ORIGINAL RESEARCH

Association of Venous Thromboembolism and Early Mortality in Patients with Newly Diagnosed Metastatic Non-Small Cell Lung Cancer

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Purpose: To explore the relationship between venous thromboembolism (VTE) and early mortality (within six months) in Chinese patients with newly diagnosed metastatic non-small cell lung cancer (NSCLC) after entering the era of precision treatment.

Methods: A cohort of 706 consecutive subjects with newly diagnosed metastatic NSCLC were prospectively observed. Clinical and survival data were recorded over a six-month follow-up period. The predictive factors for the occurrence of VTE and the relationship with early mortality were evaluated through univariate and multivariate analyses.

Results: During the six-month follow-up period, VTE events occurred in 12.2% (86/706) of the enrolled patients. In the multivariate analyses for VTE, an age older than 70 years (vs < 70: sub-distribution hazard radio [SHR], 1.678; 95% confidence interval (CI), 1.073–2.600; P=0.022), an Eastern Cooperative Oncology Group performance status ≥2 (vs 0/1: SHR, 1.946; 95% CI, 1.277–2.970; P=0.002), and having an *ALK* rearrangement (vs non-rearrangement: SHR, 2.377; 95% CI, 1.186–4.760; P=0.015) were significantly associated with the occurrence of VTE. Within six months, 116 subjects (16.4%) died, and the occurrence of VTE (vs no VTE: adjusted HR: 1.863; 95% CI: 1.178–2.947, P=0.008) was remarkably associated with early mortality. Further analysis showed 98 patients (13.9%) with early mortality had *EGFR*/*ALK* wild-type genes, with a risk of early mortality 5.935-fold higher than that of patients with an *EGFR* mutation/*ALK* rearrangement. Finally, subgroup analyses showed that VTE occurrence was a significant factor for predicting early mortality in patients with *EGFR*/*ALK* wild-type genes (adjusted HR: 1.682; 95% CI: 1.023–2.768, P=0.041).

Conclusion: Patients with an *EGFR* mutation/*ALK* rearrangement had a significantly decreased risk of early mortality in the era of targeted therapy; however, VTE occurrence remained an important predictor for early mortality in metastatic NSCLC patients, especially in patients with *EGFR*/*ALK* wild-type genes.

Keywords: venous thromboembolism, non-small cell lung cancer, early mortality

Introduction

Venous thromboembolism (VTE) can be a fatal complication of malignant tumors and is the second leading cause of death after that associated with the malignant tumor itself.[1,2] The risk of VTE occurrence in patients with cancer is approximately 4- to 6.5-fold higher than in those without cancer,[3,4] and the risk is highest in the first six months after cancer diagnosis.[5] Lung cancer is associated with a high risk of occurrence of VTE. Our previous multicenter study showed a high prevalence of VTEs in patients with newly diagnosed lung cancer, especially metastatic non-small

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cell lung cancer (NSCLC).[6] Thereafter, assessments of our own cohorts and other studies have also revealed an association between driver oncogene alterations and VTE occurrence in NSCLC patients.[7–10]

The rates of early mortality vary greatly based on the cancer type, stage, and treatment, although the rate is especially high in patients with advanced cancer,[11] and approximately 60% of all newly diagnosed NSCLC patients have advanced disease.[12] Molecular testing has become a standard procedure in patients with metastatic NSCLC, and targeted agents for various genetic alterations have led to significant improvements in survival.[13,14] Previous studies have shown that cancer patients with VTE experience a greater risk of early all-cause mortality than those without VTE.[15,16] However, in the modern era of molecular targeted therapy, the association between the occurrence of VTE and early mortality in metastatic NSCLC remains underdefined. Therefore, we conducted a prospective, observational, cohort study in consecutive patients with metastatic NSCLC to explore the association between the occurrence of VTE and early mortality within six months in a real-world clinical practice environment after entering the era of precision treatment.

Materials and Methods
Study Population
The study was conducted at Beijing Chao-Yang Hospital, Capital Medical University. Patients who were newly diagnosed with NSCLC between January 2014 and December 2019 were consecutively enrolled. The inclusion criteria were as follows: confirmation of NSCLC by cytological or histological examination; stage IV Tumor Node Metastasis (TNM) classification;[17] identification of epidermal growth factor receptor (*EGFR*), Kirsten rat sarcoma (*KRAS*) mutations, and anaplastic lymphoma kinase (*ALK*) alterations; and voluntary participation. This cohort excluded patients who had a history of VTE (diagnosed more than three months before enrollment) and continuous anticoagulant drug use. Patients in this cohort were observed prospectively from the time of diagnosis to six months later, unless a patient voluntarily withdrew from the study, was lost to follow-up, or death occurred. All subjects provided written informed consent. The Ethics Committees of Beijing Chao-Yang Hospital, Capital Medical University (No. 2009–4 and 2016–79) provided approval to conduct this prospective

cohort study.[9,10] This study conformed with the tenets of the Declaration of Helsinki.

Data Collection
Clinical and examination data were recorded from the patients' medical records. Survival data were collected from the patients' 2-, 4-, and 6-month follow-up calls and outpatient visits. Finally, the following variables were recorded for each subject for group comparisons: age (<70 vs ≥ 70 years); sex (male vs female); Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0–1 vs ≥ 2); history of smoking (current/former vs never); histology type (adenocarcinoma vs squamous cell carcinoma vs other NSCLC); body mass index (BMI) (<25 vs ≥ 25 kg/m^2); *EGFR* (mutated vs wild-type), *KRAS* (mutated vs wild-type), and *ALK* (rearrangement vs non-rearrangement) genotypes; intracranial metastasis (yes vs no); VTE status; VTE time; and early mortality during the six-month follow-up period.

Driver Oncogene Evaluation
EGFR and *KRAS* mutations were examined via amplification refractory mutation system polymerase chain reaction (ARMS-PCR). *ALK* rearrangements were confirmed by fluorescence in situ hybridization. Detailed information pertaining to these evaluation techniques has been provided in our previous publications.[9,10]

Diagnosis of VTE
Symptomatic patients underwent imaging examinations to confirm the occurrence of VTE events (venous ultrasound imaging or computed tomography (CT) venous angiography for deep vein thrombosis (DVT); CT pulmonary angiography or ventilation/perfusion scanning for pulmonary embolism). All VTE events were finally submitted to a panel of vascular and radiologic experts for review. All incidentally detected VTE cases were included. The panel determined if an incidental VTE event was of clinical significance. The VTE time was recorded from the date of the first objective diagnosis of metastatic NSCLC to either the date of the VTE occurrence or the last medical follow-up record, whichever occurred earlier.

Diagnosis of Early Mortality
Survival time was recorded from the day of first diagnosis of metastatic NSCLC to either the day of death or loss to follow-up. Subjects who died within six months after diagnosis were assigned to the early mortality group.

Statistical Analysis

All variables were considered to be categorical and are described by frequencies and percentages. In the univariate analysis for VTE, Gray's test was performed to compare variables between subgroups of patients with and without VTE. A death/withdrawal competing risk model was employed to determine the independent variables for the multivariate analyses. In the multivariate analysis, the included variables were those with statistical significance ($P < 0.05$) in the univariate analysis. The cumulative incidence of early mortality was analyzed using Kaplan–Meier survival curves, and differences between the groups were evaluated through Log rank testing. Univariate and multivariate Cox proportional hazards regression analyses were used to identify the independent predictors of early mortality. All statistical tests were two-tailed, and a P-value < 0.05 was considered statistically significant. R 4.0.2 software (R Foundation, Vienna, Austria) was used to conduct Gray's test and the Fine-Gray regression analysis. Cox proportional hazards regression analyses were performed using Statistical Package for the Social Sciences (SPSS) 24.0 (IBM, Armonk, NY, USA). An epidemiologist reviewed the study.

Results

Population

In total, 718 patients with newly diagnosed stage IV NSCLC were recruited for this study. Overall, seven patients were excluded due to a history of VTE spanning longer than three months before enrollment, and five patients were excluded due to the continuous administration of anticoagulant drugs. Finally, 706 subjects with metastatic NSCLC were included in the present cohort (Figure 1) and the analysis.

Of these patients, 83% (n=586) had been diagnosed with adenocarcinoma. The median age of all the patients at diagnosis was 64 years, and 73.1% (n=516) of patients were younger than 70 years of age. In terms of sex, 55.0% (n=388) were male, and 45.3% (n=320) were former or current smokers. Furthermore, 23.8% (n=168) of patients exhibited a poor ECOG PS, and only 30.9% (n=218) had a BMI ≥ 25 kg/m^2. The identified driver oncogene types included mutations of *EGFR* (43.3%, n=306) and *KRAS* (11.3%, n=80), and *ALK* rearrangements (5.1%, n=36). Intracranial metastasis was noted in 14.4% (n=102) of patients at diagnosis. Treatments administered during the observation period included targeted therapy with tyrosine kinase inhibitors (TKIs) (40.2%, n=284), chemotherapy (37.8%, n=267), and other types of anticancer therapy (immunotherapy, radiotherapy, palliative surgery, and palliative support treatment) (22.0%, n=155) (Table 1).

Development of VTE and Early Mortality

Overall, 86 patients developed VTE (12.2%), 10.4% (n=9) of whom experienced a pulmonary embolism (PE), 68.6% (n=59) of whom had DVT (including upper extremity, lower extremity, or neck DVT), and 20.9% (n=18) of whom experienced both PE and DVT. Most patients received low-molecular-weight heparin and/or warfarin or rivaroxaban anticoagulant therapy, although seven patients did not receive anticoagulant therapy due to contraindications. Hematuria occurred in one patient, and one patient experienced hemoptysis, although both recovered quickly after discontinuing the administration of anticoagulant agents. No major bleeding events occurred.

The proportion of patients who experienced early mortality during the six-month follow-up period was 16.4% (n=116). At the time of the final analysis for VTE, 18.7% of patients (n=132) had experienced death from a competing event or had withdrawn from the study. The baseline characteristics and the treatments administered during observation days are provided in Table 1.

Risk Factors Associated with VTE

In the univariate analysis, the occurrence of VTE was higher in patients older than 70 years of age (Gray's test $P = 0.024$) and in patients with an ECOG PS ≥ 2 (Gray's test $P < 0.001$). *ALK* alterations were also significantly associated with the occurrence of VTE (Gray's test, $P = 0.014$), whereas *EGFR* mutations were negatively associated with VTE occurrence (Gray's test, $P = 0.018$), and there was no significant association between other clinical features/driver oncogene alterations and the occurrence of VTE (Table 2).

Subsequently, Fine-Gray regression analysis was conducted to identify the possible risk factors for VTE occurrence, including age, ECOG PS, the presence of *EGFR* alterations, and *ALK* status. Ultimately, an age older than 70 years (vs < 70 years: sub-distribution hazard radio [SHR], 1.678; 95% confidence interval (CI), 1.073–2.600; $P=0.022$), an ECOG PS ≥ 2 (vs 0/1: SHR, 1.946; 95% CI, 1.277–2.970; $P=0.002$), and the presence of an *ALK* rearrangement (vs non-rearrangement: SHR, 2.377; 95% CI, 1.186–4.760; $P=0.015$) were identified as independent risk factors for VTE occurrence (Table 2).
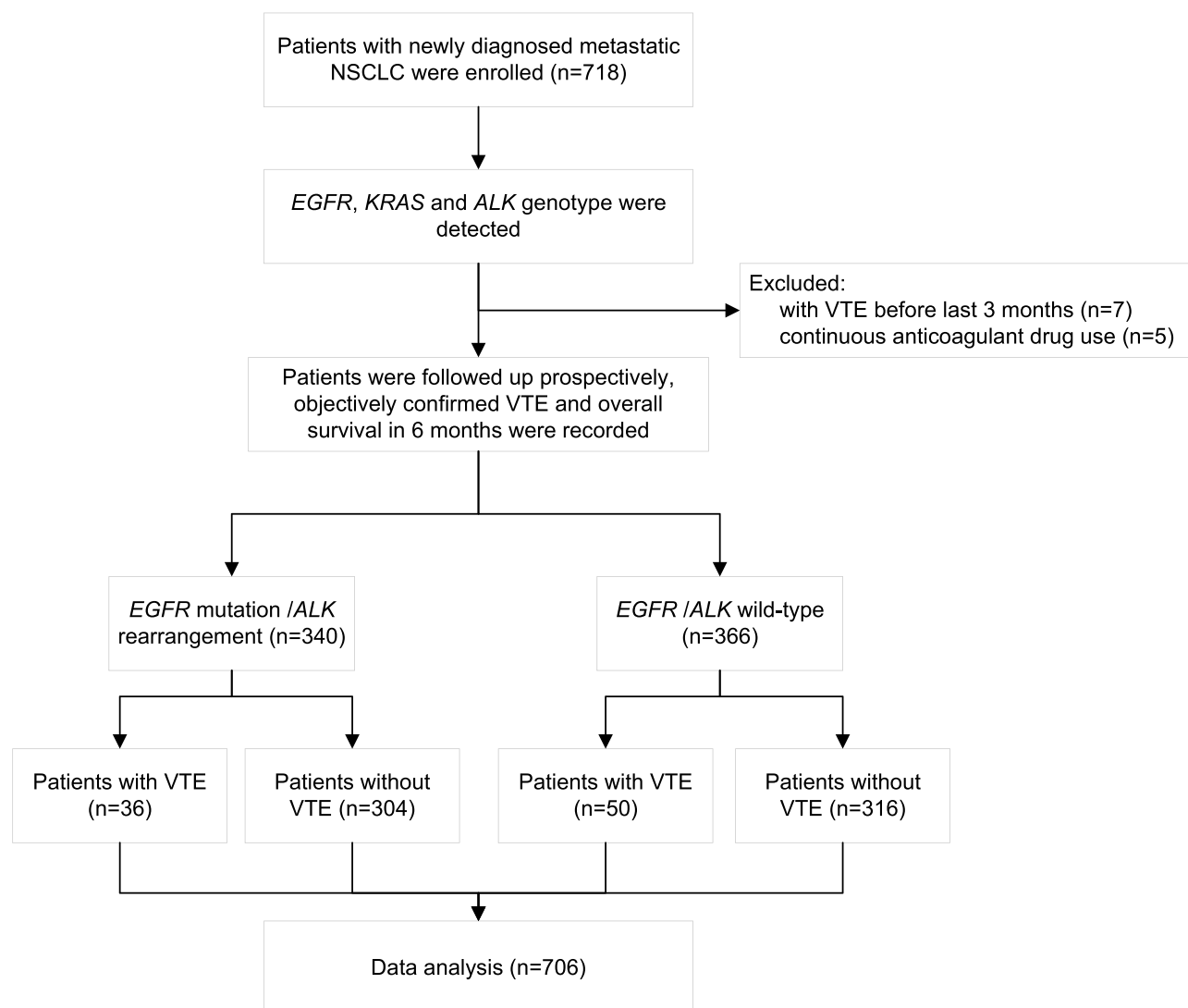
Figure 1 Study flow diagram.
Abbreviations: NSCLC, non-small cell lung cancer; *ALK*, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; *KRAS*, Kirsten rat sarcoma; VTE, venous thromboembolism.

Association of VTE with Early Mortality

The Kaplan–Meier survival analyses showed that the risk of early mortality was significantly higher in the VTE group (vs no VTE: *P*=0.001), and the multivariate Cox analysis (adjusted for sex, age, BMI, intracranial metastasis, tumor histology, and driver oncogene type) also confirmed that VTE (adjusted HR: 1.863; 95% CI: 1.178–2.947, *P*=0.008) was an independent risk factor for early mortality (Figure 2A). Further analysis showed that 98 patients who experienced early mortality had *EGFR/ALK* wild-type genes, and their risk of early mortality was 5.935-fold higher than that of patients with an *EGFR* mutation/*ALK* rearrangement (Figure 2B). In addition, subgroup analyses were performed according to driver oncogene alterations, which showed significant

differences in the rate of early mortality among the driver oncogene groups with different VTE statuses based on the Log rank tests (*P* < 0.0001). More specifically, the group with *EGFR/ALK* wild-type genes who experienced VTE displayed the poorest survival outcomes (Figure 2C). Finally, after adjusting for sex, age, BMI, intracranial metastasis, tumor histology, and treatment method, the occurrence of VTE was a significant factor for predicting early mortality only in patients with *EGFR/ALK* wild-type genes (adjusted HR: 1.682; 95% CI: 1.023–2.768, *P*=0.041) (Table 3).

Discussion

In this real-world cohort study of Chinese patients with metastatic NSCLC, we examined the predictive factors for

Table 1 Patient Demographics and Clinical Characteristics and Primary Study Outcomes

Characteristic	Patients n (%)	Patients with VTE n (%)	Patients with Early Mortality n (%)
Overall	706 (100)	86 (12.2)	116 (16.4)
Age (years)	64	65	67
25th-75th percentile	56–70	54.8–72	57–73
< 70	516 (73.1)	54 (10.5)	70 (13.6)
≥ 70	190 (26.9)	32 (16.8)	46 (24.2)
Sex			
Male	388 (55.0)	48 (12.4)	85 (21.9)
Female	318 (45.0)	38 (11.9)	31 (9.7)
Smoking history			
Never	386 (54.7)	47 (12.2)	41 (10.6)
Former/current	320 (45.3)	39 (12.2)	75 (23.4)
ECOG PS			
0–1	538 (76.2)	52 (9.7)	58 (10.8)
≥ 2	168 (23.8)	34 (20.2)	58 (34.5)
BMI (kg/m2)			
< 25	488 (69.1)	60 (12.3)	86 (17.6)
≥ 25	218 (30.9)	26 (11.9)	30 (13.8)
Tumor histology			
Adenocarcinoma	586 (83.0)	76 (13.0)	84 (14.3)
Non-adenocarcinoma	120 (17.0)	10 (8.3)	32 (26.7)
Squamous cell carcinoma	106 (15.0)	8 (7.5)	26 (24.5)
Other NSCLC	14 (2.0)	2 (14.3)	6 (42.9)
Driver oncogene type			
EGFR mutated	306 (43.3)	27 (8.8)	15 (4.9)
KRAS mutated	80 (11.3)	10 (12.5)	24 (30.0)
ALK rearrangement	36 (5.1)	9 (25.0)	4 (11.1)
Intracranial metastasis			
Yes	102 (14.4)	11 (10.8)	15 (14.7)
No	604 (85.6)	75 (12.4)	104 (17.2)
Treatment method			
Targeted Therapy	328 (46.5)	32 (9.8)	14 (4.3)
Without targeted therapy	378 (53.5)	54 (14.3)	102 (26.9)
Chemotherapy	244 (34.6)	29 (9.5)	45 (18.4)
Other	134 (18.9)	25 (34.2)	57 (42.5)
VTE type	706 (100)	86 (100)	
PE alone	9 (1.3)	9 (10.4)	4 (44.4)
DVT alone	59 (8.5)	59 (68.6)	16 (26.7)
PE and DVT	18 (2.5)	18 (20.9)	4 (22.2)
No VTE	620 (87.7)	0 (0.0)	92 (14.9)

Abbreviations: NSCLC, non-small cell lung cancer; VTE, venous thromboembolism; ECOG, Eastern Cooperative Oncology Group; PS, performance status; BMI, Body mass index; *EGFR*, Epidermal growth factor receptor; *KRAS*, Kirsten rat sarcoma; *ALK*, anaplastic lymphoma kinase; PE, Pulmonary embolism; DVT, deep vein thrombosis.

the occurrence of VTE and the relationship with early mortality. Our results showed that the risk of VTE occurrence in metastatic NSCLC patients with *ALK* rearrangements was significantly higher than the risk in *ALK* wild-type patients. With the approved use of driver oncogene targeted therapies, patients with an *EGFR*

Table 2 Univariable and Multivariable Factors Associated with Risk of VTE in Patients with Metastatic NSCLC

Variables	VTE Univariate Analysis	VTE Multivariate Analysis		
	p value	*p* value	SHR	95% CI
Age (years) (≥ 70 vs < 70)	0.024	0.022	1.678	1.073–2.600
Sex (male vs female)	0.894	–	–	–
ECOG PS (≥ 2 vs 0/1)	< 0.001	0.002	1.946	1.277–2.970
Smoker (current/former vs never)	0.987	–	–	–
BMI (kg/m^2) (≥ 25 vs < 25)	0.869	–	–	–
Driver oncogene type				
EGFR (mutated vs wild-type)	0.018	0.140	0.712	0.452–1.120
KRAS (mutated vs wild-type)	0.924	–	–	–
ALK (rearrangement vs wild-type)	0.014	0.015	2.377	1.186–4.760

Abbreviations: NSCLC, non-small cell lung cancer; VTE, venous thromboembolism; SHR, sub-distribution hazard ratio; ECOG, Eastern Cooperative Oncology Group; PS, performance status; BMI, Body mass index; *EGFR*, Epidermal growth factor receptor; *KRAS*, Kirsten rat sarcoma; *ALK*, anaplastic lymphoma kinase.

mutation/*ALK* rearrangement had significantly lower rates of early mortality; however, the occurrence of VTE remained an important risk factor for early mortality in metastatic NSCLC patients, especially in those with *EGFR/ALK* wild-type genes.

Risk Analysis for VTE
Age and VTE
An age of 70 years or older at diagnosis was significantly associated with the occurrence of VTE in our cohort; this finding is consistent with that of a previous report showing that an age greater than 77 years was an independent risk factor for PE in lung cancer patients.[18] Older patients with metastatic NSCLC are vulnerable to developing VTE, with a higher risk of immobilization and complications like heart and pulmonary disease.

ECOG PS and VTE
Higher rates of VTE were observed in patients with a poor ECOG PS, which is consistent with the findings of previous research.[19,20] Patients with a poor PS commonly suffer from more complications than do those with a better PS, and they lose mobility, which increases the risk of VTE occurrence. In this study, we also found that the VTE events were most pronounced in the first 60 days. Even after accounting for competing risk of death and study withdrawal, the increased cumulative risk of VTE remained the highest during the first 60 days. However, it may be that the patients' PS was improved or their tumor burden was reduced after initiating anticancer therapy.

Driver Oncogene Alterations and VTE
Currently, *EGFR, KRAS*, and *ALK* are the most common driver oncogenes tested in patients with metastatic

NSCLC. Our study revealed that the risk of VTE occurrence was 2.377-fold higher in patients exhibiting an *ALK* rearrangement than in patients with an *ALK* wild-type gene.

Previous studies[7,8,10,21] have likewise shown that assessing the *ALK* status might help determine the risk of VTE among NSCLC subtypes. Therefore, clinicians should pay attention to symptoms of thrombosis in patients exhibiting an *ALK* rearrangement, both at the time of diagnosis and during follow-up to quickly identify the existence of a VTE event. *EGFR* mutations, however, were not independent predictors for the occurrence of VTE in this study, which is inconsistent with previous findings demonstrating that *EGFR* mutations had a negative relationship with VTE risk in patients with NSCLC.[9,22] Possible explanations for these differential outcomes may be that our study only included stage IV NSCLC patients and that the follow-up period was limited to six months. Thus, the long-term incidence of VTE needs to be explored further.

Other Factors and VTE
No differences in the occurrence of VTE were observed based on sex or smoking history. Although a BMI ≥ 35 kg/m^2 was reported to be a significant risk factor in previous research,[23] in this Chinese patient cohort, only five patients had a BMI in this range; therefore, we reduced the cut-off to ≥ 25 kg/m^2. No significant difference in the occurrence of VTE was observed based on the BMI, which is similar to the findings of previous Asian studies.[24,25]

Post hoc analysis of data from a multicenter, prospective trial[26] demonstrated that anemia was a risk factor for VTE in cancer patients,[27] and our previous cross-sectional
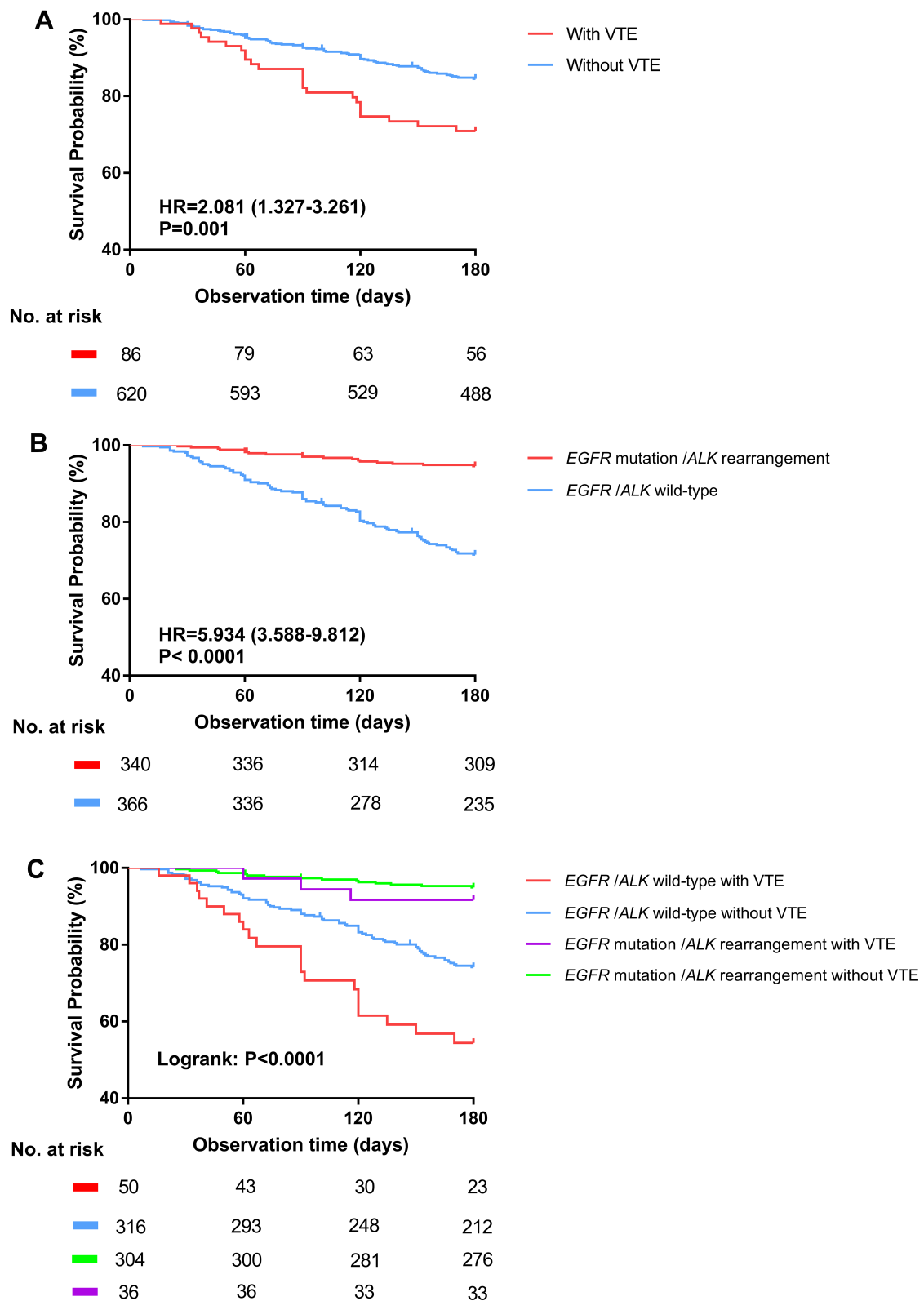
Figure 2 The hazard analysis of early mortality. (**A**) Patients with occurrence of VTE showed significantly associated with early mortality. (**B**) Patients with *EGFR* mutation / *ALK* rearrangement showed a significant protective effect for early mortality. (**C**) Early mortality among the driver oncogene groups with different VTE status differed significantly using log-rank test (P < 0.0001).
Abbreviations: *EGFR*, epidermal growth factor receptor; *ALK*, anaplastic lymphoma kinase; VTE, venous thromboembolism.

Table 3 Univariate and Multivariate Cox Regression Analyses of VTE Status with Early Mortality

Survival Outcomes	Early Mortality			
	Univariate Analysis		Multivariate Analysis	
	p value	HR (95% CI)	*p* value	Adjusted HR (95% CI)
Overall cohort (n=706) VTE (yes vs no)	0.001	2.081 (1.327–3.261)	0.008	1.863 (1.178–2.947)
EGFR mutation/*ALK* rearrangement (n=340) VTE (yes vs no)	0.417	1.670 (0.484–5.770)	–	–
EGFR/ALK wild-type (n=366) VTE (yes vs no)	0.003	2.091 (1.290–3.390)	0.041	1.682 (1.023–2.768)

Abbreviations: VTE, venous thromboembolism; *EGFR*, Epidermal growth factor receptor; *ALK*, anaplastic lymphoma kinase; HR, hazard ratio; CI, confidence interval.

study also revealed that anemia was related to the occurrence of VTE in lung cancer patients.[6] In the present study, we also evaluated whether anemia was related to the occurrence of VTE; however, after adjusting for driver oncogene alterations, there was no statistically significant difference between patients with hemoglobin < 10g/dl and ≥ 10g/dl. In future studies, we plan to expand the sample size for further validation.

Association Between VTE and Early Mortality

In our cohort, patients with VTE remained at a remarkably higher risk of early mortality than those without VTE, even after adjusting for other factors like sex, age, BMI, intracranial metastasis, tumor histology, and driver oncogene type (Figure 2A). This is consistent with previously published reports indicating that cancer patients with VTE experienced a higher risk of all-cause mortality than those without VTE during chemotherapy.[15,28]

However, in the modern era of driver oncogene targeted therapy, subgroups of patients with *EGFR* mutations/*ALK* rearrangements experienced significantly improved survival outcomes, and our cohort did show that the risk of early mortality was much higher in patients with *EGFR/ALK* wild-type genes. The stratified analyses demonstrated that the group with *EGFR* mutations/*ALK* rearrangements who did not experience VTE displayed the lowest early mortality rate, whereas the *EGFR/ALK* wild-type group who experienced VTE displayed the poorest survival, with higher rates of early mortality compared with the former group. We suggest the possibility that actively targeted therapies reduced the tumor burden quickly and improved the hypercoagulable state in these

patients, thereby abrogating the risks of VTE on patient survival.

In the *EGFR/ALK* wild-type subgroup, the patients who experienced VTE exhibited worse survival outcomes compared to those who did not, and the multivariate analysis showed it was a notable predictor of early mortality. It is speculated that several factors may increase the risk of early mortality in these patients. For example, the occurrence of VTE reflected the fact that the hemostatic system becomes activated by carcinoma cells, resulting in cancer progression from a dormant, non-vascularized state toward a metastatic phenotype.[11,29,30] Besides, the occurrence of VTE itself is associated with a high risk of mortality, such as PE-associated sudden death, except for the side effects of chemotherapy and extra anticoagulation treatment.

Limitations

This study has several limitations. Firstly, this was a single-center study and was, therefore, subject to potential biases that may have influenced our results. Secondly, not all patients were tested for rare mutations, such as ROS1, and only a few positive ones have been identified in this cohort, so no further analysis was performed. Finally, the prevalence of VTE may have been underestimated, as we did not screen for venous thrombosis in all enrolled patients and some asymptomatic VTE cases might have been overlooked.

Conclusion

In this prospective, real-world, Chinese cohort study, we confirmed that patients with *ALK* rearrangements, those with poor ECOG performance, and those older than 70 years of age experienced a higher risk of VTE, and the occurrence of VTE remained a notable predictor of early

mortality in metastatic NSCLC patients, especially in the *EGFR*/*ALK* wild-type subgroup. Clinicians should pay more attention to the occurrence of VTE in metastatic NSCLC patients to ensure timely interventions. Further studies with a goal of reducing early mortality in this subgroup of patients who experience VTE are needed.

Abbreviations

VTE, venous thromboembolism; NSCLC, non-small cell lung cancer; DVT, deep venous thromboembolism; PE, pulmonary embolism; BMI, body mass index; *EGFR*, epidermal growth factor receptor; *KRAS*, Kirsten rat sarcoma; *ALK*, anaplastic lymphoma kinase; Cl, Confidence interval; ECOG, Eastern Cooperative Oncology Group; PS, performance status; SHR, sub-distribution hazard radio; HR, hazard ratio; TKI, tyrosine kinase inhibitor.

Data Sharing Statement

All data analyzed during the current study are available from the corresponding author.

Acknowledgments

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare.

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