Vascular Specialist International
pISSN 2288-7970 • eISSN 2288-7989
(2021) 37:46

Original Article

Risk Factors of Unfavorable Outcomes, Major Bleeding, and All-Cause Mortality in Patients with Venous Thromboembolism

Han Young Lee[1], Tae Hoon Yeo[1], Tae Kyung Heo[1], Young Gyu Cho[1], Dong Hui Cho[1], and Kyung Bok Lee[2]

[1]Department of Surgery, Seoul Medical Center, Seoul, [2]Department of Surgery, Dongguk University Ilsan Hospital, Goyang, Korea

Purpose: This study aimed to analyze the clinical outcomes of venous thromboembolism (VTE) patients and identify the risk factors for VTE-related unfavorable outcomes, major bleeding, and 30-day all-cause mortality.

Materials and Methods: From January 2016 to December 2020, 198 patients with confirmed VTE were enrolled. Potential risk factors for unfavorable outcomes, major bleeding, and all-cause mortality were analyzed.

Results: VTE-related unfavorable outcomes developed in 13.1%, while 30-day all-cause mortality was 8.6%. In the multivariate analysis, a pulse ≥110/min and respiratory rate ≥30/min were statistically significant predictors for VTE-related unfavorable outcomes. Diabetes was a significant risk factor for major bleeding. In addition, a history of malignancy, no anticoagulation treatment, and need for mechanical ventilation were significant predictors of all-cause mortality.

Conclusion: VTE-related mortality and morbidity rates remained high. In cases of tachycardia and tachypnea, early aggressive treatment is needed to prevent unfavorable outcomes. Patients with risk factors should be closely monitored.

Key Words: Venous thromboembolism, Risk factors, Mortality, Anticoagulants

Received June 14, 2021
Revised August 17, 2021
Accepted November 16, 2021
Published on December 31, 2021

Corresponding author: Kyung Bok Lee
Department of Surgery, Dongguk University Ilsan Hospital, 27 Dongguk-ro, Ilsandong-gu, Goyang 10326, Korea
Tel: 82-2-961-7027
E-mail: md.kblee@outlook.com
https://orcid.org/0000-0003-1111-118X

Cite this article; Vasc Specialist Int 2021. https://doi.org/10.5758/vsi.210041

INTRODUCTION

Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), is generally considered a common and similar disease entity that expresses different clinical features [1,2]. VTE is a major cause of morbidity and mortality in most Western countries [3]. VTE is the leading cause of preventable early death with appropriate treatment. Hip fracture, major general surgery, major trauma, malignancy/chemotherapy, bed rest >3 days, and recent pregnancy (within 3 months of delivery) are well-known risk factors for the occurrence of VTE [4]. The incidence of VTE is lower in Asian countries than in Western countries. Several population-based studies have shown that, although the overall incidence of PE is reduced, the average mortality rate remains high at 14% to 30% [5].

VTE can be confirmed using computed tomography (CT) for PE and a combination of compression ultrasound (CUS) and CT for DVT. CUS is the most common imaging modality for DVT. For the diagnosis of proximal DVT, CUS shows a sensitivity of 90.1% and specificity of 97.3% [6]; however, recent advances in imaging technologies have replaced CUS with CT for diagnosing DVT.

The introduction of anticoagulant therapy reduces VTE-related mortality and morbidity [7]. The recent American College of Chest Physician guidelines recommend at least

three months of a new oral anticoagulant (NOAC; such as dabigatran, rivaroxaban, apixaban, and edoxaban) alone over warfarin for acute VTE [8]. The advent of acute-phase anticoagulant treatment strategies might improve the clinical outcomes of patients with VTE. The absence of anticoagulation therapy is associated with a 3.2-fold increase in mortality [9].

This study aimed to analyze the clinical outcomes of VTE patients and identify the predictors of VTE-related unfavorable outcomes, such as major bleeding and 30-day all-cause mortality.

MATERIALS AND METHODS

From January 2016 to December 2020, 198 patients with confirmed VTE were enrolled. DVT was diagnosed using CUS or CT venography (CTV). PE was confirmed using CT pulmonary angiography (CTPA). All CTV and CTPA results were elucidated by two board-certified radiologists specializing in vascular imaging.

DVT was classified into proximal or distal. Proximal DVT was defined as a thrombus affecting the popliteal or proximal vein (Fig. 1). Each PE was diagnosed using CTPA (Fig. 2). Additionally, the simplified pulmonary embolism severity index (sPESI) was calculated. A high sPESI was defined as age >80 years; systolic blood pressure <100 mmHg; heart rate >110 bpm; O_2 saturation <90%; or current diagnosis of cancer, heart failure, or chronic obstructive pulmonary disease (COPD) [10]. Anticoagulation regimens included unfractionatedor low molecular weight heparin followed by oral vitamin K antagonist or NOACs for at least three months. An international normalized ratio of 1.5 to 2.5 was considered an appropriate therapeutic range.

In this study, patients with confirmed VTE were classified into isolated DVT or PE (PE with or without DVT) groups. Their clinical characteristics and risk factors (age >70 years; previous VTE; immobilization ≥3 days; history of trauma or surgery ≤4 weeks prior; history of malignancy and/or chemotherapy, hypertension, diabetes, coronary artery disease, heart failure, chronic kidney disease, cere-

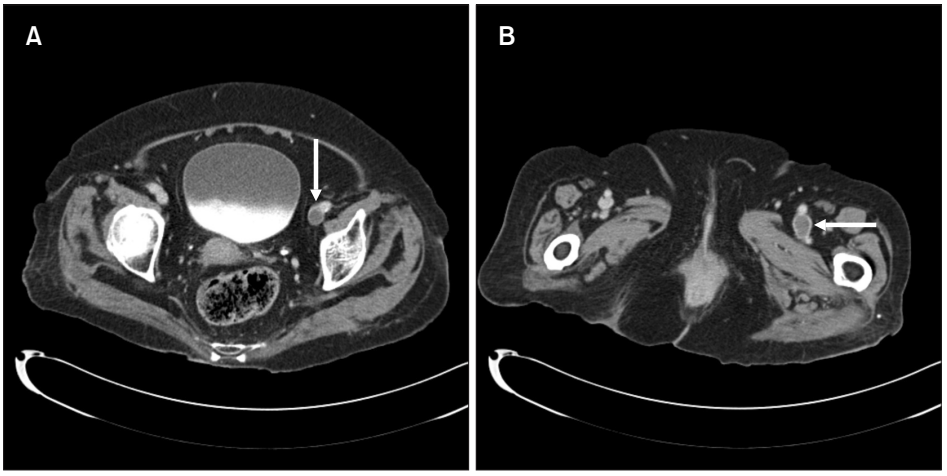

Fig. 1. Computed tomography angiograms of proximal deep vein thrombosis (DVT). (A) The arrow indicates DVT in the left external iliac vein. (B) The arrow indicates DVT in the left common femoral vein.

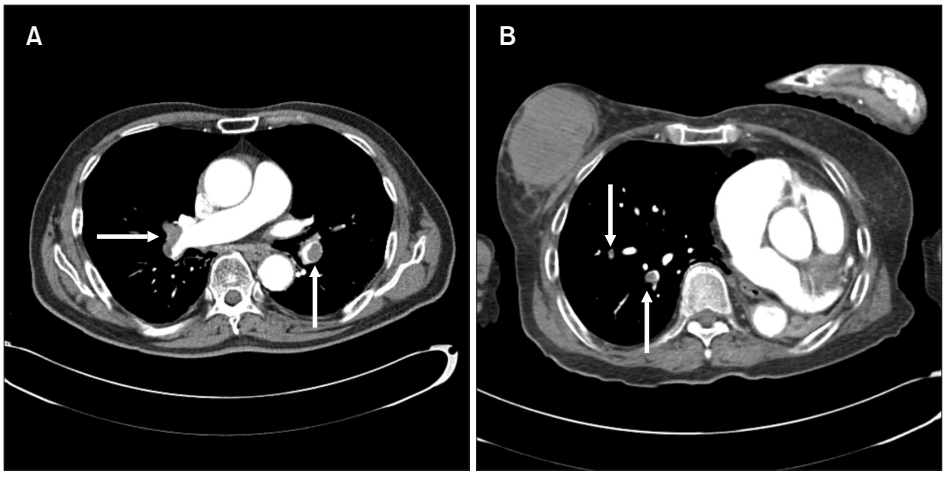

Fig. 2. Computed tomography angiograms of patients with pulmonary embolism (PE). (A) Bilateral PEs in the lobar arteries (arrows). (B) PE in the right segmental pulmonary arteries (arrows).

brovascular accident, dementia, or COPD) for unfavorable outcomes and early all-cause mortality were evaluated.

A recent event was defined as any event that occurred within one month after a VTE diagnosis. VTE-related clinical outcomes were divided into unfavorable outcomes, major bleeding, and all-cause mortality. VTE-related unfavorable outcomes were defined when at least one of the following criteria was met: 1) hypotension (SBP <100 mmHg) or shock; 2) need for mechanical ventilation; 3) need for catecholamines to maintain organ perfusion; 4) need for cardiopulmonary resuscitation; and 5) all-cause death. Major bleeding was defined as life-threatening bleeding requiring transfusion of at least two units of packed red blood cells associated with a decrease in hemoglobin level >2 g/dL or the presence of retroperitoneal, intracranial, or intraocular bleeding. Massive PE was defined as PE associated with systemic hypotension (systolic blood pressure <90 mmHg), PE requiring cardiopulmonary resuscitation, or the need for catecholamines.

Clinical outcomes such as unfavorable outcome, major bleeding, and 30-day all-cause mortality for patients with VTE were analyzed, and the clinical characteristics were compared between the DVT and PE groups using Fisher's exact test and the Chi-squared test. We also performed a univariate analysis of troponin I using enzyme immunoassay and d-dimer using enzyme-linked immunosorbent assay as risk factors for the development of unfavorable outcomes, major bleeding, and all-cause mortality.

Specified risk factors for unfavorable outcomes, major bleeding, and all-cause mortality within one month of diagnosis were analyzed using univariate and multiple logistic regression analyses. Candidate predictors (P<0.25 after univariate analysis) and several variables possibly associated with VTE outcome were included in each multivariate regression analysis. All P-values were two-tailed. Statistical significance was considered at P<0.05. All statistical analyses were performed using SPSS Statistics for Windows version 27 (IBM, Armonk, NY, USA).

Our study was approved by the Institutional Review Board of Seoul Medical Center (IRB no. 2021-05-001-002).

RESULTS

1) Clinical characteristics and outcomes

A total of 198 patients with VTE were enrolled, including 62 (31.3%) patients with isolated DVT, 100 (50.5%) with both DVT and PE, and 36 (18.2%) with PE alone. In addition, 49 (24.7%) had calf vein thrombosis and 113 (57.1%) had proximal DVT. The mean age was 71.6±15.06 years and the mean body mass index was 23.2±4.69. VTE-related unfavorable outcomes occurred in 26 (13.1%) patients, with a 30-day all-cause mortality of 17 (8.6%) patients. Of 62 patients with isolated DVT, 7 (11.3%) had unfavorable outcomes and 5 (8.1%) had all-cause mortality. Among 100 patients with DVT and PE, 13 (13.0%) had unfavorable outcomes and 8 (8.0%) had all-cause mortality. Of 36 patients with PE alone, 6 (16.7%) had unfavorable outcomes and 4

Table 1. Demographic features

Demographic feature	All patient (n=198)	Isolated DVT (n=62, 31.3%)	PE (n=136, 68.7%)	P-value[a]
Age (y)	71.58±15.06	-	-	-
≤50	19 (9.6)	6 (9.7)	13 (9.6)	-
51-70	55 (27.8)	20 (32.3)	35 (25.7)	-
≥71	124 (62.6)	36 (58.1)	88 (64.7)	0.370
Body mass index	23.22±4.69	-	-	-
>25	64 (32.3)	20 (32.3)	44 (32.4)	0.989
Sex, male	78 (39.4)	25 (40.3)	53 (39.0)	-
Vital sign				
Pulse rate ≥110/min	27 (13.6)	3 (4.8)	24 (17.6)	0.014
Systolic blood pressure <90 mmHg	20 (10.1)	6 (9.7)	14 (10.3)	0.894
Respiratory rate ≥30/min	16 (8.1)	3 (4.8)	13 (9.6)	0.400
Body temperature <36°C	3 (1.5)	0 (0.0)	3 (2.2)	0.553
Risk factor for VTE				
History of VTE	16 (8.1)	5 (8.1)	11 (8.1)	0.995
Immobilization ≥3 days	106 (53.5)	40 (64.5)	66 (48.5)	0.036
Recent surgery <4 weeks	53 (26.8)	25 (40.3)	28 (20.6)	0.004
Active malignancy and/or chemotherapy	46 (23.2)	10 (16.1)	36 (26.5)	0.110

Table 1. Continued

Demographic feature	All patient (n=198)	Isolated DVT (n=62, 31.3%)	PE (n=136, 68.7%)	P-value[a]
Comorbidities				
Hypertension	114 (57.6)	36 (58.1)	78 (57.4)	0.925
Diabetes mellitus	57 (28.8)	17 (27.4)	40 (29.4)	0.774
Coronary artery disease	16 (8.1)	3 (4.8)	13 (9.6)	0.400
Chronic kidney disease	9 (4.5)	3 (4.8)	6 (4.4)	>0.999
Chronic heart failure	11 (5.6)	1 (1.6)	10 (7.4)	0.178
Smoking	29 (14.6)	13 (21.0)	16 (11.8)	0.089
Pneumonia	38 (19.2)	6 (9.7)	32 (23.5)	-
Chronic obstructive pulmonary disease	18 (9.1)	1 (1.6)	17 (12.5)	0.014
All pulmonary disease	56 (28.3)	8 (12.9)	48 (35.3)	0.001
Cerebrovascular accident	41 (20.7)	12 (19.4)	29 (21.3)	-
Dementia	29 (14.6)	9 (14.5)	20 (14.7)	-
Location of PE				
Main & lobar arteries	2 (1.0)	0 (0.0)	2 (1.5)	-
Segmental & subsegmental arteries	45 (22.7)	0 (0.0)	45 (33.1)	-
Massive PE	24 (12.1)	7 (11.3)	17 (12.5)	0.809
Location of DVT				
Distal	49 (24.7)	16 (25.8)	33 (24.3)	-
Proximal	113 (57.1)	46 (74.2)	67 (49.3)	-
High sPESI	124 (62.6)	29 (46.8)	95 (69.9)	0.002
Inferior vena cava filter insertion	40 (20.2)	15 (24.2)	25 (18.4)	0.345
Anticoagulation treatment	185 (93.4)	55 (88.7)	130 (95.6)	0.070
Novel oral anticoagulants	122 (61.6)	32 (51.6)	90 (66.2)	0.051
Need for mechanical ventilation	8 (4.0)	2 (3.2)	6 (4.4)	>0.999
Need for inotropics	14 (7.1)	4 (6.5)	10 (7.4)	>0.999
Need for thrombolysis or thrombectomy	1 (0.5)	0 (0.0)	1 (0.7)	-
Cardiopulmonary resuscitation	3 (1.5)	0 (0.0)	3 (2.2)	0.553
Unfavorable outcome	26 (13.1)	7 (11.3)	19 (14.0)	0.605
Major bleeding	6 (3.0)	2 (3.2)	4 (2.9)	>0.999
PE-related death	3 (1.5)	0 (0.0)	3 (2.2)	0.553
All-cause mortality	17 (8.6)	5 (8.1)	12 (8.8)	0.860
	Total (n=133)	DVT only (n=31, 23.3%)	PE±DVT (n=102, 76.7%)	
Arterial saturation <90%	30 (22.6)	7 (22.6)	23 (22.5)	-
	Total (n=158)	DVT only (n=41, 25.9%)	PE±DVT (n=117, 74.1%)	
Elevated D-dimer	151 (95.6)	38 (92.7)	113 (96.6)	-
	Total (n=129)	DVT only (n=31, 24.0%)	PE±DVT (n=98, 76.0%)	
Elevated troponin I	36 (27.9)	7 (22.6)	29 (29.6)	-

Values are presented as mean±standard deviation or number (%).
DVT, deep venous thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; sPESI, simplified pulmonary embolism severity score; -, not available.
[a]Chi-squared test or Fisher exact test, logistic regression model.

(11.1%) had all-cause mortality.

Several clinical characteristics showed statistically significant differences between the DVT and PE groups (Table 1). The prevalence of those with immobilization ≥3 days, recent surgery ≤4 weeks, the presence of COPD, pulse ≥110/min, and a high sPESI was significantly higher in the PE group. Unfavorable outcomes (11.3% in the DVT group vs. 14.0% in the PE group, P=0.605) and all-cause mortality (8.1% vs. 8.8%, P=0.860) were lower in the DVT group than in the PE group, but the difference was not significant (Table

Table 2. Characteristics of patients with unfavorable outcomes (n=26)

Risk factor	Unfavorable outcome (n=26, 13.1%)	Univariate	Multivariate	
		P-value[a]	P-value[a]	95% CI
Age (y)	74.5±13.2	0.449	-	-
≥71	19 (73.1)	-	0.305	0.566-6.169
Body mass index	22.55±7.94	-	-	-
>25	5 (19.2)	0.126	0.890	0.255-3.277
Symptom of DVT and PE	20 (76.9)	0.227	0.415	0.501-5.343
Subjective leg symptom (edema)	10 (38.5)	0.650	-	-
Subjective chest symptom	11 (42.3)	0.338	-	-
Risk factor for VTE				
History of VTE	2 (7.7)	>0.999	-	-
Immobilization ≥3 d	19 (73.1)	0.032	0.092	0.849-8.644
Recent surgery <4 wk	7 (26.9)	0.985	-	-
Active malignancy and/or chemotherapy	8 (30.8)	0.329	0.457	0.464-5.518
Comorbidities				
Hypertension	15 (57.7)	0.990	-	-
Diabetes mellitus	11 (42.3)	0.102	0.637	0.443-3.777
Coronary artery disease	3 (11.5)	0.447	0.228	0.544-12.774
Chronic kidney disease	2 (7.7)	0.336	-	-
Chronic heart failure	2 (7.7)	0.641	-	-
Smoking	5 (19.2)	0.478	-	-
Pneumonia	6 (23.1)	0.589	-	-
Chronic obstructive pulmonary disease	4 (15.4)	0.266	0.456	0.082-3.072
All pulmonary disease	11 (42.3)	0.102	-	-
Cerebrovascular accident	4 (15.4)	0.608	-	-
Dementia	6 (23.1)	0.192	0.385	0.118-2.285
Vital sign				
Pulse rate ≥110/min	13 (50.0)	0.001	<0.001	3.418-44.744
Systolic blood pressure <90 mmHg	20 (76.9)	0.001	-	-
Respiratory rate ≥30/min	8 (30.8)	0.001	0.013	1.429-21.392
Body temperature <36°C	2 (7.7)	0.046	0.512	0.108-86.780
Types of VTE				
Isolated DVT	7 (26.9)	0.605	-	-
PE	19 (73.1)	0.605	-	-
Inferior vena cava filter insertion	6 (23.1)	0.695	-	-
Anticoagulation treatment	23 (88.8)	0.385	0.075	0.050-1.155
	(n=23, 12.4%)			
Novel oral anticoagulants (total n=185)	14 (60.9)	0.583	-	-
	(n=24, 18.0%)			
Arterial saturation <90% (total n=133)	12 (50.0)	0.001	-	-
	(n=22, 13.9%)			
Elevated D-dimer (total n=158)	22 (100.0)	0.594	-	-
	(n=24, 18.6%)			
Elevated troponin I (total n=129)	11 (45.8)	0.030	-	-

Values are presented as mean±standard deviation or number (%).
CI, confidence interval; DVT, deep venous thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; -, not available.
[a]Chi-squared test or Fisher exact test, logistic regression model.

1). Among 46 patients with malignancy±chemotherapy, lung cancer was the most common malignancy (n=11 [23.9%]), and the prevalence of PE was higher than that of DVT (78.3% vs. 21.7%). However, the difference between the two groups was not statistically significant (P=0.110).

2) Predictors for unfavorable outcome

VTE-related unfavorable outcomes were observed in 26 (13.1%) patients. Among the 16 patients with a respiratory rate ≥30/min, 8 (50.0%) showed an unfavorable outcome (Table 2). Univariate analysis of risk factors revealed that immobilization ≥3 days (P=0.032), pulse ≥110/min (P=0.001), respiratory rate ≥30/min (P= 0.001), and temperature <36°C (P=0.046) were statistically significant risk factors (Table 2). In addition, the troponin I test was performed in 129 patients, and an elevated level was identified as a statistically significant factor for VTE-related unfavorable outcomes in the univariate analysis (P=0.030). We obtained arterial blood gas analysis data for 133 of 198 patients with VTE. An arterial saturation <90% was statistically significant in the univariate analysis (P=0.001). However, the presence of coronary artery disease and congestive heart failure, VTE type, VTE location, anticoagulation treatment, and elevated d-dimer levels were not significantly associated. The multivariate analysis revealed that pulse ≥110/min (odds ratio [OR], 12.4; 95% confidence interval [CI] [6], 3.4-44.7; P=0.001) and respiratory rate ≥30/min (OR, 5.5; 95% CI, 1.4-21.4; P=0.013) were statistically significant predictors of VTE-related unfavorable outcomes (Table 2).

3) Risk factors for major bleeding

Major bleeding occurred in 6 (3.0%) patients (Table 3). The major bleeding rate in patients with a history of recent surgery ≤4 weeks was higher than that in patients without a history (4/53 [7.5%] vs. 2/145 [1.4%]). With regard to recent surgery, hip surgery was the most common (n=14 [26.4%]), followed by spine surgery (n=9 [17.0%]). Major bleeding occurred in the brain, hip joint, and stomach in each of those two cases. Risk factors for major bleeding were subjected to univariate analysis, and a history of recent surgery was statistically significant (P=0.045). However, in the multivariate analysis, diabetes was statistically significant (P=0.043).

4) Predictors for all-cause mortality

All-cause mortality was observed in 17 patients (8.6%). A history of malignancy±chemotherapy was present in 46 of 198 patients. Lung cancer was the most common (n=11 [23.9%]), followed by colon cancer (n=8 [17.4%]). Stage IV cancer was the most common (n=14 [30.4%]). Among the 24 patients with massive PE, all-cause mortality occurred in 10 (41.7%). Among the 124 patients with high sPESI, all-cause mortality occurred in 15 (12.1%). Anticoagulation treatment was administered to 185 (93.4%). All-cause mortality occurred in 4 (30.8%) patients not treated with anticoagulants and in 13 (7.0%) patients treated with anticoagulants. In addition, 6 of 8 (75.0%) patients who needed mechanical ventilation died within 30 days of their hospital stay. The univariate analysis revealed no NOACs, arterial

Table 3. Characteristics of patients with major bleeding (n=6)

Risk factor	Major bleeding (n=6, 3.0%)	Univariate P-value[a]	Multivariate P-value[a]	95% CI
Age (y)	71.83±16.52	0.364	-	-
≤50	0 (0.0)	-	-	-
51-70	3 (50.0)	-	-	-
≥71	3 (50.0)	-	-	-
Body mass index	21.87±1.93	-	-	-
>25	0 (0.0) (n=5, 2.5%)	0.180	0.996	-
Symptom of DVT and PE (total n=197)	3 (60.0)	>0.999	-	-
Subjective leg symptom (edema)	1 (20.0)	0.661	-	-
Subjective chest symptom	2 (40.0)	>0.999	-	-
Risk factor for VTE				
History of VTE	0 (0.0)	>0.999	-	-
Immobilization ≥3 d	5 (83.3)	0.219	0.642	0.132-26.737
Recent surgery <4 wk	4 (66.7)	0.045	0.254	0.407-29.980
Active malignancy and/or chemotherapy	1 (16.7)	>0.999	-	-

Table 3. Continued

Risk factor	Major bleeding (n=6, 3.0%)	Univariate P-value[a]	Multivariate P-value[a]	95% CI
Comorbidities				
Hypertension	2 (33.3)	0.404	-	-
Diabetes mellitus	4 (66.7)	0.058	0.043	1.074-68.319
Coronary artery disease	1 (16.7)	0.401	-	-
Chronic kidney disease	0 (0.0)	>0.999	-	-
Chronic heart failure	0 (00)	>0.999	-	-
Smoking	1 (16.7)	>0.999	-	-
Pneumonia	2 (33.3)	0.325	-	-
Chronic obstructive pulmonary disease	0 (0.0)	>0.999	-	-
All pulmonary disease	2 (33.3)	>0.999	-	-
Cerebrovascular accident	2 (33.3)	0.606	-	-
Dementia	1 (16.7)	>0.999	-	-
Vital sign				
Pulse rate ≥110/min	1 (16.7)	0.590	-	-
Systolic blood pressure <90 mmHg	1 (16.7)	0.477	-	-
Respiratory rate ≥30/min	2 (33.3)	0.076	0.113	0.589-147.536
Body temperature <36°C	0 (0.0)	>0.999	-	-
Types of VTE				
Isolated DVT	2 (33.3)	>0.999	-	-
PE	4 (66.7)	>0.999	-	-
Inferior vena cava filter insertion	3 (50.0)	0.098	0.089	0.702-140.721
Anticoagulation treatment	5 (83.3)	0.338	0.379	0.017-4.677
	(n=5, 2.7%)			
Novel oral anticoagulants (total n=185)	3 (60.0)	>0.999	-	-
	(n=6, 4.5%)			
Arterial saturation <90% (total n=133)	2 (33.3)	0.617	-	-
	(n=4, 2.5%)			
Elevated D-dimer (total n=158)	4 (100.0)	>0.999	-	-
	(n=4, 3.1%)			
Elevated troponin I (total n=129)	0 (0.0)	0.576	-	-

Values are presented as mean±standard deviation or number (%).
CI, confidence interval; DVT, deep venous thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; -, not available.
[a]Chi-squared test or Fisher exact test, logistic regression model.

saturation <90%, history of malignancy±chemotherapy, pulse ≥110/min, systolic blood pressure <90 mmHg, respiratory rate ≥30/min, massive PE, high sPESI, anticoagulation treatment, need for mechanical ventilation, need for inotropics, and cardiopulmonary resuscitation were risk factors for all-cause mortality (Table 4). Multivariate regression analysis showed that a history of malignancy±chemotherapy (OR, 7.38; 95% CI, 1.219-44.681; P=0.030), anticoagulation treatment (OR, 0.061; 95% CI, 0.006-0.590; P=0.016), and need for mechanical ventilation (OR, 235.220; 95% CI, 4.954-11168.024; P=0.006) were statistically significant predictors of all-cause mortality (Table 4).

DISCUSSION

VTE, including DVT and PE, is common in hospitalized patients. DVT and PE have the same disease processes but different clinical manifestations. However, few studies have reported the overall clinical outcomes of VTE. Despite recent advances in medicine, the 30-day all-cause mortality of VTE remains high around 8% to 11% [9,11]. Our study findings also indicated that the 30-day all-cause mortality rate was relatively high (8.6%). Tagalakis et al. [11] reported that the 30-day mortality rate after VTE was 10.6%. The all-cause mortality rates of DVT and PE were similar (8.1%

vs. 8.8%).

Our multivariate analysis showed that a high pulse and respiratory rate were statistically significant predictors of unfavorable outcomes. As expected, tachycardia and tachypnea were early signs of shock and cardiopulmonary resuscitation. This should be interpreted as physicians employing aggressive intervention for tachycardia and tachypnea in VTE patients to prevent unfavorable outcomes.

In several randomized controlled trials, the incidence of major bleeding at 3 to 6 months is as high as 4% [12,13]. In the present study, 30-day major bleeding occurred in 6 of 198 (3.0%) of the enrolled patients, a rate slightly lower than that reported in previous studies. Of the 185 patients who underwent anticoagulation treatment, 5 (2.7%) had major bleeding. Our multivariate analysis showed that diabetes mellitus was the only predictor of VTE-related major bleeding. The present study found that major bleeding was not associated with all-cause mortality.

Several studies have reported that increased age is associated with mortality [14,15]. In our study, 14 of 124 (11.3%) patients older than 70 years and 3 of 74 (4.1%) patients younger than 70 years died; the difference was not statistically significant. Those with a systolic blood pressure <90 mmHg at the initial event showed a higher all-cause mortality rate (30.0% vs. 6.2%). In addition, massive PE (41.7%), high sPESI (12.1%), and a respiratory rate >30/min (30.0%)

Table 4. Demographics of all-cause mortality (n=17)

Risk factor	All-cause mortality (n=17, 8.6%)	Univariate P-value[a]	Multivariate P-value[a]	95% CI
Age (y)	76.24±14.83	0.24	-	-
≤50	1 (5.9)	-	-	-
51-70	2 (11.8)	-	-	-
≥71	14 (82.4)	-	0.242	0.376-48.124
Body mass index	22.36±5.19	-	-	-
>25	3 (17.6)	0.277	-	-
	(n=16, 8.1%)			
Symptom of DVT and PE	11 (68.8)	0.842	-	-
Subjective leg symptom (edema)	7 (43.8)	0.418	-	-
Subjective chest symptom	5 (31.3)	0.808	-	-
Risk factor for VTE				
History of VTE	2 (11.8)	0.633	-	-
Immobilization ≥3 d	10 (58.8)	0.648	-	-
Recent surgery <4 wk	3 (17.6)	0.568	-	-
Active malignancy and/or chemotherapy	8 (47.1)	0.015	0.030	1.219-44.681
Comorbidities				
Hypertension	12 (70.6)	0.256	-	-
Diabetes mellitus	5 (29.4)	0.953	-	-
Coronary artery disease	3 (17.6)	0.146	0.070	0.847-48.882
Chronic kidney disease	1 (5.9)	0.562	-	-
Chronic heart failure	3 (17.6)	0.057	0.299	0.321-40.396
Smoking	4 (23.5)	0.284	-	-
Pneumonia	4 (23.5)	0.747	-	-
Chronic obstructive pulmonary disease	3 (17.6)	0.190	>0.999	0.084-11.891
All pulmonary disease	6 (35.3)	0.535	-	-
Cerebrovascular accident	1 (5.9)	0.206	0.071	0.003-1.272
Dementia	4 (23.5)	0.284	-	-
Vital sign				
Pulse rate ≥110/min	7 (41.2)	0.001	0.484	0.180-37.384
Systolic blood pressure <90 mmHg	6 (35.3)	0.001	-	-
Respiratory rate ≥30/min	5 (29.4)	0.001	0.213	0.466-30.763
Body temperature <36°C	1 (5.9)	0.237	0.783	0.000-8562.725

Table 4. Continued

Risk factor	All-cause mortality (n=17, 8.6%)	Univariate P-value[a]	Multivariate P-value[a]	95% CI
Types of VTE				
Isolated DVT	5 (29.4)	0.860	-	-
PE	12 (70.6)	0.860	-	-
Massive PE	10 (58.8)	0.001	0.795	0.047-54.305
High sPESI	15 (88.2)	0.033	-	-
Inferior vena cava filter insertion	3 (17.6)	>0.999	-	-
Anticoagulation treatment	13 (76.5)	0.017	0.016	0.006-0.590
Novel oral anticoagulants	4 (23.5)	0.583	-	-
Need for mechanical ventilation	6 (35.3)	0.001	0.006	4.954-11168.024
Need for inotropics	8 (47.1)	0.001	0.754	0.061-47.367
Need for thrombolysis or thrombectomy	0 (0.0)	>0.999	-	-
Cardiopulmonary resuscitation	2 (11.8)	0.020	0.291	0.098-2310.987
Major bleeding	1 (5.9)	0.421	-	-
Arterial saturation <90%	9 (60.0)	0.001	-	-
Elevated D-dimer	15 (100.0)	>0.999	-	-
Elevated troponin I	7 (50.0)	0.051	-	-

Values are presented as mean±standard deviation or number (%).
CI, confidence interval; DVT, deep venous thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; sPESI, simplified pulmonary embolism severity score; -, not available.
[a]Chi-squared test or Fisher exact test, logistic regression model.

had higher all-cause mortality rates. Regarding the anticoagulant treatment strategies, the NOAC group showed a lower mortality rate than the other anticoagulant groups (3.3% vs. 14.3%). The better results in the NOAC versus vitamin K antagonist group are thought to be attributed to the convenience of use, minor drug and food interactions, consistent pharmacokinetics and pharmacodynamics, and good compliance [16]. The multivariate regression analysis showed that a history of malignancy±chemotherapy, anticoagulation treatment, and need for mechanical ventilation were statistically significant predictors of all-cause mortality. This group of patients should be monitored closely, and aggressive interventions are needed to prevent mortality.

CONCLUSION

VTE-related mortality and morbidity rates remained high (8.1%-8.8%). In cases of tachycardia and tachypnea, early aggressive treatment is needed to prevent unfavorable outcomes. Patients with a history of malignancy, no anticoagulation use, and need for mechanical ventilation should be monitored closely to prevent mortality.

FUNDING

None.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

ORCID

Han Young Lee
https://orcid.org/0000-0002-6509-4154
Tae Hoon Yeo
https://orcid.org/0000-0002-6705-3540
Tae Kyung Heo
https://orcid.org/0000-0001-8275-2377
Young Gyu Cho
https://orcid.org/0000-0001-9665-0945
Dong Hui Cho
https://orcid.org/0000-0003-4515-521X
Kyung Bok Lee
https://orcid.org/0000-0003-1111-118X

AUTHOR CONTRIBUTIONS

Conception and design: HYL, KBL. Analysis and interpretation: HYL, KBL. Data Collection: THY, TKH. Writing the article: HYL, KBL. Critical revision of the article: YGC, DHC. Final approval of the article: all authors. Statistical analysis: KBL. Obtained funding: None. Overall responsibility: KBL

REFERENCES

1) Schulman S, Ageno W, Konstantinides SV. Venous thromboembolism: past, present and future. Thromb Haemost 2017;117:1219-1229.
2) Tritschler T, Kraaijpoel N, Le Gal G, Wells PS. Venous thromboembolism: advances in diagnosis and treatment. JAMA 2018;320:1583-1594.
3) Arcelus JI, Caprini JA, Monreal M, Suárez C, González-Fajardo J. The management and outcome of acute venous thromboembolism: a prospective registry including 4011 patients. J Vasc Surg 2003;38:916-922.
4) Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. Circulation 2003;107(23 Suppl 1):I9-I16.
5) Nakamura M, Fujioka H, Yamada N, Sakuma M, Okada O, Nakanishi N, et al. Clinical characteristics of acute pulmonary thromboembolism in Japan: results of a multicenter registry in the Japanese Society of Pulmonary Embolism Research. Clin Cardiol 2001;24:132-138.
6) Bhatt M, Braun C, Patel P, Patel P, Begum H, Wiercioch W, et al. Diagnosis of deep vein thrombosis of the lower extremity: a systematic review and meta-analysis of test accuracy. Blood Adv 2020;4:1250-1264.
7) Hyers TM, Agnelli G, Hull RD, Morris TA, Samama M, Tapson V, et al. Antithrombotic therapy for venous thromboembolic disease. Chest 2001;119(1 Suppl):176S-193S.
8) Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016;149:315-352.
9) Nakamura M, Miyata T, Ozeki Y, Takayama M, Komori K, Yamada N, et al. Current venous thromboembolism management and outcomes in Japan. Circ J 2014;78:708-717.
10) Spirk D, Husmann M, Hayoz D, Baldi T, Frauchiger B, Engelberger R, et al. Predictors of in-hospital mortality in elderly patients with acute venous thrombo-embolism: the SWIss Venous ThromboEmbolism Registry (SWIVTER). Eur Heart J 2012;33:921-926.
11) Tagalakis V, Patenaude V, Kahn SR, Suissa S. Incidence of and mortality from venous thromboembolism in a real-world population: the Q-VTE Study Cohort. Am J Med 2013;126:832.e13-832.e21.
12) Fiessinger JN, Huisman MV, Davidson BL, Bounameaux H, Francis CW, Eriksson H, et al. Ximelagatran vs low-molecular-weight heparin and warfarin for the treatment of deep vein thrombosis: a randomized trial. JAMA 2005;293:681-689.
13) Büller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, et al. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. Ann Intern Med 2004;140:867-873.
14) Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. Arch Intern Med 1999;159:445-453.
15) Andresen MS, Sandven I, Brunborg C, Njaastad AM, Strekerud F, Abdelnoor M, et al. Mortality and recurrence after treatment of VTE: long term follow-up of patients with good life-expectancy. Thromb Res 2011;127:540-546.
16) Mekaj YH, Mekaj AY, Duci SB, Miftari EI. New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. Ther Clin Risk Manag 2015;11:967-977.