in NSCLC cells (31). EMT triggers a procoagulant state through TF (32); therefore, in the present study, we examined TF protein expression in ALK-rearrangement tumors and ALK-negative tumors. As expected, TF protein expression in ALK-rearrangement tumors was much higher than that in ALK-negative tumors (P=0.015). We then analyzed the relationship between TF protein expression and the incidence of VTE. As with ALK rearrangement, the TF protein expression in VTE patients was significantly higher than that in VTE-negative patients (P=0.013). Therefore, ALK rearrangement may increase the incidence of VTE by inducing TF protein expression. Future studies are needed to explore the exact mechanism. Additionally, ALK rearrangement and TF protein expression may be used as biomarkers to predict VTE in high-risk groups.

Although our study found that ALK-rearrangement advanced lung adenocarcinoma patients had a higher incidence of VTE in a Chinese cohort, there are still some limitations that should be addressed. First, because it was a small population and a single-center study, further validation is required with more patients and other centers. Second, patients with asymptomatic VTE did not have venous ultrasound performed regularly; therefore, a diagnosis of VTE may be overlooked in a minority. Finally, we only detected ALK and TF protein expression; further biochemical studies and functional experiments are required to validate our results.

Conclusions

In the present study, we found that Chinese advanced lung adenocarcinoma patients with positive ALK-rearrangement had a similar VTE incidence compared with other populations in previously published studies. The VTE incidence in ALK-rearrangement advanced lung adenocarcinoma patients was higher than that in ALK-negative patients, and both were closely related to TF protein expression. As the present study was a single-center study with a small number of patients, further research is warranted.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-6619). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by Ethics Committee of Henan Cancer Hospital (No. 2019060). All the patients in the present study have signed informed consent.

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