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Postoperative venous thromboembolism after surgery for stage IA non-small-cell lung cancer: A single-center, prospective cohort study

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Abstract

Background: Venous thromboembolism (VTE) is a common postoperative complication of lung cancer, but the incidence and risk stratification of postoperative VTE in stage IA non-small-cell lung cancer (NSCLC) patients remains unclear, therefore we conducted a single-center prospective study.

Methods: A total of 314 consecutive patients hospitalized for lung cancer surgery and diagnosed with stage IA NSCLC from January 2017 to July 2021 were included. The patients were divided into the VTE group and the non-VTE group according to whether VTE occurred after the operation. The patient's age, operation time, D-dimer (D-D) value, tumor pathology, and Caprini score were recorded. The different items were compared and included in logistic regression analysis to obtain independent risk factors, and the area under the receiver operating characteristics curve (AUC) was calculated.

Results: The incidence of VTE was 7.3%. Significant differences in age, operation time, preoperative and postoperative day 1 D-D value, neuron-specific enolase value, forced expiratory volume in 1 second, maximum ventilation, carbon monoxide diffusion capacity, and pathological diameter were noted between the two groups. Age (95% confidence interval [CI] 1.056–1.216) and postoperative day 1 D-D value (95% CI 1.125–1.767) were independent risk factors. The incidence of VTE in the low-, medium-, and high-risk groups with Caprini scores was 0%, 7.3%, and 11.5%, respectively. The AUC of the Caprini score was 0.704 ($p < 0.05$).

Conclusions: The incidence of postoperative VTE in patients with stage IA NSCLC was 7.3%. Age and postoperative day 1 D-D value were independent risk factors for VTE. The Caprini score has a certain value in the diagnosis of postoperative VTE of stage IA NSCLC.

KEYWORDS
non-small-cell lung cancer, risk factors, venous thromboembolism

INTRODUCTION

Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), is a common perioperative complication of thoracic surgery. VTE after lung cancer surgery can increase the mortality,[1] hospitalization cost, and complication rate[2] of patients. VTE in patients with lung cancer mainly occurs within 1 month after the operation.[3] Without preventive measures, the incidence of VTE in patients with lung cancer after surgery is 8.1%–23.1%.[4–9] Therefore, attention should be given to the occurrence of VTE in patients after thoracic surgery, especially the screening of high-risk patients.

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Risk factors for VTE mainly include patient factors (such as age, related complications, hospitalization, etc.), tumor factors (tumor type, stage, histological grade, etc.), and treatment factors (chemotherapy, surgery, radiotherapy, etc.).[10] Early-stage lung cancer patients exhibit certain particular biological behaviors. Surgical methods are mostly thoracoscopic subpulmonary lobectomy to reduce the injury as much as possible. Therefore, the risk, prevention, and treatment strategies for VTE may have certain features that need to be further studied. In recent years, the number of patients with stage IA non-small-cell lung cancer (NSCLC) undergoing thoracic surgery has increased significantly because a large number of patients with pulmonary nodules have been found due to the wide application of high-resolution low-dose CT,[11] and their VTE is still unclear.

In surgical inpatients, the Caprini risk assessment model (Caprini RAM) is mainly used to assess the risk of VTE (Table 1). Research has shown that Caprini RAM can effectively reduce the incidence of VTE after thoracic surgery.[12,13] Patients were divided into a low-risk group (0–4 points), a medium-risk group (5–8 points) and a high-risk group (≥9 points) according to the Caprini score. In previous studies, the incidence of VTE in low-, medium- and high-risk groups after lung surgery was 0%, 7.5%–12.3%, and 12.3%–40%, respectively.[4,14] The risk stratification of postoperative VTE in patients with stage IA NSCLC is unclear. Therefore, the purpose of this study was to explore the incidence and risk factors of postoperative VTE in patients with stage IA NSCLC and to evaluate the effectiveness of the Caprini score.

TABLE 1 Modified Caprini risk assessment model

Caprini risk factor	Caprini score
Age 40–59 (year)	1
Abnormal pulmonary function	1
Acute myocardial infarction (<1 month)	1
Body mass index ≥30 (kg/m^2)	1
Congestive heart failure (<1 month)	1
History of inflammatory bowel disease	1
History of prior major surgery (<1 month)	1
Complications of pregnancy	1
Oral contraceptive use or HRT	1
Sepsis (<1 month)	1
Serious acute lung disease (<1 month)	1
Swollen legs (current)	1
Varicose veins	1
Age 60–74 (year)	2
Central venous access	2
Confined to bed (>72 h)	2
Major open surgery (≥45 min)	2
Present cancer	2
Prior cancer, except nonmelanoma skin	2
Age ≥ 75 (year)	3
History of VTE	3
Family history of VTE	3
Chemotherapy	3
Positive anticardiolipin antibody	3
Positive lupus anticoagulant	3
Acute spinal cord injury (<1 month)	5
Major surgery ≥6 h	5

Abbreviations: HRT, hormone replacement therapy; VTE, venous thromboembolism.

METHODS

Study population

This study is a single-center prospective cohort study that was approved by the ethics committee of Beijing Chaoyang Hospital Affiliated with Capital Medical University (2017-ke-1) and exempted from informed consent. Patients with stage IA NSCLC who were hospitalized for thoracic surgery from January 2017 to July 2021 were included (Figure 1). All patients had primary lung tumors and underwent radical surgery. Both lower extremity veins were examined by ultrasonography before and after surgery. Stage IA NSCLC was confirmed by pathological diagnosis as follows: the diameter of the lesion was ≤3 cm and there was no lymph node or distant metastasis. The diagnosis of lung cancer is based on pathological results, and the staging is based on the TNM staging of lung cancer in the eighth edition.

Patients with the following conditions were excluded: (1) with lung metastasis; (2) refused to undergo surgery; (3) no ultrasound examination of the lower extremity vein was performed before or after the operation; (4) VTE was confirmed before the operation; (5) blood system-related diseases; (6) anticoagulant drugs were used before or after the operation for other reasons; and (7) distant metastases. The included patients were divided into a VTE group and a non-VTE group according to the occurrence of postoperative VTE.

Data collection

We used the electronic medical record system to collect the following information for patients: sex, age, body mass index (BMI), smoking history, hypertension, diabetes, hyperlipidemia, coronary heart disease, and past cancer history. Operation information included the operation approach (video-assisted thoracic surgery, thoracotomy), operation scope (wedge resection, segment resection, lobectomy), operation time, and bleeding amount. Platelet (PLT), activated partial thrombokinase time (APTT), prothrombin time (PT), and D-dimer (D-D) were measured before and on the first day after the operation. In addition, tumor markers, including gastrin-releasing peptide precursor (ProGRP), carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), and cytokeratin 19 fragment (CYFRA21-1), were included. Imaging information included tumor location and nodule morphology. Preoperative pulmonary function indices

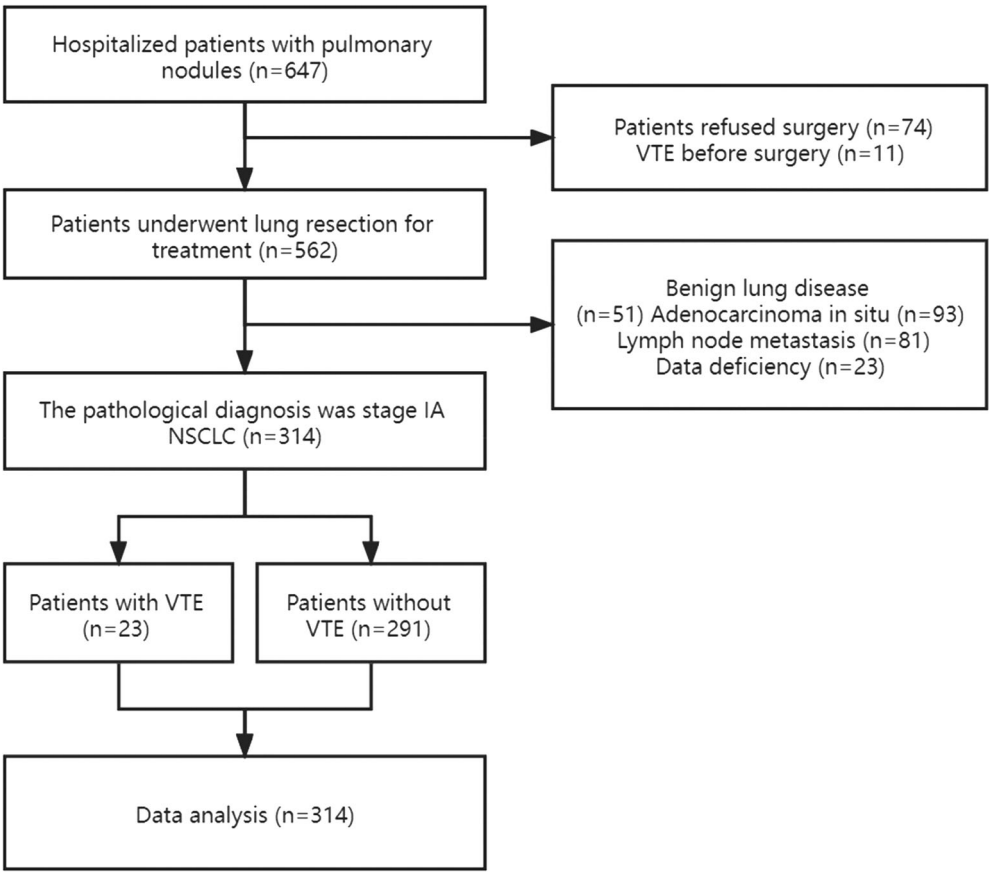

FIGURE 1 Selection of the study cohort. NSCLC, non-small cell lung cancer; VTE, venous thromboembolism

included forced expiratory volume in 1 second (FEV1) and maximum ventilation (MVV). Pathological information included pathological diameter, number of lymph nodes removed, and pathological type (lepidic adenocarcinoma, acinar adenocarcinoma, papillary adenocarcinoma, squamous cell carcinoma, etc.).

All patients underwent ultrasonography of both lower extremity veins 1–5 days before the operation and 3–5 days after the operation to evaluate DVT of the lower extremities. If the patients with VTE and typical pulmonary embolism symptoms have elevated D-D value, hypoxemia shown by arterial blood gas analysis, T-wave changes of V1–V4 and ST segment abnormalities indicated by ECG, and right ventricular afterload indicated by echocardiography, CT pulmonary angiogram (CTPA) should be further performed for definite diagnosis. Postoperative VTE events referred to patients without VTE before the operation and newly diagnosed VTE after the operation. The diagnostic criteria of DVT include the following: the venous lumen cannot be compressed or only partially compressed and the blood flow cannot be completely filled. The diagnostic criteria of PE were as follows: CTPA shows complete pulmonary vascular occlusion and different degrees of intraluminal filling defects.[15]

Statistical analysis

All data were statistically analyzed using IBM SPSS 26.0 software. Continuous variables were tested for normality, and those that did not conform to the normal distribution were expressed as M (Q_1, Q_3) and analyzed using the Mann–Whitney U test. Data that conformed to the normal distribution are presented as the means ± standard deviation and were analyzed using t-tests to compare the differences. Categorical variables were analyzed using the χ^2 test or Fisher's precision test. Variables with statistically significant differences after the above test were included in logistic regression analysis to obtain the independent risk factors for postoperative VTE in stage IA NSCLC. The area under the curve (AUC) of the independent risk factors and Caprini score were calculated according to the subject working curve (receiver operating characteristic, ROC). In this study, AUCs equal to 0.5–0.7, 0.7–0.9 and >0.9 were regarded as low, medium and high, respectively. A p value <0.05 was considered statistically significant.

RESULTS

Patient characteristics and incidence rate of VTE

A total of 314 patients were included in this study. The overall characteristics are shown in Table 2. There were 117 males (37.3%) and the median age was 57 years. A total of 99.0% ($n = 311$) of the patients underwent thoracoscopic surgery and 1.0% ($n = 3$) of the patients underwent

TABLE 2 Patient characteristics ($n = 314$)

Characteristic	Number (%) or mean ± SD
Age (years), median [range]	57 [28, 81]
Gender (male), *n* (%)	117 (37.3)
BMI (kg/m^2)	24.44 ± 3.21
Hospitalization time (days)	9.88 ± 4.19
Hypertension	91 (29.0)
Diabetes mellitus	28 (8.9)
Cardiovascular disease	12 (3.8)
Hyperlipemia	15 (4.8)
Smoking, *n* (%)	55 (17.5)
History of alcohol intake	32 (10.2)
Tumor history	7 (2.2)
Family history	31 (9.9)
Surgical procedure	
Wedge resection	50 (15.9)
Segment resection	44 (14.0)
Lobectomy	220 (70.1)
Surgical approach	
Thoracotomy	3 (1.0)
VATS	311 (99.0)
Duration of operation (min)	2.14 ± 0.85
Bleeding amount (ml)	50 (30,100)
Adhesion	13 (4.1)
Substantial proportion	
LU	70 (22.3)
LL	46 (14.6)
RU	117 (37.3)
RM	28 (8.9)
RL	53 (16.9)
Nodule morphology	
GGO	117 (37.3)
Mixed solid	107 (34.1)
solid	90 (28.6)
Tumor pathology	
Lepidic adenocarcinoma	144 (45.9)
Acinar adenocarcinoma	80 (25.5)
Papillary adenocarcinoma	16 (5.1)
Micropapillary adenocarcinoma	6 (1.9)
Solid adenocarcinoma	4 (1.3)
Invasive mucious adenocarcinoma	3 (1.0)
Minimally invasive adenocarcinoma	46 (14.6)
Squamous cell carcinoma	13 (4.1)
Others	2 (0.6)
Pathological diameter(cm)	1.33 ± 0.61
Number of lymph nodes dissected	10.44 ± 7.50
Tumor stage	
IA1	139 (44.3)
IA2	142 (45.2)
IA3	33 (10.5)
Laboratory values (pre-op)	
PLT, $\times 10^9$/L	225.21 ± 61.54
APTT (s)	25.75 ± 6.23
PT (s)	11.68 ± 0.63
D-dimer (μg/mL)	0.19 (0.14, 0.33)
ProGRP (pg/ml)	30.46 ± 12.00
CEA (ng/ml)	1.28 ± 1.07
NSE (ng/ml)	14.41 ± 5.13
Cyfra 21-1 (ng/ml)	1.01 (1.37, 1.96)
Laboratory values (post-op)	
PLT, $\times 10^9$/L	213.24 ± 53.53
APTT (s)	25.13 ± 2.94
PT (s)	12.09 ± 0.67
D-dimer (μg/mL)	0.90 (0.59, 1.40)
Lung function	
FEV 1 (L)	2.53 (2.17, 2.96)
FVC (L)	3.28 (2.89, 3.83)
MVV (L/min)	103.75 (88.94, 124.01)
DLCOcSB (mmol/min/kPa)	7.17 (6.26, 8.36)
Caprini score, *n* (%)	
0–4	13(4.1)
5–8	275(87.6)
≥9	26(8.3)

Abbreviations: APTT, activated partial thromboplastin time; BMI, body mass index; CEA, carcinoembryonic antigen; DLCOcSB, CO-diffusion capacity corrected for hemoglobin; FEV 1, forced expiratory volume in 1 second; FVC, forced vital capacity; GGO, ground glass opacity; LU, left upper lobe; LL, left lower lobe; MVV, maximal voluntary ventilation; NSE, neuron-specific enolase; PLT, platelet; PT, prothrombin time; ProGRP, progastrin-releasing peptide; RU, right upper lobe; RM, right middle lobe; RL, right lower lobe; VATS, video-assisted thoracoscopic surgery.

thoracotomy, including wedge resection in 50 cases (15.9%), segment resection in 44 cases (14.0%), and lobectomy in 220 cases (70.1%). The main pathological types were lepidic adenocarcinoma (144 cases, 45.9%), acinar adenocarcinoma (80 cases, 25.5%), papillary adenocarcinoma (16 cases, 5.1%), micropapillary adenocarcinoma (six cases, 1.9%), solid adenocarcinoma (four cases, 1.3%), invasive mucinous adenocarcinoma (three cases, 1.0%), minimally invasive adenocarcinoma (46 cases, 14.6%), squamous cell carcinoma (13 cases, 4.1%), and other pathological types (two cases, 0.6%). In terms of pathological stages, 139 cases (44.3%), 142 cases (45.2%), and 33 cases (10.5%) were stage IA1, IA2, and IA3, respectively. The total incidence of VTE in all patients was 7.3% ($n = 23$), of which 4.3% ($n = 1$) had DVT with PE and 95.7% ($n = 22$) had simple DVT. According to the Caprini score, 4.1% ($n = 13$) of patients were in the low-risk group, 87.6% ($n = 275$) were in the medium-risk group, and 8.3% ($n = 26$) were in the high-risk group. The incidence of VTE in the low-, medium- and high-risk groups was 0%, 7.3% ($n = 20$), and 11.5% ($n = 3$), respectively.

TABLE 3 Comparison of characteristics between VTE group and non-VTE group

Characteristic	VTE ($n = 23$)	Non-VTE ($n = 291$)	Z/t	p value
Age (years)	65 (58, 71)	57 (51, 64)	−3.835	0.000
Gender (male/female)	(8/15)	(109/182)	0.065	0.975
BMI (kg/m^2)	24.51 (22.87, 25.94)	24.31 (22.24, 26.68)	−0.268	0.788
Hospitalization time (days)	9 (7, 11)	8 (7,11)	−0.309	0.757
Hypertension	9 (39.1)	82 (28.2)	1.242	0.265
Diabetes mellitus	0 (0)	28 (9.6)	–	0.244
Cardiovascular disease	1 (4.3)	11 (3.8)	–	0.605
Hyperlipemia	1 (4.3)	14 (4.8)	–	1.000
Smoking, *n* (%)	4 (17.4)	51 (17.5)	–	1.000
History of alcohol intake	3 (9.4)	29 (10.0)	–	0.717
Tumor history	0 (0)	7 (2.4)	–	1.000
Family history	3 (13.0)	28 (9.6)	–	0.485
Surgical procedure			–	0.793
Wedge resection	3 (13.0)	47 (16.2)		
Segment resection	2 (8.7)	42 (14.4)		
Lobectomy	18 (78.3)	202 (69.4)		
Surgical approach			–	0.205
Thoracotomy	1(4.3)	2 (0.7)		
VATS	22(95.7)	289 (99.3)		
Duration of operation (mins)	2.66(1.62, 3.50)	2.00 (1.50, 2.63)	−2.075	0.038
Bleeding amount (ml)	100.00(27.50, 137.50)	50.00 (20.00, 100.00)	−1.557	0.119
Adhesion	2 (8.7)	11 (3.8)	–	0.245
Substantial proportion			–	0.571
LU	6 (26.1)	64 (22.0)		
LL	1 (4.3)	45 (15.5)		
RU	11 (47.8)	106 (36.4)		
RM	1 (4.3)	27 (9.3)		
RL	4 (17.4)	49 (16.8)		
Nodule morphology			0.942	0.624
GGO	7 (30.4)	110 (37.8)		
Mixed solid	10 (43.5)	97 (33.3)		
solid	6 (26.1)	84 (28.9)		
Tumor pathology			–	0.586
Lepidic adenocarcinoma	14 (60.9)	130 (44.7)		
Acinar adenocarcinoma	6 (26.1)	74 (25.4)		
Papillary adenocarcinoma	0 (0)	16 (5.5)		
Micropapillary adenocarcinoma	1 (4.3)	5 (1.7)		
Solid adenocarcinoma	0 (0)	4 (1.4)		
Invasive mucious adenocarcinoma	0 (0)	3 (1.0)		
Minimally invasive adenocarcinoma	1 (4.3)	45 (15.5)		
Squamous cell carcinoma	1 (4.3)	12 (4.1)		
Others	0 (0)	2 (0.7)		
Pathological diameter (cm)	1.50 (1.02, 2.00)	1.10 (0.80, 1.55)	−2.152	0.031
Number of lymph nodes dissected	13 (6,21)	10 (4, 15)	−1.480	0.139
Tumor stage			–	0.054
IA 1	5 (21.7)	134 (46.0)		
IA 2	15 (65.2)	127 (43.6)		
IA 3	3 (13.0)	30 (10.3)		

(Continues)

TABLE 3 (Continued)

Characteristic	VTE ($n = 23$)	Non-VTE ($n = 291$)	Z/t	p value
Laboratory values (pre-op)				
PLT, $\times 10^9$/L	225.41 ± 54.20	251.93 ± 55.78	−1.539	0.124
APTT (s)	25.10 (23.57, 26.80)	25.40 (24.00, 27.00)	−0.777	0.437
PT (s)	11.70 (11.35, 12.00)	11.60 (11.30, 12.00)	−0.023	0.981
D-dimer (μg/mL)	0.47 (0.21, 0.695)	0.19 (0.14, 0.29)	−4.827	0.000
ProGRP (pg/mL)	28.79 (18.63, 52.07)	27.32 (22.5, 34.83)	−0.418	0.676
CEA (ng/mL)	1.06 (0.50, 1.34)	1.06 (0.37, 1.90)	−0.629	0.530
NSE (ng/mL)	15.87 (12.14, 18.56)	13.55 (11.81, 15.89)	−2.614	0.009
Cyfra 21-1 (ng/mL)	1.75 (1.33, 2.12)	1.33 (0.97, 1.96)	−1.398	0.162
Laboratory values (post-op)				
PLT, $\times 10^9$/L	220.00 (172.25, 254.75)	206.00 (179.00, 243.50)	−0.319	0.750
APTT (s)	25.25 (24.05, 26.00)	24.90 (23.60, 26.60)	−0.279	0.780
PT (s)	12.00 (11.72, 12.20)	12.00 (11.60, 12.40)	−0.271	0.786
D-dimer (μg/mL)	3.69 (1.66, 4.47)	0.85 (0.56, 1.24)	−5.717	0.000
Lung function				
FEV 1 (L)	2.09 (1.65, 2.75)	2.56 (2.27, 3.02)	−1.978	0.048
FVC (L)	2.94 (2.19, 3.49)	3.28 (2.89, 3.95)	−1.888	0.059
MVV (L/min)	90.96 ± 25.69	108.27 ± 27.20	−3.002	0.003
DLCOcSB (mmol/min/kPa)	6.69 (5.93, 7.54)	7.24 (6.30, 8.29)	−2.110	0.035
Caprini score, n (%)			–	0.495
0–4	0 (0)	13 (4.5)		
5–8	20 (87.0)	255 (87.6)		
≥9	3 (13.0)	23 (7.9)		

Abbreviations: APTT, activated partial thromboplastin time; BMI, body mass index; CEA, carcinoembryonic antigen; DLCOcSB, CO-diffusion capacity corrected for hemoglobin; FEV 1, forced expiratory volume in 1 second; FVC, forced vital capacity; GGO, ground glass opacity; LU, left upper lobe; LL, left lower lobe; MVV, maximal voluntary ventilation; NSE, neuron-specific enolase; PLT, platelet; PT, Prothrombin time; ProGRP, progastrin-releasing peptide; RU, right upper lobe; RM, right middle lobe; RL, right lower lobe; VTE, venous thromboembolism; VATS, video-assisted thoracoscopic surgery.

TABLE 4 Logistic regression analysis

	B	SE	Wald	p value	OR	95% CI	
						Lower	Upper
Age (years)	0.125	0.036	12.108	0.001	1.133	1.056	1.216
D-dimer (post-op)	0.343	0.115	8.892	0.003	1.410	1.125	1.767
Constant	−10.583	2.365	20.016	0.000	0.000		

Abbreviations: B, regression coefficient; CI, confident interval; OR, odds ratio; SE, standard error.

TABLE 5 ROC curve analysis of risk factors and the Caprini score

	AUC	p value	95% CI	Cut-off value	Sensitivity	Specificity	Youden's index
Age (years)	0.728	0.000	0.611–0.796	57.500	0.864	0.537	0.400
D-dimer (post-op)	0.866	0.000	0.778–0.953	1.510	0.818	0.829	0.647
Caprini score	0.704	0.001	0.622–0.835	6.500	0.864	0.564	0.428

Abbreviations: AUC, area under the curve; CI, confident interval; ROC, receiver operating characteristic curve.

Risk factor analysis of VTE

In the VTE group, age (65 [58, 71] vs. 57 [51, 64], $p = 0.000$), duration of operation (2.66 [1.62, 3.50] vs. 2.00 [1.50, 2.63], $p = 0.038$), preoperative D-D value (0.47 [0.21, 0.695] vs. 0.19 [0.14, 0.29]), D-D value on the first day after operation (3.69 [1.66, 4.47] vs. 0.85 [0.56, 1.24], $p = 0.000$), NSE value (15.87 [12.14, 18.56] vs. 13.55 [11.81, 15.89],

$p = 0.009$), and pathological diameter (1.50 [1.02, 2.00] vs. 1.10 [0.80, 1.55], $p = 0.031$) were significantly higher than in the non-VTE group. FEV1 (2.09 [1.65, 2.75] vs. 2.56 [2.27, 3.02]), MVV (90.96 ± 25.69 vs. 108.27 ± 27.20), and carbon monoxide diffusion capacity (DLCOcSB) (6.69 [5.93, 7.54] vs. 7.24 [6.30, 8.29]) were significantly lower in the VTE group compared with the non-VTE group ($p < 0.05$). Forced vital capacity [2.94 (2.19, 3.49) vs. 3.28 (2.89, 3.95)] and the number of lymph nodes removed in the VTE group were greater than that in the non-VTE group [13 (6, 21) vs. 10 (4, 15)], but the difference was not significant. There was no significant difference in pathological type, tumor stage or imaging findings between the two groups. The patients' age, operation time, preoperative D-D value, postoperative D-D value on the first day, NSE value, FEV1, MVV, DLCOcSB, and pathological diameter were included in the binary logistic regression analysis. The results showed that age (OR 1.133, 95% CI 1.056–1.216) and postoperative D-D value on the first day (OR 1.410, 95% CI 1.125–1.767) were independent risk factors for postoperative VTE in patients with stage IA NSCLC (Tables 3 and 4).

ROC curve analysis of risk factors and Caprini score

According to ROC curve analysis, the AUC of the D-D value on the first day after the operation was 0.866, the cut-off value was 1.51, the sensitivity was 0.818, and the specificity was 0.829. The AUC of age was 0.728, the cut-off value was 57.5, and the sensitivity and specificity were 0.864 and 0.537, respectively. The AUC of the Caprini score was 0.704, the cut-off value was 6.5, and the sensitivity and specificity were 0.864 and 0.436, respectively. (Table 5)

DISCUSSION

Systematic studies on the incidence of perioperative stage IA NSCLC are lacking. The study of Cui[14] included 179 cases of lung cancer at stage 0 + I, and the incidence rate of VTE was 11.2% after the operation. In Wang's research,[16] 379 cases of lung cancer had diameters less than 3 cm and 10% of these cases were diagnosed as postoperative VTE. The incidence of VTE in our study was 7.3%, which was lower than that in a previous study and was mainly caused by the difference in surgical approach. In a study from the St. Joseph Medical Center and Toronto General Hospital in Canada, the incidence of VTE in patients with lung cancer within 30 days after surgery was 12.1%, of which the incidence of stage IA patients was 15.9% (7/44).[9] This value was significantly higher than the incidence in our study. The diversity may be explained by ethnic differences given that the study demonstrated that Asians had a lower incidence of VTE.[7]

In this study, a significant difference in the incidence of postoperative VTE was noted between stage IA1 and stage IA2 (3.6% vs. 10.6%, $p = 0.035$). No significant differences between stage IA2 and stage I A3 (10.6% vs. 9.1%) or between stage IA1 and stage IA3 (3.6% vs. 9.1%) were noted ($p > 0.05$). This finding may be explained by the notion that there were few stage IA3 patients. Thus, the correlation between tumor stage and VTE cannot be confirmed in stage IA patients. There were 299 patients with adenocarcinoma and 13 patients with squamous cell carcinoma. As noted above, the common pathological type in stage IA is adenocarcinoma, and the number of patients with squamous cell carcinoma is low. Further analysis showed no significant difference in the incidence of VTE between patients with adenocarcinoma and squamous cell carcinoma (7.4% vs. 7.7%, $p > 0.05$).

In a prospective study of the center in 2018, Song[4] et al. concluded that the incidence of VTE in the low-, medium-, and high-risk groups was 0%, 12.3% (22/179), and 40% (8/20), respectively, based on the Caprini score. A retrospective study performed at Boston University School of Medicine[17] showed that the incidence of VTE in the low-, medium-, and high-risk groups was 0%, 1.7% (2/119), and 10.3% (10/97), respectively. Compared with this study, the incidence of VTE in stage IA NSCLC in the medium-risk group was between that after overall thoracic malignant tumor operation and that after lung cancer operation, and the incidence of VTE in stage IA NSCLC in the high-risk group was lower.

The results of this study suggested that the independent risk factors for VTE after stage IA NSCLC were age (OR 1.133, 95% CI 1.056–1.216) and D-D value on the first day after operation (OR 1.410, 95% CI 1.125–1.767). The incidence of VTE in patients under 60 years old ($n = 189$), 61–74 years old ($n = 118$), and over 75 years old ($n = 7$) was 3.2%, 12.7%, and 28.6%, respectively. The results showed that the incidence of VTE increased with age, which was consistent with previous reports.[14,16]

Continuous monitoring of postoperative D-D levels of lung cancer patients can be performed to effectively evaluate the occurrence of VTE.[16] Studies have shown that adjusting the critical value of D-D according to age, surgical method, and tumor stage can achieve a better diagnostic effect.[18–20] In this study, the mean postoperative D-D values of the VTE and non-VTE groups were 3.44 ± 0.61 and 1.23 ± 0.12 μg/mL, respectively, both of which are >500 ng/mL. Thus, the routine threshold did not seem to be suitable for patients with stage IA NSCLC. In this study, the AUC of the D-D value on the first day after the operation was 0.866, the cut-off value was 1.51 μg/mL, and the sensitivity and specificity were 0.818 and 0.829, respectively. These values were similar to Cui's[14] results. Therefore, the individualized D-D limit may be more meaningful.

Prolonged operation time, increased bleeding, and open surgery can significantly increase the risk of postoperative VTE.[21] In this study, 99.3% of stage IA NSCLC patients underwent thoracoscopy. Although there was no significant difference in operation methods, the VTE group had a longer operation time and more bleeding.

Tumor necrosis factor (TNF) in tumor tissue plays an important role in the occurrence of VTE, and NSE levels may have predictive value for the staging and prognosis of NSCLC.[22,23] In this study, a significant difference in CEA was noted between the VTE group and the non-VTE group, which may be related to the larger pathological diameter and later staging of patients in the VTE group. VTE is related to lung diseases, such as chronic obstructive pulmonary disease, which is characterized by low pulmonary function in the VTE group. The FEV, MVV, and DLCOcSB of this study in the VTE group were significantly lower than those in the non-VTE group. Previous studies showed that FEV1[5] and MVV[24] were independent risk factors for VTE after lung cancer surgery, which had not been confirmed in stage IA NSCLC.

Caprini score plays an important role in the risk assessment of VTE after thoracic surgery, but its diagnostic value is not fully reflected in patients with stage IA NSCLC. In this study, the AUC of the Caprini score was 0.704, indicating that the diagnosis and prediction of VTE in patients with stage IA NSCLC needed to be improved. Many studies have confirmed that advanced stage,[25] metastasis,[26] and adenocarcinoma[27] in patients with NSCLC are significantly correlated with a high risk of VTE. The Caprini score was directly related to tumors only in "present cancer" and "prior cancer, except non-melanoma skin", and there was no risk assignment on histological classification and tumor stage. Therefore, we hope to continuously improve the Caprini score in future studies to obtain better diagnostic results.

Although perioperative VTE mainly occurred within 1 week after the operation, some patients still experienced VTE after discharge.[9,28] The follow-up of this study ended at the time of discharge and there was no long-term follow-up after discharge, which may have impacted the results. On the other hand, CTPA was not applied to all patients, so the incidence of postoperative VTE might be underestimated. This study was a single-center study and the results might be biased. This notion needs to be verified by a large number of multicenter studies.

In conclusion, in this study the incidence of VTE after surgery was 7.3% for stage IA NSCLC, 4.3% ($n = 1$) for DVT combined with PE, and 95.7% ($n = 22$) for simple DVT. The incidence of VTE in the low-, medium-, and high-risk groups according to the Caprini score was 0%, 7.3% ($n = 20$), and 11.5% ($n = 3$), respectively. The independent risk factors for postoperative VTE in stage IA NSCLC were age and D-D value on the first day after the operation. Caprini score has a certain value in the diagnosis of postoperative VTE of stage IA NSCLC.

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CONFLICT OF INTEREST

All authors declare that there are no conflicts of interest.

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