Risk factors and prognostic impact of venous thromboembolism in Asian patients with non-small cell lung cancer

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Summary

Although the overall risk of venous thromboembolism (VTE) is high in patients with non-small cell lung cancer (NSCLC), risk identification is limited. The goal of this study was to estimate the incidence, risk factors and prognostic implications of VTE, and to evaluate a genetic link between oncogenes and the risk of VTE in Asian patients with NSCLC. A total of 1,998 consecutive patients with NSCLC were enrolled and analysed retrospectively. Since the effects of therapeutics on VTE development were modified by stage, stratified analyses were performed. When comparing overall survival in terms of VTE development, a propensity score-matching method was adopted to minimise potential confounding. The six-month and two-year cumulative incidences of VTE were 4.2% and 6.4%, respectively. The risk of VTE increased 2.45-fold with each advancing stage in NSCLC ($p<0.001$). The independent predictors of VTE were advanced age, pneumonectomy and palliative radiotherapy in localised NSCLC and ineligibility for surgery and palliative radiotherapy in locally advanced NSCLC. Adenocarcinoma histology (vs squamous cell) and former/current smoking status were significant predictors of VTE in metastatic NSCLC. A significant association between VTE and decreased survival was observed only among patients with localised NSCLC. *EGFR* mutations ($p=0.170$) and *ALK* rearrangements ($p=0.159$) were not associated with VTE development in lung adenocarcinoma. In conclusion, the two-year cumulative incidence of VTE is 6.4% in Asian patient with NSCLC. The significant predictors of VTE are different across stages of NSCLC. The prognostic impact of VTE on poor survival was limited to localised NSCLC.

Keywords

Venous thromboembolism, non-small cell lung carcinoma, epidermal growth factor receptor, risk factor, prognosis

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Introduction

Patients with malignancy experience a hypercoagulable condition (1, 2). There are multiple risk factors for thrombosis and patients with malignancy face a four- to seven-fold increased risk of venous thromboembolism (VTE) compared to patients without malignancy (3-6).

Several molecules contribute to haemostasis, but tissue factor is an important component of tumour procoagulant activity (7-9). Recently, it was discovered that the expression of tissue factor by cancer cells is controlled by oncogenes and tumour suppressor genes, including the epidermal growth factor receptor (*EGFR*) family, *RAS*, *TP53*, and *PTEN* (10). This indicates a genetic link between cancer genes and tumour procoagulant activity. However, little is known about the clinical relevance of this link.

The risk of VTE varies according to cancer type, tumour burden at diagnosis, and cancer treatment (4, 11, 12), but the overall risk of VTE is high in patients with non-small cell lung cancer (NSCLC) (5, 11, 13, 14). Recently, a large epidemiologic study reported that the two-year cumulative incidence of VTE among patients with NSCLC was 3.6% (15). Although previous studies suggested that VTE increases the likelihood of death in lung cancer, the interpretation of the results is limited because the analyses used a population registry without treatment information (15) and with incomplete histology data (16). Furthermore, since ethnicity significantly influences the risk of developing VTE, studies focusing on Asian patients are necessary (15, 17-19).

Therefore, our goal was to describe the incidence, risk factors and prognostic implications of VTE in Asian patients with NSCLC. We also evaluated the association between specific gene mutations and the risk of VTE.

Methods

Study population

Between January 2006 and June 2010 we consecutively enrolled all patients diagnosed with NSCLC at Seoul National University Hospital. All diagnoses were confirmed by pathology. We retrospectively collected the patients' demographic information, tumour features and treatment characteristics. We excluded patients who had visited our hospital to get a second opinion and patients with a history of prior malignancy, except for those who had been disease-free for more than five years after curative treatment.

The 6th edition of the tumour node metastasis staging system was used to stage NSCLC (20). The therapeutic plan for NSCLC primarily depends on tumour stage, so NSCLC was further categorised into localised (stage I & II), locally advanced (stage III), and metastatic (stage IV) NSCLC. In accordance with the International Association for the Study of Obesity in the Western Pacific Region, obesity was defined as a body mass index (BMI) of ≥ 25 kg/m^2 (21). To evaluate comorbidities, we documented histories of ischaemic heart disease, heart failure, hypertension, diabetes, dyslipidaemia, cerebrovascular disease, and chronic pulmonary, kidney, and liver diseases. Data for *EGFR* mutations and *ALK* gene rearrangement were also collected.

Identification of VTE

We defined VTE to include deep-vein thrombosis (DVT), pulmonary embolism (PE), and thrombosis in other vascular territories except for superficial thrombophlebitis. To identify VTE, we retrieved all reports of radiologic (computerized tomography [CT], CT angiography, Doppler ultrasonography, and conventional angiography) or nuclear medicine (ventilation/perfusion scans) studies performed on each patient from the respective electronic medical record (EMR). Two independent investigators (Y-G LEE, EY LEE) double-checked the diagnoses of VTE by reviewing each relevant EMR. VTE cases were classified according to their anatomic location and the presence of symptoms. PE was further evaluated as central, segmental, or subsegmental PE. Medication records including prescription code for unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) were also retrieved from EMR and double checked by two investigators.

Statistical analysis

The time-to-VTE was measured from the date of cancer diagnosis to the first date of VTE identification. The time-to-VTE was assigned to day 1, when cancer and VTE were diagnosed simultaneously. Patients without developing VTE were censored at the last date of follow-up or death from any cause. The cumulative incidences of VTE were estimated using the Nelson-Aalen method and compared by log-rank tests. Univariate and multivariate (backward stepwise selection method with probability for removal of 0.10) Cox's proportional hazards regression models were used to identify the strongest predictors of VTE development, and each variable's biologic relevance was considered. When a linear effect of categorical variable was suspected, we tested a departure from linear trend using a likelihood-ratio test. We also tested if the effect of each variable on VTE development was modified by stage.

Overall survival (OS) was measured from the date of cancer diagnosis to death from any cause. Information regarding vital status was obtained through June 11, 2012 from the National Population Registry of the Korea National Statistical Office. To assess the impact of VTE on survival, we compared the OS of patients who developed VTE to those who did not. To reduce the potential confounding in this study, substantial adjustments were made using the propensity score matching method for the following characteristics: age group, gender, obesity, smoking status, number of comorbidities, histology, stage, type of tumour resection, chemotherapy, and radiotherapy. To establish propensity score-matched pairs, the nearest neighbor-matching algorithm was used without replacement to yield a 1:1 match (22). After the propensity-score matches were performed, we assessed the balance in baseline covariates between patients with and without VTE with McNemur's test or marginal homogeneity test for categorical variables. Stratified log-rank tests were used to compare OS between groups. All analyses were performed using Stata 12.0 software (Stata Corp LP, College Station, TX, USA).

This study complied with the principles of the Declaration of Helsinki, and this study was approved by the Institutional Review Board of Seoul National University Hospital (IRB No: H-1102–013–349).

Results

Characteristics of the study population

A total of 1,998 patients met the criteria for inclusion. The median age at diagnosis was 65 years (range 23–90 years). Adenocarcinoma was the most frequent histology (55.4%). Most NSCLC was categorised as localised (40.7%), followed by metastatic (35.6%) and locally advanced (23.7%). Approximately half of the patients received curative resection of the tumour, and only 0.4% of those received perioperative thromboprophylaxis. The median follow-up period was 3.8 years (interquartile range 2.8–4.9 years). Among the 962 patients receiving curative treatments, 290 (30%) experienced cancer recurrence during the follow-up period. A total of 1100 deaths (55.1%) were documented at the time of final analysis.

Incidence and risk factors for VTE

Among 1,998 patients, 131 (6.6%) were diagnosed with VTE. The six-month and two-year cumulative incidences of VTE were 4.2% (95% confidence interval [CI] 3.4–5.3) and 6.4% (95% CI 5.3–7.8), respectively. The cumulative incidence of VTE, based on demographic and clinical characteristics, and the hazard ratio (HR) from univariate analyses are presented in ▶Table 1. The two-year cumulative incidences of VTE were 2.5% (95% CI 1.6–3.9), 5.5% (95% CI 3.5–8.5), and 14.1% (95% CI 10.8–18.3) in localised, locally advanced, and metastatic NSCLC, respectively ($p<0.001$; ▶Figure 1). A linear trend of increasing VTE was observed with

advancing stage (common HR 2.5; p for trend <0.001). In univariate analyses, former/current smoking status (vs never smoking), pneumonectomy (vs lobectomy), ineligibility for surgery (vs lobectomy), palliative chemotherapy (vs no chemotherapy), and palliative radiotherapy (vs no radiotherapy) were significantly associated with an increased risk of VTE.

In multivariate analyses, the effects of therapeutic variables including surgery, chemotherapy, and radiotherapy on the development of VTE were modified by NSCLC stage. Therefore, we calculated stratum-specific HRs by performing stratified analyses for each stage (▶Table 2). In localised NSCLC, advanced age, pneumonectomy (vs lobectomy), and palliative radiotherapy (vs no

Table 1: The cumulative incidence of venous thromboembolism (VTE) according to demographic and clinical characteristics in patients with non-small cell lung cancer.

Variables	Patients		VTE cases observed		Cumulative incidence of VTE (univariate analysis)		
	No	%	No	%	6-month	2-year	HR (95% CI)
Total patients	1998	100	131	7	4.2	6.4	–
Age groups							
<50 years	213	11	15	7	3.9	7.2	1
50–59 years	423	21	23	5	3.2	4.9	0.8 (0.4–1.5)
60–69 years	756	38	55	7	4.6	6.5	1.1 (0.6–1.9)
≥70 years	606	30	38	6	4.7	7.5	1.1 (0.6–1.9)
Gender							
Male	1338	67	81	6	4.3	6.2	1
Female	660	33	50	8	4.1	6.8	1.1 (0.8–1.6)
Obesity*							
Non-obese	1421	71	98	7	4.3	6.9	1
Obesity	577	29	33	6	4.0	5.5	0.8 (0.5–1.1)
Smoking							1
Never smoker	488	24	19	8	2.5	3.5	1.9 (1.1–3.1)
Former smoker	832	42	66	4	4.6	7.6	1.9 (1.1–3.2)
Current smoker	638	32	44	7	5.1	7.3	
Unknown	40	2	2	5	-	-	
No. of comorbidities							
0	895	45	58	7	4.0	6.2	1
1	675	34	46	7	4.6	6.7	1.1 (0.7–1.6)
2	323	16	20	6	4.6	6.1	1.0 (0.6–1.7)
≥ 3	105	5	7	7	3.1	8.3	1.1 (0.5–2.4)
Histology							
Squamous cell	581	29	32	6	3.7	5.1	1
Adenocarcinoma	1106	55	79	7	4.1	6.7	1.2 (0.8–1.8)
Others	311	16	20	6	5.9	7.9	1.3 (0.7–2.2)
Stage							
Localised	813	41	24	3	1.7	2.5	1
Locally advanced	473	24	33	7	3.9	5.5	3.2 (1.9–5.5)
Metastatic	712	36	74	10	7.8	14.1	6.4 (4.0–10.3)
Type of tumour resection							
Lobectomy	953	48	30	3	1.3	1.9	1
Pneumonectomy	41	2	5	12	9.7	14.5	5.2 (2.0–13.4)
No surgery	1004	50	96	10	7.2	12.5	5.7 (3.7–8.8)
Chemotherapy							
None	807	40	21	3	2.3	2.8	1
Perioperative only	194	10	7	4	1.6	2.8	1.1 (0.5–2.6)
Palliative (± perioperative)	997	50	103	10	6.3	10.6	4.8 (3.0–7.8)
Radiotherapy							
None	1416	71	67	5	3.2	5.0	1
Curative intent	167	8	10	6	4.4	6.3	1.4 (0.7–2.7)
Palliative intent	415	21	54	13	7.8	11.5	3.4 (2.4–5.0)

VTE, venous thromboembolism; HR, hazard ratio; 95% CI, 95% confidence interval. Percentages may not total 100 because of rounding. *Obesity was defined as a body mass index of ≥ 25 kg/m^2.

Table 2: Hazard ratios for the development of VTE stratified by stage.

Variables	Localised				Locally advanced				Metastatic			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age groups*	2.7 (1.5–5.0)	0.001	2.4 (1.3–4.4)	0.008	0.9 (0.7–1.3)	0.687			1.1 (0.9–1.4)	0.338		
Female (vs male)	0.2 (0.0–0.7)	0.014	0.3 (0.1–1.2)	0.076	1.0 (0.5–2.2)	0.907			1.6 (1.0–2.5)	0.044		
Obese (vs non-obese)	0.6 (0.3–1.6)	0.351			0.6 (0.3–1.5)	0.279			1.0 (0.6–1.7)	0.989		
Former/current smoker (vs never)	1.0 (0.4–2.4)	0.910			1.1 (0.5–2.4)	0.872			3.6 (1.5–8.9)	0.006	3.2 (1.3–8.0)	0.012
Comorbidity*	1.8 (1.3–2.5)	0.001			0.8 (0.5–1.2)	0.208			1.0 (0.8–1.3)	0.816		
Adenocarcinoma (vs squamous)	0.3 (0.1–0.7)	0.005			0.8 (0.4–0.7)	0.605			2.9 (1.2–6.7)	0.014	2.5 (1.1–5.9)	0.033
Pneumonectomy (vs lobectomy) No surgery (vs lobectomy)	8.2 (2.4–27.7) 1.2 (0.2–9.3)	0.001 0.832	7.7 (2.2–26.4)	0.001	2.8 (0.6–13.0) 3.0 (1.4–6.7)	0.190 0.007	2.4 (1.1–5.3)	0.034	–			
Perioperative chemotherapy (vs no) Palliative chemotherapy (vs no)	1.5 (0.5–4.6) 2.7 (1.1–6.9)	0.470 0.031			2.0 (0.2–19.6) 7.8 (1.1–56.9)	0.544 0.044	2.5 (0.9–7.5)	0.095	–			
Curative radiation therapy (vs no) Palliative radiation therapy (vs no)	1.7 (0.2–13.1) 7.2 (3.1–17.1)	0.595 0.000	5.1 (2.1–12.5)	0.000	3.6 (1.3–9.7) 10.2(4.2–24.6)	0.012 0.000	5.7(2.8–11.6)	0.000	0.9 (0.6–1.4)	0.574		

VTE, venous thromboembolism; HR, hazard ratio; 95% CI, 95% confidence interval. *As the modelling with separate effects for 'Age groups' and 'No. of comorbidities' (Table 1) did not significantly improve the fit of the model, we assumed a linear trend in these variables and displayed common HR from one group to the next.

radiotherapy) were independent predictors for VTE. In locally advanced NSCLC, ineligibility for surgery (vs lobectomy) and palliative radiotherapy (vs no radiotherapy) were independently associated with an increased risk of VTE. Radiation field (central vs peripheral) made no significant difference in the risk of VTE in both localised (p=0.743) and locally advanced (p=0.243) NSCLC. In metastatic NSCLC, adenocarcinoma (vs squamous cell) and former/current smoker (vs never smoker) were the independent predictors for VTE development.

Specific gene mutation and the development of VTE

Testing for *EGFR* mutations and *ALK* gene rearrangement is generally recommended in metastatic or recurrent NSCLC with adenocarcinoma histology, in which these genetic abnormalities are frequently found, and effective treatments are available (23). Therefore, subgroup analyses were performed for metastatic or recurrent NSCLC with adenocarcinoma (▶Table 3). Among 1,116 patients with adenocarcinoma, we tested 670 (60.0%) for *EGFR* mutations and 250 (22.4%) for *ALK* rearrangements. *EGFR* mutations and *ALK* rearrangements were detected in 340 (50.7%) and 24 (9.6%) of tested patients, respectively.

In univariate analyses, *EGFR* mutations (p=0.170) and *ALK* rearrangements (p=0.159) were not significantly associated with VTE development. In both univariate and multivariate analyses, former/current smoker status, EGFR tyrosine kinase inhibitor (TKI) treatment, and palliative radiotherapy were significantly associated with an increased risk of VTE.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age groups*	1.0 (0.8–1.2)	0.931		
Female (vs male)	1.0 (0.7–1.6)	0.877		
Obese (vs non-obese)	0.9 (0.5–1.4)	0.570		
Former/current smoker (vs never)	2.5 (1.2–5.5)	0.020	2.5 (1.1–5.4)	0.022
Comorbidity*	0.9 (0.7–1.2)	0.455		
EGFR mutation† (vs wild type) *EGFR* not tested (vs wild type)	0.7 (0.4–1.2) 1.2 (0.7–1.9)	0.170 0.559		
ALK rearrangement (vs wild type) *ALK* not tested (vs wild type)	2.2 (0.7–6.4) 0.8 (0.5–1.4)	0.159 0.503		
EGFR TKI treatment (vs no)	2.8 (1.8–4.4)	0.000	1.7 (1.0–2.8)	0.037
Palliative radiation therapy (vs no)	4.2 (2.7–6.6)	0.000	3.3 (1.1–5.4)	0.022

VTE, venous thromboembolism; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor; HR, hazard ratio; 95% CI, 95% confidence interval. *We assumed a linear trend in these variables and displayed common HR from one group to the next. †*EGFR* mutations are deletions in exon 19, a mutation in exon 21 (L858R) and exon 18 (G719X).

Table 3: Hazard ratios for the development of VTE based on specific gene mutation in patients with adenocarcinoma.

Characteristics	Symptomatic	Asymptomatic	Total	P-value*
	Number of patients (%)			
All	100 (76)	31 (24)	131 (100)	
Multiplicity of VTE				0.021
Solitary	36 (36)	19 (61)	55 (42)	
Multiple	64 (64)	12 (39)	76 (58)	
Location of VTE				0.003
Pulmonary embolism	54 (54)	18 (58)	72 (55)	
Deep-vein thrombosis	15 (15)	1 (3)	16 (12)	
Pulmonary embolism + deep vein thrombosis	22 (22)	2 (7)	24 (18)	
Inferior or superior vena cava	3 (3)	3 (10)	6 (5)	
Neck vein	3 (3)	4 (13)	7 (5)	
Portal vein	1 (1)	3 (10)	4 (3)	
Other sites	2 (2)	0 (0)	2 (2)	
Stage of VTE development				0.025
At cancer diagnosis	21 (21)	7 (23)	28 (21)	
Post-operative	7 (7)	0 (0)	7 (5)	
Post-treatment follow-up	4 (4)	5 (16)	9 (7)	
Palliative treatment	45 (45)	17 (55)	62 (47)	
Terminal phase	23 (23)	2 (7)	25 (19)	
Tumour response status				0.067
At cancer diagnosis	21 (21)	7 (23)	28 (21)	
Stable disease, partial or complete response	28 (28)	15 (48)	43 (33)	
Progression of disease	51 (51)	9 (29)	60 (46)	
Anticoagulation				0.000
Warfarin	9 (9)	7 (23)	16 (12)	
LMWH followed by warfarin	15 (15)	2 (7)	17 (13)	
LMWH	72 (72)	14 (45)	86 (66)	
No anticoagulation	4 (4)	8 (26)	12 (9)	

VTE, venous thromboembolism; LMWH, low-molecular-weight heparin. * P-value was derived from Chi-square test or Fisher's exact test as appropriate.

Table 4: Clinical characteristics of symptomatic and asymptomatic VTEs.

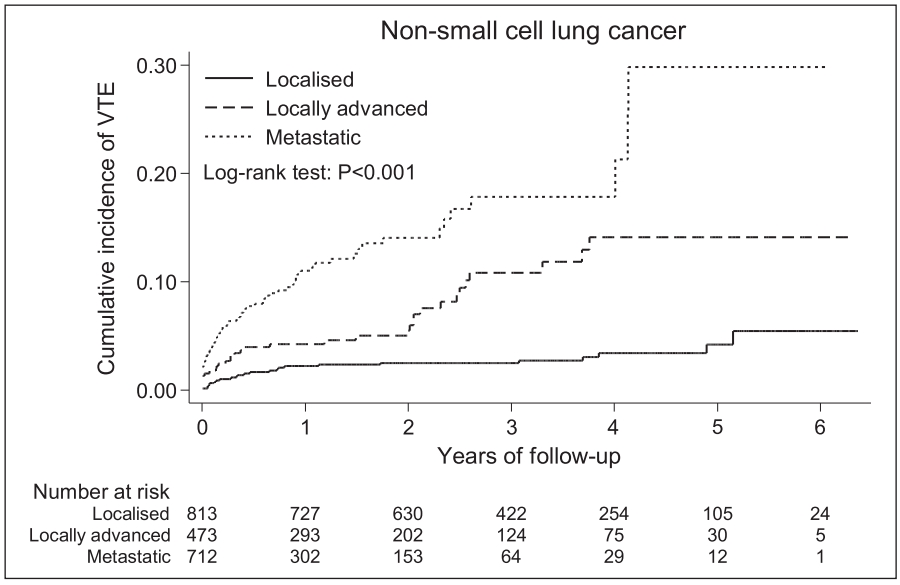

Figure 1: The cumulative incidence of VTE increases with advancing stage in patients with non-small cell lung cancer (common HR 2.5; p for trend <0.001).

Clinical characteristics of VTE development

Among a total of 131 cases of VTE, 100 (76.3%) cases were symptomatic. Symptomatic VTEs were significantly associated with multiple thrombi, DVT, and cancer progression (►Table 4). Asymptomatic VTE tends to develop with solitary thrombus in locations other than deep veins during routine surveillance, compared to symptomatic VTE. Among 96 PE, more than half of the thrombi were located in central (55.2%), followed by segmental (38.5%) and subsegmental (6.3%) artery. Anticoagulation therapy was administered to 90.8% of the patients with VTE. Asymptomatic VTE was treated with anticoagulation therapy less than symptomatic VTEs (74.2% vs 96.0%).

Impact of VTE on survival

►Figure 2 shows Kaplan-Meier survival curves of patients with and without VTE, along with propensity score-matching for age group, gender, obesity, smoking status, number of comorbidities, histology, stage (localised), type of tumour resection (localised, locally advanced), chemotherapy, and radiotherapy. Propensity score-matching yielded 23, 32, and 74 patient-pairs in the localised, locally advanced, and metastatic NSCLC groups, respectively. In the matched groups, there was no significant difference between patients with and without VTE for any covariates (data are not shown). Among the propensity score-matched cohort, a significant survival difference was observed between patients with and without VTE in localised NSCLC (►Figure 2A; p=0.017), but not in locally advanced (►Figure 2B; p=0.80) or metastatic NSCLC (►Figure 2C; p=0.23). When OS was compared without propensity-score matching, the same findings were observed (see Suppl. Figure 1, available online at www.thrombosis-online.com).

Among patients with VTE, we evaluated the relationship between the kind of VTE and OS. For 96 patients with PE, there was no survival differences between patients with central, segmental, and subsegmental PE (Suppl. Figure 2A, available online at www.thrombosis-online.com; p=0.165). When central and segmental PE are grouped together, patients with subsegmental PE showed better survival than patients with central and segmental PE (Suppl. Figure 2B, available online at www.thrombosis-online.com; p=0.065). However, the survival difference was marginally significant due to a low number of subsegmental PE.

Discussion

This study had two main purposes: 1) to estimate the incidence, risk factors and prognostic implications of VTE and 2) to evaluate the association between oncogenes and the risk of VTE in NSCLC. The six-month and two-year cumulative incidences of VTE were 4.2% and 6.4%, respectively. The significant predictors of VTE are different across stages of NSCLC. The association between VTE and decreased survival was observed only in localised NSCLC. *EGFR* mutations and *ALK* rearrangements were not associated with VTE development in lung adenocarcinoma.

Recent studies investigating the prevalence of VTE in Caucasian reported that about 14% to 15% of lung cancer patients developed VTE (24, 25). Our result of 6.4% is less than half the incidence reported in the Western studies. Considering that having an Asian ethnicity was associated with about a 60% lower risk of VTE development in patients with NSCLC (15), our study provides reliable estimates of risk regarding VTE in Asian patients.

The effects of treatment, including surgery, chemotherapy, and radiotherapy, on the development of VTE were significantly modified by NSCLC stage. The presence of interaction is understandable, since initial treatment modalities primarily depend on tumour stage. In localised NSCLC, in which surgical resection is the initial treatment, advanced age and pneumonectomy (vs lobectomy) were independent predictors of VTE development. This is consistent with a previous study that reported an increased inci-

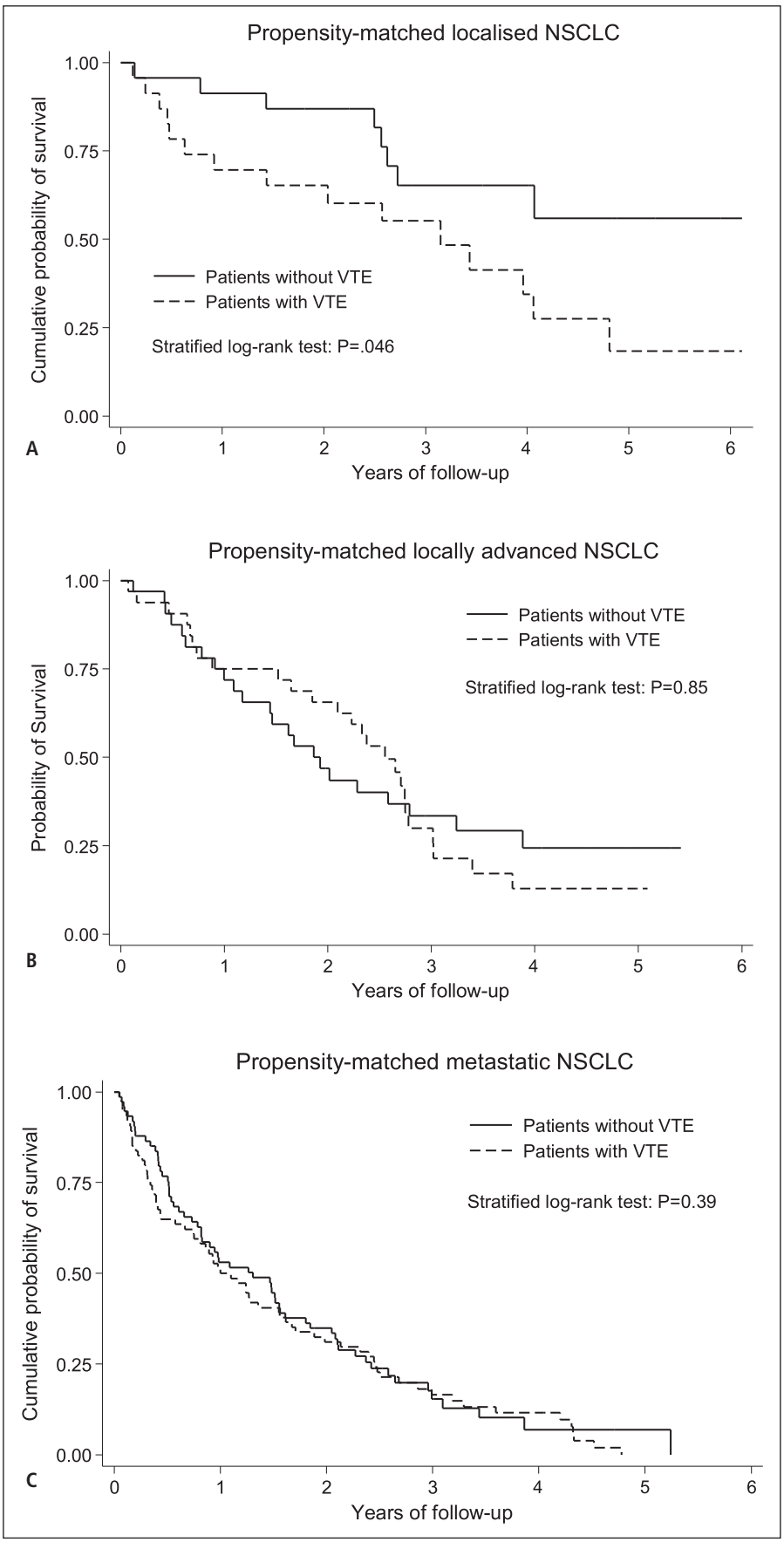

Figure 2: Comparison of overall survival between patients with and without VTE using propensity-score matching methods in (A) localised NSCLC (n=46; HR 3.0; p=0.017), (B) locally advanced NSCLC (n=64; HR 1.1; p=0.80), (C) metastatic NSCLC (n=148; HR 1.2; p=0.23).

dence of VTE in lung cancer patients who received extensive surgery (26). Overall, our results will be helpful in identifying patients with a particularly high risk of VTE who may benefit from thromboprophylaxis. For example, in the case of the five patients who underwent pneumonectomy and then developed VTE, the median time between operation and VTE was 30 days (range 13–100 days). No patient received perioperative thromboprophylaxis. Therefore, we can assume that some of the five patients who underwent pneumonectomy may have benefitted from routine thromboprophylaxis. In locally advanced NSCLC, in which multimodal treatments are required, ineligibility for surgery was associated with VTE. This reflects the selection of individuals with high tumour burden and distant nodal involvements, who were ineligible for curative resection. This is a consistent finding among colorectal, breast, and lung cancers (15, 18, 19). In recurrent cases of localised and locally advanced NSCLC, receiving palliative radiotherapy was the strongest independent predictor for VTE, conferring more than five-fold higher risk of VTE compared to patients who did not receive it. This reflects the thrombogenic effects of radiotherapy due to the release of procoagulants and cytokines from damaged tumour cells.

Adenocarcinoma histology and smoking history were the independent risk factors for increased risk of VTE in metastatic NSCLC (15, 27). Patients with metastatic NSCLC are not eligible for surgery and most of them (84% in our study) receive palliative chemotherapy. Therefore, these treatment-related factors could not influence clinically meaningful differences in the incidence of VTE.

In our study, the proportion of patients who received perioperative thromboprophylaxis was very low (0.4%). Due to the scarcity of reliable information and the relatively low incidence of VTE among people of Asian ethnicity, active perioperative thromboprophylaxis has not received attention in Korea. However, Korean guidelines for the prevention of VTE were published in 2010 (28), and we now strongly recommended appropriate thromboprophylaxis based on individual risk assessments.

For an unbiased estimation of VTE effects on survival per se, we adopted a propensity score-matching method that made a sampling of patients without VTE comparable on all observed covariates to patients with VTE. Interestingly, the association between VTE and decreased survival was limited to localised NSCLC. Prior studies noted that this association was greatest among patients with initially local or regional stage colorectal, breast and ovarian cancers as well as NSCLC (15, 18, 19, 29). The strong association we observed between VTE and the increased rate of recurrence (risk ratio 2.0; p=0.009) can explain the significant difference in survival in localised NSCLC. However, when comparing recurrence-free interval in terms of VTE development, there was no significant difference between patients with and without VTE (557 vs 619 days; p=0.734).

In our subgroup analysis, treatment with EGFR TKI was associated with a 60% increased risk of VTE, which is consistent with the recent study by Yang et al. (30). However, *EGFR* mutations and *ALK* rearrangements were not associated with VTE development. Preclinical data suggests that EGFR inhibition reduces expression of tissue factor, which regulates tumour procoagulant activity (31). Therefore, we assumed that the inhibition of EGFR by targeted therapy decreases the expression of tissue factor, which may, in turn, reduce the incidence of VTE. Our conflicting results can likely be explained by the fact that patients receiving EGFR TKI underwent more advanced chemotherapy (2.6 vs 3.5 lines of chemotherapy; p<0.001) and showed longer survival (1.6 vs 0.9 years; P<0.001) than patients not receiving TKI.

Although the present study is the largest report that has specifically focused on VTE in Asian patients with NSCLC, there are limitations. First, the unrecognized bias from the retrospective nature of our study conducted in a single referral institution limits the interpretation of the results. Second, approximately 9% of the patients without VTE were lost to follow-up, which can underestimate the real incidence of VTE. Therefore, more studies are necessary to confirm our results. Still, the use of an accurate and nearly complete dataset that included treatment and genetic information allowed us to conduct extensive analyses that were impossible in previous studies.

In conclusion, the two-year cumulative incidence of VTE is 6.4% in Asian patient with NSCLC. Tumour stage is the most important predictor of VTE. The significant predictors of VTE are different across stages of NSCLC. The association between the VTE and decreased survival was limited to localised NSCLC. *EGFR* mutations and *ALK* rearrangements were not associated with VTE development in lung adenocarcinoma.

What is known about this topic?

- The overall risk of venous thromboembolism (VTE) is high in patients with non-small cell lung cancer (NSCLC). Since ethnicity significantly influences the risk of developing VTE, studies focusing on Asian patients with NSCLC are necessary.
- Recently, several studies suggest a genetic link between cancer genes and tumor procoagulant activity. However, little is known about the clinical relevance of this link.

What does this paper add?

- In our study, the two-year cumulative incidences of VTE were 2.5%, 5.5%, and 14.1% in localised, locally advanced, and metastatic NSCLC, respectively. Considering the protective effect of Asian ethnicity on VTE development, the risk of VTE in Asian patients with NSCLC is not lower than Western patients.
- The significant predictors of VTE are different across stages of NSCLC. A significant association between VTE and decreased survival was observed only among patients with localised NSCLC.
- *EGFR* mutations and *ALK* rearrangements were not associated with VTE development in lung adenocarcinoma.

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Conflicts of interest

None declared.

References

1. Rickles FR. Mechanisms of cancer-induced thrombosis in cancer. Pathophysiol Haemost Thromb 2006; 35: 103–110.
2. Zwicker JI, Furie BC, Furie B. Cancer-associated thrombosis. Crit Rev Oncol Hematol 2007; 62: 126–136.
3. Davila M, Amirkhosravi A, Coll E, et al. Tissue factor-bearing microparticles derived from tumour cells: impact on coagulation activation. J Thromb Haemost 2008; 6: 1517–1524.
4. Khorana AA, Francis CW, Culakova E, et al. Risk factors for chemotherapy-associated venous thromboembolism in a prospective observational study. Cancer 2005; 104: 2822–2829.
5. Blom JW, Doggen CJ, Osanto S, et al. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. J Am Med Assoc 2005; 293: 715–722.
6. Heit JA, Silverstein MD, Mohr DN, et al. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med 2000; 160: 809–815.
7. Tesselaar ME, Romijn FP, Van Der Linden IK, et al. Microparticle-associated tissue factor activity: a link between cancer and thrombosis? J Thromb Haemost 2007; 5: 520–527.
8. Rak J, Milsom C, Yu J. Tissue factor in cancer. Curr Opin Hematol 2008; 15: 522–528.
9. Zwicker JI. Tissue factor-bearing microparticles and cancer. Semin Thromb Hemost 2008; 34: 195–198.
10. Boccaccio C, Comoglio PM. Genetic link between cancer and thrombosis. J Clin Oncol 2009; 27: 4827–4833.
11. Chew HK, Wun T, Harvey D, et al. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Arch Intern Med 2006; 166: 458–464.
12. Otten HM, Mathijssen J, ten Cate H, et al. Symptomatic venous thromboembolism in cancer patients treated with chemotherapy: an underestimated phenomenon. Arch Intern Med 2004; 164: 190–194.
13. Stein PD, Beemath A, Meyers FA, et al. Incidence of venous thromboembolism in patients hospitalized with cancer. Am J Med 2006; 119: 60–68.
14. Horsted F, West J, Grainge MJ. Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis. PLoS Med 2012; 9: e1001275.
15. Chew HK, Davies AM, Wun T, et al. The incidence of venous thromboembolism among patients with primary lung cancer. J Thromb Haemost 2008; 6: 601–608.
16. Huang H, Korn JR, Mallick R, et al. Incidence of venous thromboembolism among chemotherapy-treated patients with lung cancer and its association with mortality: a retrospective database study. J Thromb Thrombolysis 2012; 34: 446–456.
17. Lee KW, Bang SM, Kim S, et al. The incidence, risk factors and prognostic implications of venous thromboembolism in patients with gastric cancer. J Thromb Haemost 2010; 8: 540–547.
18. Chew HK, Wun T, Harvey DJ, et al. Incidence of venous thromboembolism and the impact on survival in breast cancer patients. J Clin Oncol 2007; 25: 70–76.
19. Alcalay A, Wun T, Khatri V, et al. Venous thromboembolism in patients with colorectal cancer: incidence and effect on survival. J Clin Oncol 2006; 24: 1112–1118.
20. Greene FL, American Joint Committee on Cancer., American Cancer Society. AJCC cancer staging manual. 6th ed. New York, Springer-Verlag; 2002.
21. WHO. The Asia-Pacific perspective: redefining obesity and its treatment. Geneva, Switzerland: World Health Organisation 2000.
22. Leuven E, Sianesi B. PSMATCH2: Stata module to perform full Mahalanobis and propensity score matching, common support graphing, and covariate imbalance testing. Statistical Software Components 2010.
23. Ettinger DS, Akerley W, Borghaei H, et al. Non-small cell lung cancer. J Natl Compr Canc Netw 2012; 10: 1236–1271.
24. Connolly GC, Menapace L, Safadjou S, et al. Prevalence and clinical significance of incidental and clinically suspected venous thromboembolism in lung cancer patients. Clin Lung Cancer 2013; 14: 713–718.
25. Connolly GC, Dalal M, Lin J, et al. Incidence and predictors of venous thromboembolism (VTE) among ambulatory patients with lung cancer. Lung Cancer 2012; 78: 253–258.
26. Ziomek S, Read RC, Tobler HG, et al. Thromboembolism in patients undergoing thoracotomy. Ann Thorac Surg 1993; 56: 223–227.
27. Blom JW, Osanto S, Rosendaal FR. The risk of a venous thrombotic event in lung cancer patients: higher risk for adenocarcinoma than squamous cell carcinoma. J Thromb Haemost 2004; 2: 1760–1765.
28. Bang SM, Jang MJ, Oh D, et al. Korean guidelines for the prevention of venous thromboembolism. J Korean Med Sci 2010; 25: 1553–1559.
29. Rodriguez AO, Wun T, Chew H, et al. Venous thromboembolism in ovarian cancer. Gynecol Oncol 2007; 105: 784–790.
30. Yang Y, Zhou Z, Niu XM, et al. Clinical analysis of postoperative venous thromboembolism risk factors in lung cancer patients. J Surg Oncol 2012; 106: 736–741.
31. Yu JL, May L, Lhotak V, et al. Oncogenic events regulate tissue factor expression in colorectal cancer cells: implications for tumour progression and angiogenesis. Blood 2005; 105: 1734–1741.