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ORIGINAL RESEARCH

Risk of thromboembolism in non-small-cell lung cancers patients with different oncogenic drivers, including ROS1, ALK, and EGFR mutations

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Background: Anaplastic lymphoma kinase-positive (ALK+) and ROS proto-oncogene 1 (ROS1)-positive (ROS1+) lung cancers have been reported to be associated with an elevated risk of thromboembolic events. This study aimed to assess the long-term risk of developing thromboembolism (TE) in ROS1+ lung cancer and to compare it with other oncogenic drivers in the Asian population.

Materials and methods: We retrospectively enrolled a cohort of ROS1+ lung adenocarcinoma in a medical center in Taiwan and a comparison cohort of ALK+ and epidermal growth factor receptor-positive (EGFR+) lung cancers. Venous and arterial TEs were identified throughout the cancer course, and the incidence rate was calculated.

Results: We enrolled 44 ROS1+, 98 ALK+, and 168 EGFR+ non-small-cell lung cancer (NSCLC) patients. A total of 11 (25%), 36 (36.7%), and 38 (22.6%) patients in the ROS1, ALK, and EGFR cohorts, respectively, were diagnosed with thromboembolic events throughout the follow-up course of the disease ($P = 0.042$). The incidence rates were 99.0, 91.9, and 82.5 events per 1000 person-years for the ROS1, ALK, and EGFR cohorts, respectively. The majority of thrombosis events in the ROS1 (91.6%) and ALK (85.4%) cohorts were venous. On the contrary, 43.2% of thromboembolic events were arterial in the EGFR cohort. A higher proportion of thromboembolic events were noted during cancer diagnosis in the ROS1 cohort (36.3%) than in the ALK (16.7%) and EGFR (10.5%) cohorts. The stage was the only clinical variable associated with thromboembolic risk. There was a significant difference in survival between patients with and without TE in the EGFR cohort, but not in the ALK and ROS1 cohorts.

Conclusions: Although ROS1+ and ALK+ NSCLCs had a higher cumulative incidence of TE than EGFR+ NSCLC, the person-year incidence rates were similar among the three groups. EGFR-mutated NSCLC had more arterial events. Nevertheless, ALK+ lung cancer had higher venous events than EGFR-mutated lung cancer.

Key words: ROS1 rearrangement, thromboembolism, non-small-cell lung cancer, ALK, EGFR

INTRODUCTION

Cancer-associated thrombosis is a common complication in patients with cancers. Generally, the risk of venous thromboembolism (TE) appears to increase four- to sevenfold in cancer patients and varies widely by cancer type.[1-3] The absolute incidence rates of venous TE in cancer patients vary from 0.5% to 20% and are influenced by cancer type, stage of disease, age, proximity to diagnosis, and treatment modality.[4] Lung cancer is a malignancy associated with a substantial risk of thrombotic events. Primary lung cancer has been reported to cause venous TE in 7%-15% of patients.[5,6] The incidence of thrombosis in adenocarcinoma is three- to fourfold higher than that in squamous cell carcinoma and small-cell lung cancer.[7,8]

Recently, some studies reported that anaplastic lymphoma kinase-positive (ALK+) and ROS proto-oncogene 1 (ROS1)-positive (ROS1+) lung cancers were associated with an elevated risk of thromboembolic events.[9-11] The reported incidence rate of thromboembolic events was 34.7% in a ROS1 cohort in the USA and China during the peridiagnostic period.[10] However, the incidence of TE is well known to have ethnic differences. Studies conducted in Asia have consistently reported lower rates of venous TE in Asians than in Caucasians.[12-15] The incidence of TE in ROS1+ lung adenocarcinoma has not yet been clearly reported. In addition, the prospective randomized controlled clinical trials of ROS1 tyrosine kinase inhibitor did not demonstrate a higher incidence of thromboembolic

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events.[16-22] However, the population of clinical trials was highly selective. Thrombotic events occur predominantly during the peri-diagnostic or cancer progression periods, which are outside the observation period of clinical trials. Thus, observation in clinical trials may not reflect the true incidence of thromboembolic events in clinical practice in the real world.

We conducted a retrospective analysis of patients with ROS1+ lung adenocarcinoma and compared them with cohorts of epidermal growth factor receptor-positive (EGFR+) and ALK+ lung adenocarcinomas in a tertiary hospital in Taiwan. This study aimed to clarify the association between TE and ROS1+ lung cancer and to compare it to lung cancer with other oncogenic drivers in the Asian population. Furthermore, we focused on the long-term risk of developing TE around and after the diagnosis period.

MATERIALS AND METHODS

Study population

Patients diagnosed with ROS1+ lung adenocarcinoma between December 2001 and April 2020 at the National Taiwan University Hospital were retrospectively enrolled as the primary cohort. ROS1 rearrangement was screened by immunohistochemistry and confirmed by FISH, or reverse transcription-quantitative PCR. We then collected two separate cohorts of EGFR+ and ALK+ lung adenocarcinomas diagnosed during a similar period to compare the risk of thrombosis among lung cancer patients with different driver oncogenes. We included as many cases with ROS1 or ALK mutations that could be identified through medical records as possible because of their relatively low prevalence in non-small-cell lung cancer (NSCLC). No patients were excluded by particular reasons. Since EGFR-mutated NSCLC patients were much more than NSCLC patients with ROS1 or ALK mutations, we did not enroll whole population of EGFR-mutated patients to reduce the computational burden. EGFR cohorts were formed by a 1 : 4 covariate case-control matching. Case patients included those with NSCLC harboring ROS1 mutations. The control patients were selected from the cohort of NSCLC patients with common EGFR mutations which was analyzed and reported in the previously studies.[23,24] After enrollment of one case, eligible control patients with the same sex, smoking history, and stage were recruited sequentially until four control patients were individually matched to each case patient (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100742).

Data on clinical characteristics, treatment response, and thromboembolic events were obtained from electronic medical records. Thromboembolic events that occurred within 1 year before cancer diagnosis to death or end of the study were identified by reviewing computed tomography and sonography reports, as well as outpatient and admission medical records.

The collection of human tissue samples and clinical data was approved by the Institutional Review Board of National Taiwan University Hospital (202012161RINA).

Statistics

Survival times are different in NSCLC patients with different driver mutations. Thromboembolic events could accumulate more if the survival times are longer. Thus, the person-time rate used in this study was more revealing than simple cumulative incidence with regard to the comparison of TE risk. Person-time at risk commenced 1 year before cancer diagnosis and ended at the time of thromboembolic events, death, or the last follow-up date (30 May 2021). The absolute rates of thromboembolic events (per 1000 person-years) were calculated by dividing the number of people with TE by the person-time at risk. Some patients experienced multiple thromboembolic events. However, only the first thromboembolic event in a specific patient was included in the calculation of the absolute incidence rate, analysis of risk factors, and survival analysis.

Each participant's last follow-up date and living status were captured for survival analysis. Overall survival (OS) was calculated as the interval between the date of lung cancer diagnosis and death or the last follow-up date. Survival was estimated using the Kaplan—Meier method, and the log-rank test was used to compare the survival between groups. Univariate and multivariate Cox proportional hazards models were used to adjust for potentially interacting covariates and determine the factors associated with the longitudinal risks of thromboembolic events. Statistical significance was set at $P < 0.05$.

Statistical analyses were carried out using IBM SPSS Statistics, version 22.00 (SPSS Inc., Chicago, IL).

RESULTS

Study population

There were 44, 98, and 168 patients in the ROS1, ALK, and EGFR cohorts, respectively. The baseline demographic characteristics are presented in Table 1. The mean age at diagnosis was significantly lower in the ROS1 (53.06 $\pm$ 15.41 years) and ALK (52.77 $\pm$ 11.30 years) cohorts than in the EGFR cohort (65.84 $\pm$ 12.67 years; $P < 0.0001$). The majority of patients were diagnosed at an advanced stage and were nonsmokers.

The median follow-up times for the ROS1, ALK, and EGFR cohorts were 60.9 [interquartile range (IQR): 16.0-136.3] months, 63.1 (IQR: 28.1-113.0) months, and 24.53 (IQR: 16.3-46.2) months, respectively. The difference in survival time between the three molecular driver cohorts led to disparities in the follow-up time.

Characteristics and incidence of thromboembolic events

The total number of events was 12, 41, and 44 for the ROS1, ALK, and EGFR cohorts, respectively. Some patients had more than one thromboembolic event during the disease course. Only the first thromboembolic event in a specific patient was included in the following calculation of the absolute incidence rate. Venous thromboembolic events consisted of pulmonary embolism, deep vein thrombosis of the upper or lower extremities, renal vein thrombosis,

Table 1. Demographic characteristics of patients with ROS1+, ALK+, and EGFR+ lung adenocarcinoma

N	ROS1	ALK	EGFR
	44	98	168
Sex (%)			
Female	30 (68.2)	49 (50)	118 (70.2)
Male	14 (31.8)	49 (50)	50 (29.8)
Age, mean ± SD	53.06 ± 15.41 (19-90)	52.77 ± 11.30 (26-80)	65.84 ± 12.67 (36-89)
Smoking (%)			
Nonsmoker	35 (79.5)	70 (71.4)	141 (83.9)
Former/current smoker (all tobacco)	9 (20.5)	28 (28.6)	27 (16.1)
Staging (%)			
I	1 (2.3)	3 (3.0)	19 (11.3)
II	2 (4.5)	3 (3.0)	8 (4.8)
III	8 (18.2)	28 (28.6)	17 (10.1)
IV	33 (75)	64 (65.3)	124 (73.8)
T stage (%)			
T1	7 (15.9)	19 (19.4)	25 (14.9)
T2	11 (25)	24 (24.5)	47 (28)
T3	4 (9.1)	12 (12.2)	15 (8.9)
T4	21 (47.7)	40 (40.8)	81 (48.2)
NA	1 (2.3)	3 (3.1)	0 (0)
N stage			
N0	3 (6.8)	15 (15.3)	48 (28.6)
N1	6 (13.6)	8 (8.2)	18 (10.7)
N2	14 (31.8)	37 (37.8)	49 (29.2)
N3	20 (45.5)	35 (35.7)	53 (31.5)
NA	1 (2.3)	3 (3.1)	0 (0)
M stage (%)			
M0	11 (25)	34 (34.7)	68 (40.5)
M1	33 (75)	64 (65.3)	100 (59.5)
Median overall survival (months)	60.9	63.1	24.5

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; SD, standard deviation.

hepatic vein thrombosis, and peripherally inserted central catheter-related thrombosis. Arterial thromboembolic events were mainly cerebral and coronary thromboses. Two patients in the ROS1 cohort were diagnosed with Trousseau's syndrome and presented with multiple, repeated, and medication-resistant thrombosis. The characteristics of thromboembolic events are shown in Table 2.

Throughout the follow-up course of the disease, 25% ($n = 11$), 36.7% ($n = 36$), and 22.6% ($n = 38$) of patients in the ROS1, ALK, and EGFR cohorts, respectively, had arterial or venous TEs ($X^2 = 6.35$; $df = 2$; $P = 0.042$). To calculate the incidence of thromboembolic events, a total of 11, 36, and 38 patients in the ROS1, ALK, and EGFR cohorts had a subsequent diagnosis of thromboembolic events in 111.1, 391.8, and 460.6 person-years, respectively (Table 3). The incidence rates were 99.0 [95% confidence interval (CI) 56.5-173.4)], 91.9 (95% CI: 67.3-125.4), and 82.5 (95% CI: 60.8-111.9) events per 1000 person-years for the ROS1, ALK, and EGFR cohorts, respectively. The thromboembolism events in person-years incidence rate were not significantly different when comparing the ALK or EGFR cohorts to the ROS1 cohort in multivariate analysis after adjusting for age, sex, smoking, and stage. [hazard ratio (HR) 1.19, 95% CI 0.60-2.36, $P = 0.613$; HR 0.96, 95% CI 0.47-1.94, $P = 0.90$, respectively] (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100742).

Table 2. Characteristics of thromboembolic events

Mutation cohort	ROS1	ALK	EGFR	*P* value[a]
Number of patients	44	98	168	
Number of patients with thromboembolism	11 (25%)[b]	36 (36.7%)[c]	38 (22.6%)[d]	0.042
Sex				
Male	2	18	13	
Female	9	18	25	
Type				
Arterial events	1	6	19	0.10
Location				
Coronary	0	3	2	
Cerebral	1	3	12	
Both coronary and cerebral	0	0	2	
Other	0	0	3	
Venous events	11	35	25	<0.001
Location				
PE	3	10	4	
DVT	3	20	13	
Both PE and DVT	2	2	5	
Trousseau syndrome	2	0	0	
Other	1	3	3	

ALK, anaplastic lymphoma kinase; DVT, deep vein thrombosis; EGFR, epidermal growth factor receptor; PE, pulmonary embolism.
[a]By chi-square test.
[b]One patient had both arterial and venous thrombosis.
[c]Two patients had both arterial and venous thrombosis, one of whom had both coronary and cerebral embolism. Two patients had recurrent venous thrombosis.
[d]Four patients had more than one arterial thromboembolic event. Two patients had both arterial and venous thromboses. One patient had recurrent venous thrombosis.

Table 3. Absolute and relative rates of thromboembolic events in different molecular driver cohorts

	N	Patients with TE	Total[a] events	Person-time (years)	Incidence rate—arterial and venous (per 1000 person-years)	95% CI		Relative incidence rate[b]	95% CI		Incidence rate—venous (per 1000 person-years)	Incidence rate—arterial (per 1000 person-years)[c]
						Lower	Upper		Lower	Upper		
ROS1	44	11 (25%)	12	111.1	99.0	56.5	173.4	1	—	—	99.0	9.0
ALK	98	36 (36.7%)	41	391.8	91.9	67.3	125.4	1.192 ($P = 0.61$)	0.60	2.36	79.1	12.8
EGFR	168	38 (22.6%)	44	460.6	82.5	60.8	111.9	0.956 ($P = 0.90$)	0.47	1.94	49.9	34.7

ALK, anaplastic lymphoma kinase; CI, confidence interval; EGFR, epidermal growth factor receptor; TE, thromboembolism.
[a]The total events number was higher than the number of patients with events because some patients encountered more than one thromboembolic event.
[b]Hazard ratios were estimated using Cox proportional hazards regression adjusted for sex, age, smoking, and stage.
[c]Only the first thromboembolic event in one specific patient was included in the analysis of absolute rate. One patient each from the ROS1 and EGFR group, respectively, representing arterial TE and venous TE at the same time as their first event.

Difference in the incidence of arterial and venous thrombosis

The majority of thromboembolic events in the ROS1 ($n = 11$, 91.6%) and ALK ($n = 35$, 85.4%) cohorts were venous. Arterial thromboembolic events were more common in the EGFR cohort ($n = 19$, 43.2%). The cumulated arterial thromboembolic events throughout the follow-up course among the three cohorts were not significantly different ($X^2 = 4.66$; $df = 2$; $P = 0.10$). However, there was significant difference in the cumulated venous thromboembolic events throughout the follow-up course among the three cohorts ($X^2 = 15.34$; $df = 2$; $P < 0.001$) (Table 2).

The incidence rates by 1000 person-years for venous and arterial events separately are shown in Table 3. The arterial TE in person-years incidence rate was not significantly different between the ROS1 cohort and ALK or EGFR cohorts (Table 4) (HR 1.75, 95% CI 0.209-14.99, $P = 0.61$; HR 4.21, 95% CI 0.56-31.78, $P = 0.16$, respectively, in univariate analysis). The venous TE was not significant when comparing the ROS1 to the EGFR group in univariate analysis (HR 0.51, 95% CI 0.24-1.05, $P = 0.07$). When the ALK cohort was compared to the EGFR cohort in additional analysis, the arterial TE was not significantly different (HR 0.42, 95% CI 0.15-1.14, $P = 0.09$). Nevertheless, the venous TE was significantly higher in the ALK cohort than in the EGFR cohort (HR 1.96, 95% CI 1.12-3.43, $P = 0.02$).

Time of occurrence of thromboembolic events

A total of 45.5% ($n = 5$), 63.9% ($n = 23$), and 71.1% ($n = 27$) of patients in the ROS1, ALK, and EGFR cohorts had thromboembolic events during disease progression (Table 5). A few thromboembolic events occurred even when the disease was under control. A numerically higher proportion of thromboembolic events was noted during cancer diagnosis in the ROS1 cohort ($n = 4$, 36.3%) than in the ALK ($n = 6$, 16.7%) and EGFR ($n = 4$, 10.5%) cohorts ($X^2 = 4.14$; $df = 2$; $P = 0.13$). The detailed occurrence times of the thromboembolic events are shown in Table 5. Recurrent thrombosis was noted in 37.5%, 13.9%, and 13.2% of patients in the ROS1, ALK, and EGFR cohorts, respectively ($X^2 = 1.41$; $df = 2$; $P = 0.49$).

Factors associated with thromboembolic events

The HR of thromboembolic events in the ROS1 cohort was not significantly different from that in the ALK (HR 1.192, 95% CI 0.69-2.36, $P = 0.613$) and EGFR (HR 0.956, 95% CI 0.47-1.94, $P = 0.901$) cohorts. The stage of disease was the only clinical variable associated with thromboembolic risk in both the univariate and multivariate analyses. More advanced stages resulted in significantly higher HRs for thromboembolic events ($P = 0.003$). On an average, for each unit increase in the stage, the HR of thromboembolic events was 1.62 times higher [odds ratio (OR) 1.62, 95% CI 1.18-2.22] (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100742).

To examine the specific factors associated with arterial or venous thromboembolic events, we further separated these two types of TEs in the analysis. In venous thrombosis, stage is the only risk factor associated with thromboembolic events. Regarding arterial events, age > 60 and advanced stage of disease had an increased risk of thromboembolic events (Table 4).

Thromboembolic events and survival

In the ROS1 cohort, patients with and without thromboembolic events observed during the disease course did not show a significant difference in OS [$P = 0.53$, HR 1.3 (range 0.54-3.28), log-rank test; Supplementary Figure S2A, available at https://doi.org/10.1016/j.esmoop.2022.100742]. The results were similar after adjusting for risk factors, such as age, sex, and stage [$P = 0.49$, HR 1.4 (range 0.52-3.84)]. The median survival time for patients who had thromboembolic events was 49.3 months (95% CI 10.6-88.0 months). The median survival time for patients without thromboembolic events was 77.9 months (95% CI 0-158.2 months). The survival difference was also insignificant in the ALK cohort [$P = 0.12$, HR 1.48 (range 0.90-2.42); Supplementary Figure S2B, available at https://doi.org/10.1016/j.esmoop.2022.100742]. NSCLC patients harboring EGFR mutations with TE had significantly poorer survival than those without TE [$P = 0.04$, HR 1.52 (range 1.02-2.27)], after adjusting for age, sex, and stage (Supplementary Figure S2C, available at https://doi.org/10.1016/j.esmoop.2022.100742).

DISCUSSION

Data describing the longitudinal thrombogenic risk profile of patients with NSCLC and oncogenic drivers are scarce, especially in the Asian population. Our study described the long-term risk of thromboembolic events peri and post the

Table 4. Univariate and multivariate analysis of risk factors predicting venous and arterial thrombotic events among NSCLC patients with different molecular drivers

Variable	Arterial thrombosis				Venous thrombosis			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
ROS1 versus ALK	1.749 (0.20-14.99)	0.61	1.669 (0.19-14.46)	0.64	0.991 (0.50-1.98)	0.98	1.036 (0.52-2.07)	0.92
ROS1 versus EGFR	4.205 (0.56-31.78)	0.16	3.745 (0.47-30.04)	0.21	0.505 (0.24-1.05)	0.07	0.548 (0.25-1.18)	0.13
EGFR versus ALK	0.42 (0.15-1.14)	0.09	—	—	1.96 (1.12-3.43)	0.02	—	—
Age (years, ≦60 versus >60)	0.294 (0.12-0.75)	0.01[a]	0.376 (0.14-1.02)	0.05[a]	0.817 (0.49-1.36)	0.44	1.022 (0.59-1.77)	0.94
Sex (male versus female)	1.388 (0.60-3.22)	0.44	1.827 (0.61-4.69)	0.21	0.823 (0.49-1.39)	0.47	0.600 (0.32-1.13)	0.11
Smoking (smoker versus nonsmoker)	0.804 (0.27-2.38)	0.69	0.679 (0.20-2.27)	0.53	1.111 (0.62-1.99)	0.72	1.343 (0.67-2.68)	0.40
Stage (per one stage increase)	2.908 (1.07-7.90)	0.04[a]	2.825 (1.10-7.26)	0.03[a]	1.410 (1.02-1.94)	0.04[a]	1.373 (0.98-1.92)	0.06

ALK, anaplastic lymphoma kinase; CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small-cell lung cancer.
[a]$P < 0.05$.

cancer diagnosis, focusing on the ROS1, ALK, and EGFR-mutated lung cancers. Regarding the cumulative rate of thromboembolic events, patients with ROS1+ and ALK+ lung cancers had elevated risks of thromboembolic events during the cancer course compared to those with EGFR-mutated lung cancer. However, EGFR-mutated lung cancer patients had a higher rate of arterial TE. The person-years incidence rates of thromboembolic events were similar in these three molecular driver lung cancers because the survival time was longer in ROS1+ and ALK+ lung cancers than in EGFR+ lung cancer. However, ROS1+ and ALK+ lung cancers still had twice the person-years incidence rate of venous TEs compared to EGFR+ lung cancer, which contained half the arterial TEs. Venous TE was statistically more frequent in ALK+ lung cancer, but not ROS1+, compared to EGFR+ lung cancer.

Approximately 7%-15% of advanced NSCLC patients are estimated to experience venous TE during the course of their disease.[5,6,25] Previous reports have focused mainly on venous thrombosis. The event rate could be higher when arterial events are considered. In addition, NSCLC patients with ALK or ROS1 mutations have recently been reported to have remarkably elevated rates of TE.[10,11,26,27] Higher venous TE risk in NSCLC patients with EGFR mutations than in those with wild-type EGFR has also been reported. A recent study from a Chinese cohort reported that the rate of venous TE in lung adenocarcinoma with EGFR mutations after surgical pneumonectomy was 17%.[28] The cumulative rates of TE in ALK+ and EGFR+ NSCLC in a US cohort were 45.3% and 21.2%, respectively, with a median follow-up time of 33.1 months.[27] Two other ALK+ cohorts in Canada and Israel reported a 42% and 28% cumulative rate of venous TE within 22 and 13 months of follow-up, respectively.[26] A recent report by Al-Samkari et al. showed that the overall rate of venous TE in the ALK group (42.7%) was significantly higher than that in the EGFR group (26.2%). However, the rates were similar for arterial thrombosis in the ALK (5%) and non-ALK populations (4.4%).[29] Ng et al. reported that the peri-diagnostic incidence rates of TEs were 34.7%, 22.3%, and 13.7% for the ROS1, ALK, and EGFR cohorts, respectively.[10] The incidence of TEs throughout the course of cancer in a ROS1 cohort in Spain was 46.6% with a median follow-up of 19 months.[30] Generally, ROS1+ and ALK+ lung cancers had a comparable elevated risk of TE than in EGFR lung cancer. Our study results are compatible with the findings of the aforementioned studies. However, the cumulative rates of TEs were still lower in our study than in studies with Caucasian participants. The cumulative rates of TEs in our study were 25%, 36.7%, and 22.6% for the ROS1, ALK, and EGFR cohorts, respectively, with a median follow-up time of 60.9, 62.1, and 24.5 months. The follow-up time was much longer than that in the aforementioned studies. This observation is also consistent with a previous report, which found that Asian ethnicity was associated with an ∼60% lower risk of developing venous TE development in patients with primary lung cancer.[8]

The cumulative rates were highly dependent on the follow-up time. The longer the follow-up time, which was also influenced by the survival time, the higher the rates of TE. Survival was better in the ROS1 and ALK populations than in the EGFR population.[21,22] The survival time partially contributed to the higher rates of TE in the ALK and ROS1 populations. The incidence rates in our study cohort were 99.0, 91.9, and 82.5 per 1000 person-years for the ROS1, ALK, and EGFR cohorts, respectively, which were not significantly different. Nevertheless, the incidence rates of venous TE were numerically different. A study in Taiwan

Table 5. Disease status and occurrence time of the first thrombosis event

Mutation cohort	ROS1	ALK	EGFR
Clinical status of thrombosis events			
At diagnosis	4	6	4
Partial response	1	0	1
Stable disease	1	7	6
Disease progression	5	23	27
Treatment received during thrombosis events			
Untreated	3	8	4
Operation	1	0	0
Chemotherapy	3	11	15
TKI	4	17	16
TKI + chemotherapy	0	0	3
Recurrent thrombosis			
Yes	3	5	5
No	8	31	33

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

showed that the incidence of venous TE in lung cancer was 39.5 per 1000 person-years.[31] Compared to the venous TE incidence rate of 49.9 per 1000 person-years reported in our analysis, EGFR+ lung cancer had a slightly higher incidence than overall lung cancer. Furthermore, our study showed that ALK+ and ROS1+ lung cancers had remarkably higher venous TE incidence rates of 79.1 and 99.0 per 1000 person-years, respectively.

The mechanism of hypercoagulable state related to ALK and ROS1 rearrangement has been postulated to be abundant mucin production, a known prothrombotic factor.[32,33] A higher proportion of TE events in the ROS1 cohort (36.4%) than the ALK (16.7%) and EGFR (10.5%) cohorts occurred at diagnosis in our study. Moreover, recurrent thrombosis despite anticoagulation was observed more frequently in the ROS1 cohort (27%) than in the ALK (14%) and EGFR (13%) cohorts (Table 5). The different timings of the occurrence of TE and different recurrent rates of TE may reflect the distinct nature of TE in lung cancer with different driver mutations. The cancer-specific mechanisms and molecular alterations may be associated with the underlying mechanism and play an intrinsic role in thrombus formation. The exact mechanism driving the TE process in lung cancer with different driver mutations still requires further investigation.

There are some limitations to our study. This was a retrospective cohort study. The number of patients in the ROS1 cohort was small because of the low prevalence of the driver oncogene in NSCLC. The survival difference between patients with and without TEs was demonstrated in the EGFR cohort, but not in the ROS1 and ALK cohorts. Due to the potentially insufficient sample size, we were unable to conclude the survival findings. One of the strengths of our study is the long follow-up period and focus on the longitudinal thromboembolic risk during the course of NSCLC with molecular driver mutations. We observed and collected the data on TEs occurring from peri-diagnosis until death and demonstrated the life-term TE risk since lung cancer diagnosis. In addition, we included and recorded both arterial and venous thromboembolic events, which had some similarities and have sometimes been viewed as separate pathophysiological entities. Our study revealed higher venous events in ALK+ than in EGFR-mutated lung cancer and elevated arterial events in patients with EGFR-mutated lung cancer. The patients in the EGFR cohort were significantly older than those in the ROS1 and ALK cohorts, both in our study and in the real world. This partially explains the observation of higher arterial TEs in EGFR-mutated lung cancers. We demonstrated the different TE risks in these two entities of thrombosis in NSCLC with different molecular drivers.

Conclusion

The cumulative incidence of venous and arterial TEs throughout the cancer course was higher in patients with ROS1+ and ALK+ lung cancers. The incidence rates calculated by events per 1000 person-years for the three groups were not significantly different. The peri-diagnostic thromboembolic risk was especially high in the ROS1 population. When arterial and venous events were calculated separately, ROS1+ and ALK+ lung cancers had a higher incidence rate of venous TEs than EGFR+ lung cancer. EGFR-mutated NSCLCs had more arterial TEs, which was probably related to the older age of this population.

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DISCLOSURE

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