



Analysis of risk factors for venous thromboembolism in patients after thoracic surgery: A clinical study of 167 cases

Göğüs cerrahisi sonrasında venöz tromboembolinin risk faktörlerinin analizi:
167 olguluk klinik çalışma

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ABSTRACT

Background: This study aims to identify risk factors of venous thromboembolism in the patients undergoing thoracic surgery.

Methods: A total of 167 patients (107 males, 60 females; mean age 56.7±16.8 years; range 16 to 81 years) who underwent thoracic surgery between September 2015 and December 2016 were included in this study. D-dimer and C-reactive protein values were analyzed and clinical data recorded. The patients received color Doppler ultrasound and thoracic computed tomography before and after surgery. The risk factors for venous thromboembolism were analyzed.

Results: Of the patients, 57 (34.1%) developed venous thromboembolism after thoracic surgery, among whom two patients developed pulmonary embolism and another 55 developed deep vein thrombosis. Age, D-dimer, operation time, and body mass index of venous thromboembolism patients were significantly higher than non-venous thromboembolism patients. There was no significant difference in the C-reactive protein values between the two patient groups. Age, smoking history, operation time, and body mass index were found to be the risk factors of venous thromboembolism. There was a significant difference in the incidence of venous thromboembolism among different surgeries. The patients who underwent esophagectomy had the highest incidence of thrombosis.

Conclusion: Age, smoking history, operation time and body mass index are independent risk factors for venous thromboembolism. A special attention should be given to the patients undergoing esophagectomy to prevent the development of venous thromboembolism.

Keywords: Deep venous thrombosis; pulmonary embolism; risk factors; venous thromboembolism.

ÖZ

Amaç: Bu çalışmada göğüs cerrahisi yapılan hastalarda venöz tromboembolinin risk faktörleri belirlendi.

Çalışma planı: Eylül 2015 - Aralık 2016 tarihleri arasında göğüs cerrahisi yapılan toplam 167 hasta (107 erkek, 60 kadın; ort. yaş 56.7±16.8 yıl; dağılım 16-81 yıl) bu çalışmaya alındı. D-dimer ve C-reaktif protein değerleri incelendi ve klinik veriler kaydedildi. Hastalara ameliyat öncesi ve sonrası renkli Doppler ultrason ve toraks bilgisayarlı tomografi çekildi. Venöz tromboemboli risk faktörleri değerlendirildi.

Bulgular: Hastaların 57'sinde (%34.1) göğüs cerrahisi sonrasında venöz tromboemboli gelişti ve bunların ikisinde pulmoner emboli ve diğer 55'inde derin ven trombozu izlendi. Venöz tromboemboli gelişen hastalarda yaş, D-dimer, ameliyat süresi ve vücut kütle indeksi, venöz tromboemboli gelişmeyen hastalara kıyasla, anlamlı düzeyde daha yüksekti. C-reaktif protein değerleri açısından iki hasta grubu arasında anlamlı bir fark yoktu. Yaş, sigara öyküsü, ameliyat süresi ve vücut kütle indeksi venöz tromboembolinin risk faktörleri olarak bulundu. Farklı cerrahiler arasında venöz tromboemboli insidansında anlamlı bir fark görüldü. En yüksek tromboz insidansı, özofajektomi yapılan hastalarda izlendi.

Sonuç: Yaş, sigara öyküsü, ameliyat süresi ve vücut kütle indeksi venöz tromboembolinin bağımsız risk faktörleridir. Venöz tromboemboli gelişimini önlemek için özofajektomi yapılan hastalara özel ihtimam gösterilmelidir.

Anahtar sözcükler: Derin ven trombozu; pulmoner emboli; risk faktörleri; venöz tromboemboli.

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Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a fatal disease which is associated with significant morbidity and mortality. A recent study have shown that the overall incidence of VTE among 100,000 individuals is around 422 cases, and approximately 26 cases increase per 100,000 every year.^[1] Studies have demonstrated that surgical procedures, including neurosurgery, major orthopedic surgery of the leg, thoracic surgery, abdominal surgery, renal transplantation, and cardiovascular surgery are all risk factors for VTE.^[2] Therefore, prevention and treatment of VTE in patients undergoing surgery is particularly urgent.

Thoracic surgeries are mainly composed of open chest surgeries, which are associated with more postoperative complications, take longer time, and bring more surgical trauma to patients. Postoperative VTE is one of common and serious complications in patients undergoing thoracic surgery. In the autopsy cases of thoracic surgery, the incidence of VTE was found to be as high as 6.6%.^[3] The success of thoracic surgery refers to not only the operation itself, but also the effective prevention of postoperative complications, including VTE.

In the present study, we aims to identify risk factors of VTE in the patients undergoing thoracic surgery to provide theoretical data for the prevention of VTE following thoracic surgery.

PATIENTS AND METHODS

This prospective study was approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University. A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

A total of 167 patients (107 males, 60 females; mean age 56.7±16.8 years; range 16 to 81 years) who underwent thoracic surgery in the Department of Thoracic Surgery, Beijing Friendship Hospital, Capital Medical University between September 2015 and December 2016 were included in this study. Blood samples of all the patients were taken to analyze D-dimer (DD) and C-reactive protein (CRP) at the time of admission, and all the patients underwent color Doppler ultrasound (CDU) and thoracic computed tomography (CT) before operation to identify the occurrence of VTE. Patients who had VTE before surgery were excluded from the study. Those who had cardiovascular and cerebral vascular diseases, diabetes and other documented

inflammatory, hemorrhagic, and thrombotic diseases within the past six months were also excluded. Pregnant and lactating women and women using oral contraceptives were also ruled out.

All patients were instructed to wear compression stockings on the night before surgery and took off stockings until they were able to walk. Low-molecular-weight heparin (LMWH) was allowed to be administered (5,000 IU, once daily) from the first day after surgery and discontinued until hospital discharge. After surgery, on the day thoracic drainage was ended, the patients underwent repeated CDU and thoracic CT to evaluate the development of VTE. The CDU and CT examination were performed by three professional physicians from the ultrasonography department and imaging department, respectively to ensure the accuracy of the results, and all physicians had at least five-year clinical experience. Deep vein thrombosis refers to the occurrence of new blood clot or thrombus within the venous system, and PE refers to the occurrence of new blood clot in a pulmonary artery with a subsequent obstruction of blood supply to the lung parenchyma. The patients who developed either DVT or PE or both were accepted as VTE. Data including age, gender, smoking history, body mass index (BMI), operation time, and type of surgery were collected from the medical records or electronic database.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were presented in mean ± standard deviation (SD) and median (min-max) and compared using the Student's t-test, while categorical variables were presented in frequency and percentage and compared using the chi-square test. Multivariate logistic regression analysis was used to obtain the odds ratio (OR) and corresponding 95% confidence interval (CI) to analyze the risk factors. Continuous variables were modeled linearly per unit and categorical measures were modeled with the use of indicator variables for each level compared to the lowest level. A *p* value of <0.05 was considered statistically significant.

RESULTS

A total of 75 patients (44.9%) had smoking history. Among all patients, 61 (36.5%) received pulmonary lobectomy, 44 (26.3%) received esophagectomy, and pulmonary wedge resection was applied to 42 (25.1%). Fourteen patients (8.4%) underwent mediastinal-pericardial resection, while six patients

Table 1. Demographic and clinical characteristics of patients

	n	%	Mean±SD	Range
Age (year)			56.7±16.8	16-81
Gender				
Male	107	64.1		
Female	60	35.9		
Smoking status				
Smokers	75	44.9		
Non-smokers	92	55.1		
Surgery				
Pulmonary lobectomy	61	36.5		
Esophagectomy	44	26.3		
Pulmonary wedge resection	42	25.1		
Mediastinal-pericardial resection	14	8.4		
Other	6	3.6		
Drainage time (day)			5.3±3.6	3-9
Body Mass Index (kg/m ²)				
<18.5	9	5.4		
18.5-23.9	131	78.4		
24-27.9	26	15.6		
>28	1	0.6		
Preoperative diagnosis				
Lung tumors	86	51.5		
Pneumothorax	20	12.0		
Esophagus cancer	38	22.8		
Mediastinal tumors	13	7.8		
Achalasia	3	1.8		
Esophagus leiomyoma	2	1.2		
Bronchiectasis	1	0.6		
Pulmonary abscess	1	0.6		
Esophageal cyst	1	0.6		
Pericardial cyst	1	0.6		
Substernal goiter	1	0.6		

SD: Standard deviation; Body Mass Index: calculated as weight in kilograms divided by the square of height in meters (kg/m²)

(3.6%) underwent other surgeries, such as open chest exploration, and resection of the chest wall tumor. Baseline demographic and clinical characteristics of the patients are shown in Table 1.

Postoperatively, the mean drainage duration was 5.3±3.6 (range, 3 to 9) days. Among 167 patients,

57 (34.1%) had VTE (positive group) and 110 (65.9%) had no VTE (negative group) on the day thoracic drainage was discontinued. In the positive group, two patients (3.5%) developed PE and 55 patients (96.5%) developed DVT. No complications of thromboprophylaxis such as severe bleeding and

Table 2. Analysis results of patients

Groups	Positive	Negative	<i>p</i>
	Mean±SD	Mean±SD	
Age (year)	65.3±10.1	52.3±17.8	<0.001
D-Dimer (mg/L)	1.6±2.6	0.9±0.6	0.009
C-reactive protein (mg/L)	1.6±0.5	1.5±0.7	0.477
Operation time (min)	225.1±82.2	170.5±88.9	<0.001
Body Mass Index (kg/m ²)	23.3±1.8	21.3±1.9	<0.001

SD: Standard deviation; Calculated as weight in kilograms divided by the square of height in meters (kg/m²).

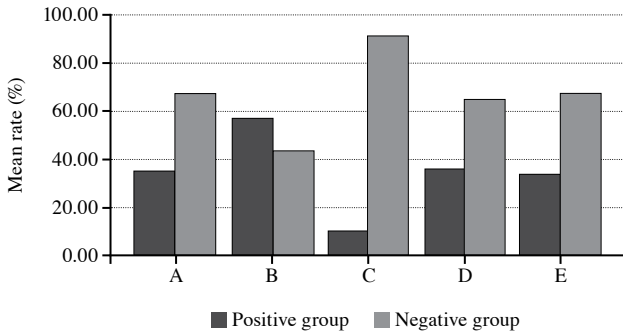


Figure 1. Rate of venous thromboembolism in different surgical groups.

A: Pulmonary lobectomy; B: Esophagectomy; C: Pulmonary wedge resection; D: Mediastinal-pericardial resection; E: Other surgeries.

hypotension were found. Age ($p<0.001$), DD ($p=0.009$), operation time ($p<0.001$), and BMI ($p<0.001$) of the positive group were higher than the negative group, indicating a significant difference between the two groups. However, there was no significant difference in the CRP values ($p=0.477$) between the two groups. The analysis results are shown in Table 2.

Among 167 patients who underwent surgery in thoracic department, 61 received pulmonary lobectomy, among whom 21 (34.4%) had VTE after surgery. A total of 44 patients received esophagectomy and, of these, 25 (56.8%) developed VTE. A total of 42 patients accepted pulmonary wedge resection, among whom four (9.5%) developed VTE. Of 14 patients who underwent mediastinal-pericardial resection, five (35.7%) had VTE after surgery. Among other six surgeries, only two patients (33.3%) had VTE after surgery (Figure 1). There was a significant difference in the incidence of VTE among different operations.

Multivariate logistic regression analysis showed that age (OR:1.065, 95% CI:1.031-1.101, $p<0.001$), smoking history (OR:1.005, 95% CI:1.001-1.010, $p=0.044$), operation time (OR:2.205, 95% CI:1.022-4.756, $p=0.016$), and BMI (OR:2.220, 95% CI:0.953-5.169, $p=0.034$) were found to be related with the incidence of VTE, suggesting that they were significant predictors of the development of VTE after thoracic surgery (Table 3).

DISCUSSION

Venous thromboembolism, including DVT and pulmonary embolism, refers to the abnormal coagulation of the blood in venous, blocking the vessels and inducing a series of clinical symptoms and complications. In the United States, VTE affects 350,000 to 600,000 individuals every year and more than 100,000 individuals die annually.^[4] Previous studies considered VTE as a rare disease in Asia.^[5,6] However, many recent studies found that the incidence of VTE was not as low as previously thought, on the contrary, incidence of VTE may be increasing in recent years.^[7] As listed at the beginning, lots of surgeries are risk factors for VTE,^[2] and the risk for thrombosis would persist over several months post-surgery;^[8] therefore, it is quite significant to do the prevention of VTE in patients postoperative.

It is widely known that VTE is predominantly a disease of older age, and studies have also demonstrated that VTE is rare in children younger than 15 years.^[9,10] In our study, age was also a risk factor for VTE, and the mean age of the positive group (65.3 ± 10.1 years) was almost 13 years older than the negative group (52.3 ± 17.8 years). We also found that none of the patients under 33 years had VTE after surgery. Therefore, our study also demonstrated that the incidence of VTE increased with age, which is consistent with previous findings.^[11,12]

Several studies showed that male patients had a higher risk than females for the development of VTE.^[13] A population-based cohort study also found that incidence of VTE was 1.3 per 1,000 person-years in men and 1.1 per 1,000 person-years in women respectively.^[14] Among 167 patients in our study, 38/107 men (35.5%) and 19/60 women (31.7%) developed VTE after surgery, which is consistent with previous findings.

Among various coagulation and inflammatory factors, more attention has been paid to DD and CRP. The former is a degradation product of cross-linked fibrin, which reflects the fibrinolytic activity and coagulation function *in vivo*. It has long been regarded as

Table 3. Results of multivariate logistic regression analysis

Factors	Ratio	SD	<i>p</i>	Odds ratio	95%CI
Age	0.063	0.017	<0.001	1.065	1.031-1.101
Operation time	0.005	0.002	0.016	1.005	1.022-4.756
Smoke	0.791	0.392	0.044	2.205	1.001-1.010
Body Mass Index	0.797	0.431	0.034	2.220	0.953-5.169

SD: Standard deviation of population mean; CI: Confidence interval.

a sensitive indicator of ruling out VTE,^[15] which means, if the DD level is negative, thromboembolic disease can be excluded. The latter is a type of acute inflammatory reaction protein, and higher levels of CRP indicate the activation of the inflammatory reaction mechanism.^[16] Evidences show that CRP levels are higher during the acute and subacute phases of VTE, and remain higher in VTE patients even months or years later.^[17,18] A study showed that patients with high values of CRP were at two-fold risk for VTE, compared to those with low values.^[19] In our study, we found that DD of positive group (1.6 ± 2.6 mg/L) was significantly higher than the negative group (0.9 ± 0.6 mg/L), while there was no significant difference in the CRP values between the two groups. However, multivariate regression analysis revealed that neither DD nor CRP were the risk factors for VTE, although this can be attributed to the small sample size.

In our study, we found that operation time of the positive group (225.1 ± 82.2 min) was significantly higher than the negative group (170.5 ± 88.9 min). Saluja and Gilling^[20] summarized the risk factors for VTE within the urological population and found the risk was further aggravated, if patients underwent an operative procedure, particularly when the time of operation was more than two hours. It is easier to understand that longer operation can cause blood flow slowly and requires more hemostatic agents in the process of anesthesia. Longer operation also brings more harm to the blood vessel wall, and injury of vessel wall disrupts the endothelial barrier. Longer operations may also prolong the time stay in bed after surgery. All these results of longer operation can thereby cause thrombus formation and increase the risk of postoperative VTE. Previous studies also have shown that obesity, assessed by BMI, is an independent risk factor for predicting VTE.^[21] It has been a preferable anthropometric measure of obesity for decades.^[22] The results of our study showed that BMI of positive group (23.3 ± 1.8 kg/m²) was significantly higher than the negative group (21.3 ± 1.9 kg/m²), and regression analysis also indicated that BMI was a risk factor of VTE.

Our study also indicated that significant difference of the incidence of VTE was found among these different operation groups, and patients received esophagectomy had the highest incidence of VTE after surgery. This may be mainly due to the longer operation time of esophagectomy, which may be different due to surgeon's surgical level and the complexity of the operation. Pulmonary wedge resection group had the lowest incidence of VTE, the reason may be that many

patients were young and the operation time was short. Therefore, our study suggests that more attention should be given to the patients undergoing esophagectomy to prevent VTE among different thoracic surgeries.

The latest guideline of the American College of Chest Physicians (ACCP) recommends that routine thromboprophylaxis should be implemented in thoracic surgery.^[23] In our study, all patients received LMWH from the first day after surgery to the day of discharge, and no complications such as bleeding were found among all these patients. However, previous studies revealed that in-patient VTE prophylaxis did not reduce the risk of post-discharge VTE,^[24] and a recently meta-analysis revealed that benefit of thromboprophylaxis was unclear;^[25] therefore, further studies should be carried out to evaluate the efficacy of thromboprophylaxis.

Nonetheless, there are some limitations to this study. First, unlike studies based on several medical centers which had large samples, our study was based on a single center and had a relatively small size. Therefore, the results may have little representation to some extent and may not be applied to other hospitals. Second, the diagnosis of VTE in our study mainly was based on the use of CDU and thoracic CT scan. Although these examinations were performed by three professional physicians, subjective error may be inevitable. In order to avoid missed diagnosis, non-VTE patients may be diagnosed as VTE patients, which may lead to the high incidence of VTE in our study. Another issue should be noted is that to prevent excessive bleeding, hemostatic drugs were used on the day of surgery, which may also affect the incidence of thrombosis in our study.

In conclusion, our study results suggest that age, smoking history, operation time, and Body Mass Index are independent risk factors for the occurrence of venous thromboembolism. Among all the thoracic surgeries, a special attention should be given to the patients undergoing esophagectomy to prevent the development of venous thromboembolism. To prevent venous thromboembolism, thromboprophylaxis should be implemented in the thoracic department and further well-designed, multi-center, large-scale studies should be carried out in the future.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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