Impact of liver cirrhosis on the outcomes of patients with venous thromboembolism: a case-control study

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Background: Venous thromboembolism (VTE) is increasingly encountered in cirrhotic patients. We conducted a retrospective case-control study to explore the difference in the clinical characteristics and outcomes between VTE patients with and without cirrhosis.

Methods: All VTE patients who were admitted between January 2011 and December 2015 were considered. Age, sex, and Charlson Comorbidity Index score (CCIs) were matched between VTE patients with and without cirrhosis.

Results: Sixteen and 160 patients were included in the case and control groups, respectively. The case group had higher Child-Pugh score, prothrombin time (PT), and international normalized ratio (INR) and lower red blood cell, platelet, and albumin than the control group. The frequency of anticoagulant therapies was significantly lower in the case group than in the control group [50% (8/16) *vs.* 90.6% (145/160), P<0.001]. The incidence of major bleeding and in-hospital mortality were significantly higher in the case group than in the control group [43.8% (7/16) *vs.* 13.8% (22/160), P=0.006; 37.5% (6/16) *vs.* 7.5% (12/160), P=0.002]. The most common origin of major bleeding in the case group is variceal [85.7% (6/7)]. In the case group, the incidence of major bleeding and in-hospital mortality were not significantly different between patients who received and did not receive anticoagulants [25% (2/8) *vs.* 62.5% (5/8), P=0.315; 25% (2/8) *vs.* 50% (4/8), P=0.608].

Conclusions: Cirrhosis may increase the risk of major bleeding and in-hospital death in patients with VTE. Anticoagulant therapies may not influence the risk of major bleeding and in-hospital death in cirrhosis with VTE.

Keywords: Deep vein thrombosis (DVT); pulmonary embolism (PE); liver cirrhosis; anticoagulant; bleeding

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Introduction

Venous thromboembolism (VTE), which is defined as deep vein thrombosis (DVT) and pulmonary embolism (PE), represents a substantial health-care burden worldwide (1,2). The incidence of VTE is 100–200 per 100,000 person years in the general population (3) and can be as high as 1,000 per 100,000 person years among the elderly patients, cancer patients, and patients with multiple comorbidities (4,5). Population-based epidemiological

data has also demonstrated a yearly increased incidence of VTE in Asian patients (6-9). Risk factors of VTE include advanced age, obesity, active cancer, major trauma, fracture, recent surgery, heart failure, respiratory failure, paralytic stroke, inherited thrombophilia, antiphospholipid syndrome, previous VTE, varicose veins, congenital venous malformation, central venous catheter or vena cava filter, long-distance travel, pregnancy/antepartum, oral contraceptives and hormone replacement therapy (3,10-17). VTE is associated with reduced survival and substantial health-care costs (18,19). Prognostic factors of VTE include advanced age, male, lower body mass index, confinement to a hospital or nursing home at the onset of VTE, congestive heart failure, chronic lung disease, serious neurologic disease, tumor stage, tumor location, and absence of timely treatment (20-24). In Europe, more than 500,000 deaths per annum are attributable to VTE and its associated complications (3).

Recently, the association of VTE with liver cirrhosis has been frequently explored. However, the impact of liver cirrhosis on the outcomes of VTE remains unclear. Herein, we conducted a case-control study to explore the difference in the clinical characteristics and outcomes between VTE patients with and without cirrhosis.

Methods

Patients

The protocol of our study was approved by the Ethics Committee of General Hospital of Shenyang Military Area (approval number: k201602). Informed written consents were waived. The diagnoses of VTE were identified by searching the International Classification Codes (ICD)-9 and discharge diagnoses in the Department of Information between January 2011 and December 2015. ICD for the diagnosis of DVT include 453, 453.4, 453.4X, 453.5X, 453.7X, 453.8X, and 451.1–451.8. ICD for the diagnosis of PE include 415.1 and 415.1X. ICD for the diagnosis of liver cirrhosis include 571, 571.2, 571.5, and 571.6.

Diagnosis of VTE was established in accordance with the medical history of thrombosis, clinical presentations, laboratory tests, and imaging examinations. DVT was confirmed by the venography, compression Doppler ultrasound, CT scan, MRI scan, or autopsy. PE was confirmed by the pulmonary angiography, spiral CT scan, MRI scan, or pathology and ventilation-perfusion scan. Diagnosis of liver cirrhosis was established in accordance with the medical history of liver disease, clinical presentations, laboratory tests, and abdominal imaging.

Cases

Case and control group were defined as VTE with and without liver cirrhosis, respectively. Patients with malignancy and repeated admission were excluded. For each identified patient with VTE and liver cirrhosis in the case group, ten patients with VTE and without liver cirrhosis in the control group were matched by the age, sex, and Charlson Comorbidity Index score (CCIs). Some patients had been included in our previous studies (9,25-28).

Data collection

An investigator (Xintong Zhang) searched the medical records regarding medical history and new onset of VTE and another investigator (Xingshun Qi) checked the data accuracy. We collected the ages, genders, total CCIs, histories of smoking, alcohol and hypertension, etiologies of liver disease, locations and final diagnostic methods of VTE, antithrombotic drugs, dosages, and lengths, lengths of stay, laboratory data (white blood cell, red blood cell, hemoglobin, platelet, C-reactive protein, total bilirubin, direct bilirubin, alanine aminotransferase, aspartate aminotransferase, albumin, glutamyltranspeptidase, blood urea nitrogen, creatinine, potassium, sodium, total cholesterin, triglyceride, international normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, and D-dimer). Locations of major bleeding and causes of in-hospital death were reviewed.

Definitions

CCIs, which were evaluated and validated for the prognostic assessment in different clinical contexts (29), were divided into four classes: group 1 (CCIs: 4), group 2 (CCIs: 5), group 3 (CCIs: 6), and group 4 (CCIs: ≥6) (*Table S1*). Definition and classification of arterial hypertension were determined according to the guideline (30). Child-Pugh score was calculated according to the previous criteria (31). Major bleeding was defined in accordance with the International Society on Thrombosis and Haemostasis (ISTH) criteria (symptomatic bleeding in a critical organ; bleeding causing a fall in the hemoglobin of at least 20 g/L or leading to transfusion of at least two units of whole blood

Table 1 Characteristics of patients in the case group

Age	Sex	CCIs	CCI related diseases	Locations	Child-Pugh score	Causes of liver disease
40	F	4	Moderate or severe liver disease + peripheral disease	DVT	7	Unknown
42	F	4	Moderate or severe liver disease + peripheral disease	PE + DVT	11	HBV
46	M	4	Moderate or severe liver disease + peripheral disease	DVT	8	Alcohol
48	M	4	Moderate or severe liver disease + peripheral disease	PE	8	Alcohol + HCV
52	M	4	Moderate or severe liver disease + peripheral disease	DVT	9	Alcohol + HBV
54	F	5	Moderate or severe liver disease + peripheral disease + chronic pulmonary disease	DVT	8	Alcohol + PBC
56	M	5	Moderate or severe liver disease + peripheral disease + diabetes without end-organ damage	DVT	11	Alcohol
56	M	5	Moderate or severe liver disease + peripheral disease + diabetes without end-organ damage	DVT	10	Alcohol + HBV
63	M	5	Moderate or severe liver disease + peripheral disease + peptic ulcer disease	PE	8	Alcohol
75	F	5	Moderate or severe liver disease + peripheral disease + cerebrovascular disease	PE	10	Alcohol
47	M	6	Moderate or severe liver disease + peripheral disease + diabetes without end-organ damage + chronic pulmonary disease	PE	7	Alcohol + HBV
54	M	6	Moderate or severe liver disease + peripheral disease + history of myocardial infarction + cerebrovascular disease	DVT	8	Alcohol
71	M	6	Moderate or severe liver disease + peripheral disease + diabetes without end-organ damage + history of myocardial infarction	DVT	10	HBV
59	M	7	Moderate or severe liver disease + peripheral disease + history of myocardial infarction + moderate or severe renal disease	PE + DVT	9	HBV
69	M	7	Moderate or severe liver disease + peripheral disease + chronic pulmonary disease + moderate or severe renal disease	PE	7	Unknown
80	F	8	Moderate or severe liver disease + peripheral disease + chronic pulmonary disease + history of myocardial infarction + moderate or severe renal disease	PE	9	HBV

CCI, Charlson Comorbidity Index; DVT, deep vein thrombosis; PE, pulmonary embolism; HBV, hepatitis B virus; HCV, hepatitis C virus; PBC, primary biliary cirrhosis.

or red blood cells; or fatal bleeding) (32).

Statistical analysis

Statistical analysis was performed using SPSS Statistics version 19.0.0. Continuous variables were compared between the case group and the control group using the independent sample *t*-test or the Wilcoxon signed-rank test. Categorical variables were compared using Chi-square test or Fisher exact test. Bar chart was drawn to compare the incidence of major bleeding and in-hospital mortality between VTE patients with and without cirrhosis. A two sided $P<0.05$ was considered to be statistically significant.

Results

Patients

Sixteen patients with both VTE and cirrhosis were included in the case group (*Table 1*). Among them, eight patients were diagnosed with DVT, six patients with PE, and two

patients with both DVT and PE; eight patients had a previous history of lower extremity DVT, five patients had a previous history of PE, one patient had a previous history of both DVT and PE, one patient had a previous history of DVT and developed PE during hospitalization, and one patient developed PE during hospitalization.

One hundred and sixty patients were included in the control group. Among them, 25 patients were diagnosed with DVT, 91 patients with PE, and 44 patients with both DVT and PE; 23 patients had a previous history of lower extremity DVT, 58 patients had a previous history of PE, 32 patients had a previous history of both DVT and PE, 11 patients had a previous history of DVT and developed PE during hospitalization, 2 patients developed DVT during hospitalization, 33 patients developed PE during hospitalization, and 1 patient developed both DVT and PE during hospitalization. The age, sex, and total CCIs were comparable between the two groups.

Clinical characteristics between case and control groups

Clinical characteristics were compared between case and control groups (*Table 2*). The case group had a significantly higher proportion of history of alcohol than the control group [50% (8/16) *vs.*15% (24/160), P=0.002]. Red blood cell and platelet count were significantly lower in the case group than the control group (3.66±0.99 *vs.* 4.08±0.76, P=0.044; 113.56±78.84 *vs.* 197.23±105.34, P=0.002, respectively). Albumin was significantly lower in the case group than the control group (31.2±7.50 *vs.* 35.55±6.40, P=0.012). Total cholesterin was significantly lower in the case group than the control group (3.11±1.31 *vs.* 4.56±1.81, P=0.006). PT, APTT and INR were significantly higher in the case group than the control group (22.43±8.36 *vs.* 14.63±3.95, P=0.015; 47.20±14.24 *vs.* 38.35±8.97, P<0.001; 1.80±0.88 *vs.* 1.19±0.43, P=0.014, respectively). Fibrinogen was significantly lower in the case group than the control group (2.88±1.76 *vs.* 3.90±1.69, P=0.022). Child-Pugh score was significantly higher in the case group than the control group (8.75±1.34 *vs.* 5.90±1.09, P<0.001).

Antithrombotic therapies between case and control group

In the case group, 7 patients received anticoagulant therapies and 1 patient received both anticoagulant and thrombolytic therapies (*Table S2*). Anticoagulants included low molecular weight heparin alone (n=4), warfarin alone (n=2), and both low molecular weight heparin and warfarin (n=2). Thrombolytics included alteplase (n=1) for acute stage of PE.

In the control group, 134 patients received anticoagulant therapies and 11 patients received both anticoagulant and thrombolytic therapies (*Table S3*). Anticoagulants included low molecular weight heparin alone (n=59), unfractionated heparin alone (n=5), warfarin alone (n=15), both low molecular weight heparin and warfarin (n=64), and both unfractionated heparin and warfarin (n=2). Thrombolytics included alteplase (n=8) and urokinase (n=3) for acute stage of PE.

Rate of antithrombotic therapies was significantly lower in the case group than the control group [50% (8/16) *vs.* 90.6% (145/160), P<0.001].

Rate of anticoagulant therapies was significantly lower in the case group than the control group [50% (8/16) *vs.* 90.6% (145/160), P<0.001]. The ratio of length of anticoagulant therapy to that of hospital stay was significantly lower in the case group than the control group (41% *vs.* 87%, P<0.001).

Rate of thrombolytic therapies was not significantly different between case and control groups [6.25% (1/16) *vs.* 6.88% (11/160), P=1.000].

Major bleeding between case and control group

The incidence of major bleeding was significantly higher in the case group than the control group [43.8% (7/16) *vs.* 13.8% (22/160), P=0.006]. Location of major bleeding was shown in *Table 3*. After the exclusion of variceal bleeding, the incidence of major bleeding was not significantly different between case and control groups [6.2% (1/16) *vs.* 13.8% (22/160), P=0.698].

In the case group, the incidence of major bleeding was not significantly different between patients who received and did not receive anticoagulant therapies [25% (2/8) *vs.* 62.5% (5/8), P=0.315]. The interval between the initiation of anticoagulation and occurrence of major bleeding is 5 or 6 days in the two patients who received anticoagulant therapies (*Table S2*). The incidence of major bleeding was not significantly different between patients who received and did not receive thrombolytic therapies [0% (0/1) *vs.* 46.7% (7/15), P=1.000].

In the control group, the incidence of major bleeding was not significantly different between patients who received and did not receive anticoagulant therapies [13.1% (19/145) *vs.* 20% (3/15), P=0.437]. The average interval between the initiation of anticoagulation and occurrence of major

Table 2 Comparison between case group and control group

Variables	Case group (n=16)		Control group (n=160)		P value
	No. pts available	Results	No. pts available	Results	
Age (year)	16	57.00±11.81; 55 [41–80]	160	59.70±11.80; 60 [37–84]	0.384
Sex (M/F)	16	11/5	160	110/50	1.000
CCIs	16	5.31±1.25; 5 [4–8]	160	5.33±1.25; 5 [4–8]	0.970
History of alcohol (Y/N)	16	8/8	160	24/136	0.002
History of smoking (Y/N)	16	9/7	160	49/111	0.051
Hypertension (Y/N)	16	5/11	160	65/95	0.596
Red blood cell (10^{12}/L)	16	3.66±0.99; 3.45 (1.34–5.19)	156	4.08±0.76; 4.09 (2.05–5.94)	0.044
Hemoglobin (g/L)	16	115.5±31.53; 121 [39–155]	156	125.94±24.68; 127 [60–199]	0.119
White blood cell (10^9/L)	16	8.71±6.61; 6.2 (2.1–27.6)	156	8.10±3.38; 7.25 (2.7–20.8)	0.720
Platelet (10^9/L)	16	113.56±78.84; 84 [28–348]	156	197.23±105.34; 185.5 [39–1,153]	0.002
C-reactive protein (mg/L)	6	116.58±105.83; 90.85 (3.2–313.0)	54	41.28±46.26; 19.2 (1.9–216)	0.143
Total bilirubin	16	42.26±66.90; 24.7 (3.5–285.6)	154	15.72±12.08; 12.3 (1.9–65.0)	0.134
Direct bilirubin	16	22.78±43.00; 13.1 (1.8–181.8)	154	5.97±5.63; 4.35 (0.1–35.3)	0.139
Alanine aminotransferase (U/L)	16	386.89±1094.60; 32 [7–4,307]	156	52.91±242.22; 19 [4–2,995]	0.242
Aspartate aminotransferase (U/L)	16	532.99±1549.40; 38 [17–6,209]	156	54.35±214.03; 22 [9–2,603]	0.236
Albumin (g/L)	16	31.2±7.50; 34.05 (17.4–41.2)	139	35.55±6.40; 36.1 (12.6–48.2)	0.012
Glutamyl transpeptidase (U/L)	16	101.03±109.98; 67 [8–415]	155	76.09±98.02; 46 [8–860]	0.339
Blood urea nitrogen (mmol/L)	16	8.25±5.24; 6.70 (2.96–20.91)	148	8.60±6.58; 6.94 (2.55–45.70)	0.841
Creatinine (μmol/L)	16	109.83±120.00; 71 (38.1–524)	148	106.57±148.20; 73.5 (30.8–1,346.7)	0.935
Potassium (mmol/L)	16	4.16±0.75; 3.98 (3.2–5.7)	155	4.03±0.57; 4.03 (2.2–6.2)	0.407
Sodium (mmol/L)	16	138.95±4.07; 138.5 (130.8–146.0)	155	138.96±4.54; 139 (123.9–155.5)	0.994
Total cholesterin (mmol/L)	6	3.11±1.31; 2.81 (1.86–4.77)	84	4.56±1.81; 4.09 (2.33–12.99)	0.006
Triglyceride (mmol/L)	6	0.86±0.39; 0.85 (0.22–1.39)	84	1.84±2.11; 1.37 (0.45–16.23)	0.260
Prothrombin time at admission (second)	16	22.43±8.36; 16.5 (12.9–38.8)	159	14.63±3.95; 13.6 (10.2–37.9)	0.015
Activated partial thromboplastin time at admission (second)	16	47.20±14.24; 45.5 (26.2–87.3)	159	38.35±8.97; 37.7 (0.9–76.1)	0.001
International normalized ratio at admission	16	1.80±0.88; 1.39 (1.00–3.37)	159	1.19±0.43; 1.07 (0.78–4.07)	0.014
Fibrinogen at admission	16	2.88±1.76; 2.64 (1.25–8.43)	157	3.90±1.69; 3.6 (0.53–13.85)	0.022
D-dimer at admission (μg/mL)	13	3.59±4.36; 1.7 (0.1–15.5)	156	2.42±9.21; 0.4 (0.1–80)	0.065
Child-Pugh scores	16	8.75±1.34; 8.5 [7–11]	160	5.90±1.09; 6 [5–10]	0.000

Table 3 Locations of major bleeding

Locations	Case	Control
Gastrointestinal bleeding	7	9
Variceal bleeding confirmed by endoscopy	6	0
Ulcer confirmed by endoscopy	0	2
Intestinal bleedings confirmed by endoscopy	0	1
Hemobilia	0	1
Unknown source or no endoscopic examination	1	5
Respiratory bleeding	0	3
Hemoptysis	0	2
Intracranial hemorrhage	0	1
Unknown	0	7
Total	7	22

Table 4 Causes of in-hospital death

Causes	Case	Control
Massive gastrointestinal bleeding	1	0
Liver failure	1	0
Pulmonary embolism + multiple organ failure	1	0
Pulmonary embolism	2	2
Acute myocardial infarction	1	1
Respiratory failure	0	5
Respiratory failure + massive gastrointestinal bleeding	0	1
Multiple organ failure	0	2
Cerebrovascular disease	0	1
Total	6	12

bleeding is 5.21 (1-12) days in the patients who received anticoagulant therapies (*Table S3*). The incidence of major bleeding was not significantly different between patients who received and did not receive thrombolytic therapies [0% (0/11) *vs.* 14.8% (22/149), P=0.364].

In-hospital mortality between case and control group

The in-hospital mortality was significantly higher in the case group than the control group [37.5% (6/16) *vs.* 7.5% (12/160), P=0.002]. Causes of death were shown in *Table 4*.

In the case group, the in-hospital mortality was not significantly different between patients who received and did not receive anticoagulant therapies [25% (2/8) *vs.* 50% (4/8), P=0.608]. The in-hospital mortality was not significantly different between patients who received and did not receive thrombolytic therapies [100% (1/1) *vs.* 33.3% (5/15), P=0.375].

In the control group, the in-hospital mortality was not significantly different between patients who received and did not receive anticoagulant therapies [7.6% (11/145) *vs.* 6.7% (1/15), P=1.000]. The in-hospital mortality was not significantly different between patients who received or did not receive thrombolytic therapies [0% (0/11) *vs.* 8.1% (12/149), P=1.000].

Discussion

The mortality of VTE in our study appears to be higher than the results of the Framingham Heart Study that the mortality of VTE was 145/1,000 person years (33). This phenomenon might be explained by a higher proportion of patients with CCIs of greater than 4 and a higher proportion of patients with PE in our study.

Our study demonstrated that liver cirrhosis had an unfavorable impact on the in-hospital outcomes of VTE patients. This finding seems to be consistent with that of Spencer *et al.* (34) that sicker patients are more prone to thromboembolic events and have worse prognosis. Liver cirrhosis is an end-stage of liver diseases and is often complicated by lethal portal hypertension related complications, such as variceal bleeding, ascites, encephalopathy, and infection (35). Obviously, our cirrhotic patients had higher total bilirubin, alanine aminotransferase, aspartate aminotransferase, glutamyltranspeptidase, and Child-Pugh scores and lower albumin due to liver dysfunction.

Current practice guideline provides a class 1A recommendation for the administration of thromboprophylaxis in patients with VTE. However, such recommendations may be inappropriate to the patients with liver cirrhosis (36). Use of anticoagulation for the prophylaxis and treatment of VTE in cirrhosis remains controversial due to the potential bleeding risk. Recently, several studies have demonstrated the safety of anticoagulants in patients with cirrhosis (37-40). Our previous systematic review showed that the pooled incidence of bleeding in cirrhotic patients receiving

anticoagulation was 3.3% (40). By comparison, the present study demonstrated a higher rate of major bleeding in cirrhotic patients receiving anticoagulation, which was more likely attributed to a higher CCI of ≥4. Patients with liver cirrhosis had a higher rate of major bleeding than those without. Indeed, after excluding variceal bleeding, the rate of major bleeding was lower in patients with liver cirrhosis than those without. This phenomenon suggested that the risk of bleeding in such patients should be primarily due to portal hypertension, but not systemic haemostatic impairment.

We found that the risk of major bleeding was not significantly associated with anticoagulation in patients with liver cirrhosis and VTE. In addition, there is no statistically significant association between anticoagulation and an increased risk of in-hospital death in such patients. Notably, the in-hospital mortality might be lower in cirrhotic patients with VTE who received anticoagulation than those who did not receive anticoagulation. This might reflect the benefits of anticoagulation in resolving VTE and improving the survival. Thus, anticoagulant therapy, rather than a "wait-and-see" strategy, might be considered for the management of VTE in liver cirrhosis.

Our study had several limitations. First, the patient selection bias should not be neglected due to the retrospective study in a single-center even though we have very few exclusion criteria. Second, the absence of analyses regarding therapeutic administration route (41) and dosages and quality of anticoagulation (42) may restrict our interpretation about the impact of anticoagulation. Third, there was a relatively small sample size of patients with cirrhosis and VTE. The statistical power is hardly achieved in some analyses.

In conclusion, liver cirrhosis may increase the incidence of major bleeding and in-hospital mortality in patients with VTE. Anticoagulant therapy may not be associated with the risk of major bleeding and in-hospital mortality in cirrhotic patients with VTE. Well-designed prospective randomized controlled trials are warranted to establish the risks and benefits of anticoagulation for VTE in cirrhosis.

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Footnote

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2017.02.11). The work is partially presented as a poster in the Asian Pacific Association for the Study of the Liver Single Topic Conference—6th HBV Conference, Beijing, China. Dr. Qi serves as an Editor-in-Chief of *AME Medical Journal*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The protocol of our study was approved by the Ethics Committee of General Hospital of Shenyang Military Area (approval number: k201602). Informed written consents were waived.

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Supplementary

Table S1 Charlson comorbidity index

Comorbidity	Scores
History of myocardial infarction	+1
Congestive heart failure	+1
Cerebrovascular disease	+1
Chronic pulmonary disease	+1
Connective tissue disease	+1
Peptic ulcer disease	+1
Mild liver disease (no portal hypertension, includes chronic hepatitis)	+1
Diabetes without end-organ damage	+1
Peripheral disease	+1
Hemiplegia	+2
Moderate or severe renal disease	+2
Diabetes with end-organ damage	+2
Moderate or severe liver disease	+3
AIDS	+6

AIDS, acquired immune deficiency syndrome.

Table S2 Anticoagulants and major bleeding in the case group

No.	Acute stage of VTE	Anticoagulants	Dosages of anticoagulants before major bleeding or during hospitalization	Frequency of anticoagulants (per day)	Thrombolytics	Dosages of thrombolytics before major bleeding or during hospitalization	Frequency of thrombolytics (per day)	Major bleeding	Interval between major bleeding and use of anticoagulants (days)
1	No	Warfarin	3 mg	1	–	–	–	No	–
2	No	Warfarin	3 mg	1	–	–	–	No	–
3	No	Low molecular weight heparin calcium	5,000 iu	2	–	–	–	Yes	6
4	Yes	Low molecular weight heparin calcium; Warfarin	4,250 iu; 2.5 mg	2; 1	Alteplase	50 mg	1	No	–
5	No	Low molecular weight heparin calcium	4,000 iu	1	–	–	–	Yes	5
6	No	Low molecular weight heparin calcium	6,400 iu	2	–	–	–	No	–
7	No	Low molecular weight heparin calcium	4,250 iu	2	–	–	–	No	–
8	No	Low molecular weight heparin calcium; Warfarin	6,100 u; 2.5 mg	2; 1	–	–	–	No	–

Table S3 Anticoagulants and major bleeding in the control group

No.	Acute stage of VTE	Anticoagulants	Dosages of anticoagulants before major bleeding or during hospitalization	Frequency of anticoagulants (per day)	Thrombolytics	Dosages of thrombolytics before major bleeding or during hospitalization	Frequency of thrombolytics (per day)	Major bleeding	Interval between major bleeding and use of anticoagulants (days)
1	No	Enoxaparin	20 mg	1				No	
2	Yes	Low molecular weight heparin calcium	5,000 iu	2				Yes	1
3	No	Low molecular weight heparin calcium	4,250 iu	1				No	
4	No	Low molecular weight heparin calcium	5,000 iu	2				No	
5	No	Low molecular weight heparin calcium; Warfarin	5,000 iu; 3 mg	1; 1				No	
6	No	Enoxaparin	40 mg	1				Yes	3
7	Yes	Enoxaparin	70 mg	2				Yes	4
8	No	Enoxaparin; Warfarin	40 mg; 2.25 mg	2; 1				Yes	5
9	No	Low molecular weight heparin calcium; Warfarin	4,250 iu; 3 mg	2; 1				Yes	6
10	No	Low molecular weight heparin calcium; Warfarin	5,000 iu; 3 mg	1; 1				No	
11	No	Enoxaparin	80 mg	2				No	
12	No	Low molecular weight heparin calcium	5,000 iu	2				No	
13	No	Fondaparinux sodium	2.5 mg	1				No	
14	No	Low molecular weight heparin calcium	4,250 iu	2				No	
15	No	Low molecular weight heparin calcium; Warfarin	4,250 iu; 3 mg	2; 1				No	
16	No	Low molecular weight heparin calcium; Warfarin	5,000 iu; 3 mg	1; 1				No	
17	No	Low molecular weight heparin calcium Warfarin	5,000 iu; 3 mg	2; 1				No	
18	No	Low molecular weight heparin calcium	5,000 iu	1				Yes	6
19	No	Low molecular weight heparin calcium; Warfarin	4,250 iu; 4.5 mg	1; 1				No	
20	No	Low molecular weight heparin calcium; Warfarin	5,000 iu; 3 mg	2; 1				No	
21	No	Warfarin	3 mg	1				No	
22	Yes	Low molecular weight heparin sodium	6,375 iu	2	Urokinase	50 wu	1	No	
23	No	Low molecular weight heparin calcium; Warfarin	5,000 iu; 32.5 mg	2; 1				No	
24	No	Warfarin	3 mg	1				No	
25	No	Enoxaparin; Warfarin	60 mg; 2.75 mg	2; 1				No	
26	No	Heparin calcium; Warfarin	3,750 u; 3.75 mg	1; 2				No	
27	Yes	Enoxaparin	40 mg	1				Yes	5
28	No	Low molecular weight heparin calcium	5,000 iu	1				No	
29	Yes	Low molecular weight heparin calcium	5,000 iu	1				No	
30	No	Low molecular weight heparin calcium; Warfarin	4,250 iu; 3 mg	2; 1				No	
31	No	Enoxaparin	40 mg	2				No	
32	No	Warfarin	2.25 mg	1				No	
33	Yes	Low molecular weight heparin calcium	4,250 iu	2				Yes	8
34	Yes	Low molecular weight heparin calcium	4,250 iu	1				No	
35	Yes	Low molecular weight heparin calcium; Warfarin	5,000 iu; 6 mg	2; 1				No	
36	Yes	Heparin calcium	7,500 u	1				No	
37	Yes	Low molecular weight heparin calcium	4,250 iu	2	Alteplase	50 mg	Once	No	
38	No	Low molecular weight heparin calcium	5,000 iu	2				No	
39	Yes	Low molecular weight heparin calcium; Warfarin	5,000 iu; 3 mg	2; 1				No	
40	No	Low molecular weight heparin calcium	5,000 iu	2				No	
41	No	Warfarin	3 mg	1				No	
42	Yes	Low molecular weight heparin calcium	5,000 iu	2				No	
43	Yes	Low molecular weight heparin calcium; Warfarin	4,250 iu; 4.5 mg	2; 1				No	
44	No	Low molecular weight heparin calcium	5,000 iu	2				No	
45	Yes	Low molecular weight heparin calcium	4,250 iu	2				No	
46	Yes	Enoxaparin	40 mg	2				No	
47	No	Low molecular weight heparin calcium; Warfarin	4,250 iu; 2.5 mg	2; 1				Yes	4
48	No	Low molecular weight heparin calcium	4,250 iu	1				No	
49	No	Low molecular weight heparin sodium	6,375 iu	2				No	
50	Yes	Low molecular weight heparin calcium	5,000 iu	2				No	
51	Yes	Enoxaparin; Warfarin	85 mg; 4.5 mg	2; 1				No	
52	No	Low molecular weight heparin calcium; Warfarin	4,250 iu; 3.25 mg	2; 1				No	
53	No	Warfarin	3 mg	1				No	
54	No	Warfarin	3 mg	1				No	
55	Yes	Heparin calcium	5,000 u	2				No	
56	Yes	Warfarin	4.5 mg	1				No	
57	No	Low molecular weight heparin calcium; Warfarin	5,000 iu; 3.5 mg	1; 1				No	
58	No	Enoxaparin	40 mg	2				No	
59	No	Warfarin	3 mg	1				No	
60	No	Warfarin	3 mg	1				No	
61	No	Warfarin	3 mg	1				No	
62	No	Low molecular weight heparin calcium; Warfarin	4,250 iu; 4 mg	2; 1				No	
63	No	Low molecular weight heparin calcium; Warfarin	5,000 iu; 2.75 mg	2; 1				No	
64	No	Enoxaparin	60 mg	2				No	
65	No	Low molecular weight heparin calcium; Warfarin	4,250 iu; 3 mg	2; 1				No	
66	No	Low molecular weight heparin calcium	4,000 iu	1				Yes	6
67	No	Low molecular weight heparin calcium	5,000 iu	2				No	
68	Yes	Enoxaparin	60 mg	2				No	
69	Yes	Low molecular weight heparin calcium	4,250 iu	2				No	
70	Yes	Enoxaparin	40 mg	2				No	
71	Yes	Low molecular weight heparin sodium	6,375 iu	2				No	
72	No	Low molecular weight heparin calcium; Warfarin	5,000 iu; 1.5 mg	2; 1				No	
73	Yes	Enoxaparin	40 mg	2				No	
74	No	Low molecular weight heparin calcium	4,250 iu	2				No	
75	No	Low molecular weight heparin calcium; Warfarin	5,000 iu; 3.5 mg	1; 1				Yes	2
76	Yes	Low molecular weight heparin sodium	6,375 iu	2				No	
77	No	Low molecular weight heparin sodium	6,375 iu	1				No	
78	Yes	Low molecular weight heparin calcium; Warfarin	4,000 iu; 2.5 mg	1; 1	Urokinase	50 wu	1	No	
79	No	Low molecular weight heparin calcium	7,000 iu	2				No	
80	No	Low molecular weight heparin calcium	4,250 iu	2				Yes	3
81	No	Low molecular weight heparin calcium	5,000 iu	2				No	
82	Yes	Low molecular weight heparin calcium; Warfarin	4,250 iu; 4 mg	2; 1	Alteplase	50 mg	Once	No	
83	No	Low molecular weight heparin calcium; Warfarin	5,000 iu; 4 mg	2; 1				No	
84	No	Warfarin	3 mg	1				No	
85	No	Low molecular weight heparin calcium	4,250 iu	2				No	
86	No	Warfarin	3.25 mg	1				No	
87	Yes	Low molecular weight heparin calcium; Warfarin	4,250 iu; 3 mg	2; 1	Urokinase	50 wu	1	No	
88	Yes	Low molecular weight heparin calcium; Warfarin	5,000 iu; 4 mg	2; 1	Alteplase	50 mg	Once	No	
89	Yes	Low molecular weight heparin calcium; Warfarin	4,250 iu; 4 mg	2; 1	Alteplase	50 mg	Once	No	
90	No	Low molecular weight heparin calcium; Warfarin	5,000 iu; 3.5 mg	2; 1				Yes	8
91	Yes	Fondaparinux sodium; Warfarin	2.5 mg; 3.5 mg	1; 1				No	
92	No	Warfarin	3 mg	1				No	
93	Yes	Heparin calcium	7,500 u	2				No	
94	No	Enoxaparin; Warfarin	40 mg; 3 mg	2; 1				No	
95	Yes	Low molecular weight heparin calcium	5,000 iu	2				No	
96	No	Low molecular weight heparin calcium	4,250 iu	2				No	
97	No	Low molecular weight heparin calcium	5,000 iu	2				Yes	1
98	Yes	Low molecular weight heparin sodium	6,375 iu	2				No	
99	No	Enoxaparin	40 mg	2				No	
100	No	Enoxaparin; Warfarin	60 mg; 3 mg	2; 1				No	
101	No	Low molecular weight heparin calcium; Warfarin	4,250 iu; 2.5 mg	2; 1				Yes	8
102	No	Low molecular weight heparin calcium; Warfarin	6,000 iu; 3 mg	2; 1				No	
103	No	Fondaparinux sodium; Warfarin	2.5 mg; 1.5 mg	1; 1				No	
104	No	Enoxaparin; Warfarin	40 mg; 3 mg	2; 1				No	
105	No	Low molecular weight heparin calcium; Warfarin	5,000 iu; 5 mg	2; 1				No	
106	No	Low molecular weight heparin calcium	4,250 iu	2				No	
107	Yes	Low molecular weight heparin calcium; Warfarin	4,250 iu; 2 mg	2; 1	Alteplase	50 mg	Once	No	
108	No	Enoxaparin; Warfarin	60 mg; 3 mg	2; 1				No	
109	Yes	Low molecular weight heparin calcium; Warfarin	5,000 iu; 1 mg	2; 1				No	
110	No	Low molecular weight heparin calcium; Warfarin	4,250 iu; 2.5 mg	2; 1				No	
111	No	Enoxaparin; Warfarin	20 mg; 2.75 mg	2; 1				No	
112	Yes	Low molecular weight heparin calcium; Warfarin	4,250 iu; 3 mg	2; 1	Alteplase	50 mg	Once	No	
113	No	Enoxaparin; Warfarin	40 mg; 3 mg	2; 1				No	
114	Yes	Low molecular weight heparin calcium; Warfarin	4,250 iu; 3 mg	2; 1	Alteplase	50 mg	Once	No	
115	No	Low molecular weight heparin sodium	6,375 iu	2				No	
116	No	Warfarin	3 mg	1				No	
117	No	Low molecular weight heparin calcium	5,000 iu	2				No	
118	No	Low molecular weight heparin calcium; Warfarin	4,250 iu; 2.75 mg	2; 1				No	
119	No	Low molecular weight heparin calcium; Warfarin	5,000 iu; 3 mg	2; 1				No	
120	No	Heparin calcium; Warfarin	3,750 u; 4.5 mg	1; 1				No	
121	No	Enoxaparin	40 mg	2				No	
122	Yes	Heparin calcium	7,500 u	2				Yes	7
123	Yes	Low molecular weight heparin calcium	4,000 iu	2				Yes	3
124	Yes	Low molecular weight heparin calcium; Warfarin	4,000 iu; 3 mg	2; 1				Yes	12
125	No	Fondaparinux sodium; Warfarin	2.5 mg; 3 mg	1; 1				No	
126	No	Low molecular weight heparin calcium; Warfarin	5,000 iu; 2.75 mg	2; 1				No	
127	No	Fondaparinux sodium; Warfarin	2.5 mg; 22.5 mg	1; 1				No	
128	No	Enoxaparin	60 mg	2				No	
129	No	Warfarin	3 mg	1				No	
130	No	Low molecular weight heparin calcium; Warfarin	5,000 iu; 3 mg	2; 1				No	
131	No	Fondaparinux sodium	2.5 mg	1				No	
132	No	Low molecular weight heparin calcium; Warfarin	6,000 iu; 2.5 mg	2; 1				No	
133	No	Low molecular weight heparin calcium; Warfarin	4,250 iu; 3 mg	2; 1				No	
134	No	Low molecular weight heparin calcium; Warfarin	4,250 iu; 3.25 mg	2; 1				No	
135	No	Low molecular weight heparin calcium; Warfarin	4,250 iu; 2.75 mg	2; 1				No	
136	No	Enoxaparin; Warfarin	40 mg; 3 mg	2; 1				No	
137	No	Low molecular weight heparin calcium; Warfarin	5,000 iu; 3 mg	2; 1				No	
138	No	Enoxaparin; Warfarin	40 mg; 2.75 mg	2; 1				No	
139	Yes	Enoxaparin; Warfarin	60 mg; 3 mg	2; 1				No	
140	No	Heparin calcium	5,000 u	2				Yes	7
141	No	Enoxaparin; Warfarin	60 mg; 3.25 mg	2; 1				No	
142	No	Low molecular weight heparin calcium; Warfarin	4,250 iu; 3 mg	2; 1				No	
143	Yes	Enoxaparin; Warfarin	40 mg; 2.25 mg	2; 1	Alteplase	50 mg	Once	No	
144	Yes	Low molecular weight heparin calcium; Warfarin	4,250 iu; 3 mg	2; 1				No	
145	No	Enoxaparin	40 mg	2				No	