Original Article

Clinical Characteristics, Management Practices, and In-hospital Outcomes among Trauma Patients with Venous Thromboembolism

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Abstract

Background: We aimed to assess the clinical characteristics, management practices, and inhospital outcomes of venous thromboembolism (VTE) among trauma patients. **Methods:** A retrospective analysis of all trauma patients with documented venous thromboembolic events in a level 1 trauma center was conducted. Patients were categorized into two groups based on the primary initial presentation postinjury (deep-vein thrombosis [DVT] or pulmonary embolism [PE]). **Results:** Across the study period, a total of 662 patients were confirmed to have DVT and 258 patients were diagnosed with acute PE. Among them, 84 patients were identified to have trauma-associated VTE; 56 (8.5%) had DVT and 28 (10.9%) had PE. Two patients who initially presented with DVT developed PE on follow-up. There were 38 females and 46 males with a mean age of 46 ± 18 years. Abnormal coagulation profile was reported as 7 protein C deficiencies, 5 protein S deficiencies, 6 homocystinemia, 4 antithrombin III deficiency, 4 lupus anticoagulant, and 2 Factor V Leiden. Age, sex, obesity, D-dimer level, and treatment (except for heparin) were comparable between the two groups; whereas protein S deficiency, prior history of PE, bedridden status, congestive heart failure, and history of recent surgery, were more evident in the PE group. The incidence of postthrombotic syndrome was significantly higher in the DVT group. Overall mortality rate was 8.3% (DVT; 8.9% vs. PE; 7.1%, respectively = 0.78). **Conclusion:** Coagulation profile plays an important role in posttraumatic thromboembolic disease. A thorough assessment for features of thromboembolic disorders is warranted in polytrauma patients to avoid missing this potentially life-threatening diagnosis. Larger studies are needed for better understanding and management of VTE in trauma.

Keywords: Outcomes, risk factors, trauma, venous thromboembolism

Introduction

Venous thromboembolism (VTE) [comprised of deep-vein thrombosis (DVT) and pulmonary embolism (PE)] significantly contributes to the worldwide burden of acute diseases.[1] In particular, victims of major trauma are at increased risk of thromboembolic complications secondary to coagulopathy, injury pattern, and immobility.[2] Progressive trauma-induced coagulopathy is often manifested with increased microparticle and thrombin generation; these have been implicated in the pathogenesis of VTE and organ failure among high-risk populations.[3,4]

In trauma patients, the incidence of thromboembolic events ranges from 0.36% to 58%. This huge disparity in the reported incidence is influenced by sociodemographic characteristics, nature of the injury, diagnostic modalities used, type and adherence to pharmacologic thromboprophylaxis.[3,5] Determining the true incidence of VTE and its associated

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consequences necessitates a thorough understanding of the underlying predisposing factors in trauma patients. Earlier studies have reported various risk factors for VTE in injured patients who require hospitalization.[6] Frequently identified predisposing factors for VTE in trauma patients include advanced age, lower extremity fractures, major surgery, bleeding complication, major thoracic injury, higher injury severity score, need for mechanical ventilation, and prolonged hospitalization.[5] Notably, DVT remains undiagnosed in many trauma patients due to lower extremity swelling from tissue injury or traumatic fracture. Furthermore, the development of hypoxia in trauma patients could be due to reasons other than PE, which makes the clinical diagnosis unreliable.[7] Early diagnosis of VTE requires accurate diagnostic modalities to enable appropriate interventions.

Trauma remains a leading public health concern in the Arab Middle Eastern population, particularly in Qatar with its' exponential population growth. Blunt traumatic injuries are associated with substantial morbidity and mortality in the younger population in this region.[8] The occurrence of VTE in major trauma patients in Qatar is not well-documented.

Herein, our aim is to determine the clinical characteristics, management practices, and inhospital outcomes of VTE among trauma patients.

Methods

A retrospective study was conducted to include all trauma patients who fulfilled the diagnostic criteria for DVT (January 2008 to December 2012) and/or acute PE (May 2011 to February 2015) after the clinical presentation to the tertiary trauma center in Qatar. Hospital medical records of all adult (≥15 years) trauma patients who had VTE (DVT or PE) were identified from the hospital radiology information system. Location of diagnosis (inhospital wards and outpatient clinics) and clinical follow-up were also noted. The database was searched for all patients who had a confirmed diagnosis of PE on computed tomography pulmonary angiography (CTPA) or had a positive diagnosis of DVT on color Doppler ultrasonography of the lower or upper limbs. The trauma service of our tertiary care hospital has gained the Trauma Distinction Award from Accreditation Canada International and has a well-established trauma registry database.

Data collection included patient demographics, baseline characteristics (clinical signs and symptoms), risk factors and comorbidities, laboratory investigations (routine tests, D-dimer, and thrombophilic disorders), radiological findings (presence of DVT or PE), first and recurrent VTE, initial and long-term treatment [low-molecular-weight heparin (LMWH), warfarin, antiplatelet, and thrombolytic therapy], hospital length of stay, postthrombotic syndrome (leg pain, swelling, redness, and ulcers), and mortality.

In our study, VTE was diagnosed by clinical presentation, laboratory investigations, and color Doppler ultrasonography or CTPA as described earlier.[9] The Institutional Review Board (IRB# 15002/15 and 15139/15) of Hamad Medical Corporation has approved and granted exempt status for this retrospective study.

Statistical analysis

Data were presented as proportions, mean (± standard deviation), or medians (range), as appropriate. Variables such as baseline characteristics, risk factors and comorbidities, diagnostic testing, complications, and outcome were compared between DVT and PE groups. A comparison between respective groups was performed using Student's *t*-test for continuous variables and Pearson Chi-square test for categorical variables. A significant difference was considered when the 2-tailed P was < 0.05. Data analysis was carried out using the Statistical Package for the Social Sciences version 18 (SPSS Inc. Chicago IL, USA).

Results

During the study period, a total of 662 patients were confirmed to have DVT and 258 patients were diagnosed with acute PE in our hospital. Among them, 84 patients were identified to have trauma-associated VTE; 56 (8.5%) had DVT and 28 (10.9%) had PE. On clinical follow-up, two patients that were initially diagnosed with DVT later developed PE. Table 1 shows the comparison of demographics and risk factors of trauma patients presenting with VTE (DVT versus PE). The total number of patients admitted under the trauma service during the study period was 4356. This corresponds to an overall VTE incidence of 1.9% in our cohort. The mean patient age was 46.2 ± 18.8 years, and more than half were male (55%). The groups were comparable in terms of demographic characteristics such as age, gender, and nationality. Among patients with PE, the majority were diagnosed as inpatients (64.3% vs. 28.6%; $P = 0.002$), compared to DVT where a significantly higher proportion was constituted by outpatient diagnosis (71.4% vs. 35.7%; $P = 0.002$).

Overall, frequently predisposing factors for VTE were lower extremity fracture (58.3%), history of recent surgery (36.1%), recurrent DVT (26.5%), and pelvic fracture (17.9%). Patients diagnosed with PE were more likely to have a history of recent surgery (51.9% vs. 28.6%; $P = 0.03$), bedridden status (25.0% vs. 8.9%; $P = 0.04$), and a prior PE (7.4% vs. 0.0%; $P = 0.03$) as compared to those with DVT.

Frequent comorbidities identified in VTE patients were obesity (52.9%), hypertension (25.0%), diabetes mellitus (17.9%), and hypercholesterolemia (17.9%). No significant difference was observed between the two groups with respect to comorbidities, except for a history of congestive heart failure (7.1% vs. 0.0%; $P = 0.04$) (significantly higher in patients with PE). Insertion of femoral and neck central lines was not associated with the development of VTE.

Table 2 shows the comparison of thrombophilic disorders and other laboratory findings.

Hyperhomocysteinemia (7.1%), deficiency of protein C (8.3%), protein S (6.0%), and antithrombin III (4.8%) were

Table 1: Comparison of demographics and risk factors of trauma patients presented with deep-vein thrombosis versus pulmonary embolism

Variables	Overall (*n*=84)	DVT (*n*=56)*	PE (*n*=28)	*P*
Age, mean±SD	46.2±18.8	44.4±17.1	50.0±21.7	0.20
Males, *n* (%)	46 (54.8)	29 (51.8)	17 (60.7)	0.44 for all
Females, *n* (%)	38 (45.2)	27 (48.2)	11 (39.3)	
Qatari, *n* (%)	22 (26.2)	14 (25.0)	8 (28.6)	0.72
Body mass index, mean±SD	30.6±7.4	31.6±8.0	28.3±5.2	0.09
Locations of diagnosis, *n* (%)				
Inhospital wards	34 (40.5)	16 (28.6)	18 (64.3)	0.002 for all
Outpatient clinics	50 (59.5)	40 (71.4)	10 (35.7)	
Risk factors, *n* (%)				
Lower-extremity fracture	49 (58.3)	29 (51.8)	20 (71.4)	0.08
History of surgery (>24 h)	30 (36.1)	16 (28.6)	14 (51.9)	0.03
History of DVT	22 (26.5)	14 (25.0)	8 (29.6)	0.65
Pelvic fracture	15 (17.9)	8 (14.3)	7 (25.0)	0.22
Bedridden	12 (14.3)	5 (8.9)	7 (25.0)	0.04
Neck central line	8 (9.6)	3 (5.4)	5 (18.5)	0.05
Paraplegia	3 (3.6)	2 (3.6)	1 (3.6)	1.00
History of PE	2 (2.4)	0 (0.0)	2 (7.4)	0.03
Femoral central line	2 (2.4)	1 (1.8)	1 (3.7)	0.59
Surgery (within 24 h)	1 (1.2)	1 (1.8)	0 (0.0)	0.49
Comorbidities, *n* (%)				
Obesity	37 (52.9)	29 (58.0)	8 (40.0)	0.17
Hypertension	21 (25.0)	14 (25.0)	7 (25.0)	1.00
Diabetes mellitus	15 (17.9)	8 (14.3)	7 (25.0)	0.22
Hypercholesterolemia	15 (17.9)	9 (16.1)	6 (21.4)	0.54
Hypertriglyceridemia	8 (10.5)	4 (7.1)	4 (20.0)	0.10
Coronary artery disease	5 (6.0)	2 (3.6)	3 (10.7)	0.19
Congestive heart failure	2 (2.4)	0 (0.0)	2 (7.1)	0.04

*Two patients initially presented with DVT developed PE on the follow-up. DVT: Deep-vein thrombosis, PE: Pulmonary embolism, SD: Standard deviation

the most common thrombophilic disorders. Patients with PE were more likely to have a deficiency of protein S (14.3% vs. 1.8%, P = 0.02) as compared to those with DVT. The D-dimer was tested in 60 cases after the clinical suspicion of VTE and was found positive in 90% cases. The two groups did not differ significantly with respect to the findings of other thrombophilia tests.

Transthoracic echocardiography findings were available in 35 cases; 5 patients had pulmonary artery dilation and 3 had right ventricular (RV) hypokinesis. No significant difference was noted regarding the percentage of patients undergoing echocardiographic examination between groups. Notably, the groups were comparable with regard to ejection fraction, RV wall hypokinesis, and pulmonary artery dilation.

Patients with PE were more likely to have lower mean hemoglobin (11.4 ± 2.3 vs. 12.7 ± 2.2; P = 0.01) and hematocrit (34.1 ± 8.3 vs. 38.3 ± 6.5; P = 0.01) values and higher platelet counts (363 ± 266 vs. 268 ± 97.4; P = 0.02) than the DVT group.

The common initial treatment regimens were warfarin (78.6%), enoxaparin (76.2%), dalteparin (39.3%), and aspirin (31.0%) [Table 3]. The medical treatment did not differ significantly among the two groups except for heparin (46.4% vs. 10.7%, P = 0.001), which was more frequently prescribed in the PE cohort. DVT patients were more likely to receive long-term warfarin treatment (P = 0.09), but this did not reach statistical significance. Overall, four patients received thrombolytic therapy, two in each group (P = 0.46). The median length of hospital stay was two times higher in patients with PE as opposed to those with DVT (without statistical significance). The characteristic presentation of the postthrombotic syndrome was calf pain (73.8%), leg edema (58.3%), and leg ulcer (4.8%). The frequency of calf pain (P = 0.001) and leg edema (P = 0.04) was significantly higher in the DVT group as compared to PE. Seven deaths (8.3%) occurred in patients with VTE (five died in the DVT group and seven in PE group). The mortality rate was comparable among the two groups.

Discussion

DVT and PE have been identified as significant posttraumatic complications. To the best of our knowledge, this is the first study from our region to determine the frequency and risk factors for VTE among trauma patients. The incidence of VTE in trauma patients varies considerably (0.36% to 58%), depending on the sociodemographic characteristics,

Table 2: Comparison of thrombophilic disorders and other laboratory findings

	Overall (*n*=84)	DVT (*n*=56)	PE (*n*=28)	*P*
Thrombophilic disorders, *n* (%)				
Hyperhomocysteinemia	6 (7.1)	4 (7.1)	2 (7.1)	1.00
Protein C deficiency	7 (8.3)	3 (5.4)	4 (14.3)	0.16
Protein S deficiency	5 (6.0)	1 (1.8)	4 (14.3)	0.02
Antithrombin III deficiency	4 (4.8)	1 (1.8)	3 (10.7)	0.07
Factor V leiden	2 (2.4)	2 (3.6)	0 (0.0)	0.31
Antiphospholipid syndrome	1 (1.2)	1 (1.8)	0 (0.0)	0.47
Lupus anticoagulation	4 (4.8)	3 (5.4)	1 (3.6)	0.71
SVC/IVC thrombosis	1 (1.2)	1 (1.8)	0 (0.0)	0.47
D-dimer (*n*=60)				
Positive (>0.55 mg/L), *n* (%)	54 (90.0)	37 (88.1)	17 (94.4)	0.45 for all
Negative, *n* (%)	6 (10.0)	5 (11.9)	1 (5.6)	
D-Dimer (mg/L FEU), median	8.4 (0.2-1470)	11.4 (0.2-1470)	5.6 (0.3-36.1)	0.30
Echocardiography, *n* (%)	35 (41.7)	20 (35.7)	15 (53.6)	0.11
Ejection fraction (%), mean±SD	54.6±8.4	55.7±6.6	53.2±10.4	0.39
RV wall hypokinesis, *n* (%)	3 (8.1)	2 (10.0)	1 (5.9)	0.64
Pulmonary arteries dilation, *n* (%)	5 (13.5)	4 (20.0)	1 (5.9)	0.21
Routine laboratory, mean±SD				
WBC count	10.1±4.9	9.7±4.2	10.9±6.1	0.28
Hemoglobin	12.3±2.3	12.7±2.2	11.4±2.3	0.01
Platelet count	300±177	268±97.4	363±266	0.02
Hematocrit	36.9±7.4	38.3±6.5	34.1±8.3	0.01

SVC/IVC: Superior vena cava/inferior vena cava, DVT: Deep-vein thrombosis, PE: Pulmonary embolism, RV: Right ventricular, WBC: White blood cell, SD: Standard deviation

Table 3: Management and outcome of trauma patients presented with deep-vein thrombosis versus pulmonary embolism

	Overall (*n*=84), *n* (%)	DVT (*n*=56), *n* (%)	PE (*n*=28), *n* (%)	*P*
Treatment				
Warfarin	66 (78.6)	45 (80.4)	21 (75.0)	0.57
Enoxaparin	64 (76.2)	45 (80.4)	19 (67.9)	0.20
Dalteparin	33 (39.3)	18 (32.1)	15 (53.6)	0.05
Heparin	19 (22.6)	6 (10.7)	13 (46.4)	0.001
Aspirin	26 (31.0)	17 (30.4)	9 (32.1)	0.86
Plavix	8 (9.5)	6 (10.7)	2 (7.1)	0.59
Thrombolytic therapy	4 (4.8)	2 (3.6)	2 (7.1)	0.46
Warfarin treatment for <2 years	49 (58.3)	32 (57.1)	17 (60.7)	0.75
Warfarin for life	10 (11.9)	9 (16.1)	1 (3.6)	0.09
Hospital length of stay (days)	7.5 (1-270)	7 (2-270)	14 (1-240)	0.15
Postthrombotic syndrome				
Calf pain	62 (73.8)	48 (85.7)	14 (50.0)	0.001
Leg edema	49 (58.3)	37 (66.1)	12 (42.9)	0.04
Leg ulcer	4 (4.8)	4 (7.1)	0 (0.0)	0.14
Mortality	7 (8.3)	5 (8.9)	2 (7.1)	0.78

DVT: Deep-vein thrombosis, PE: Pulmonary embolism

predisposing factors, and treatment.[5,10] A Japanese study reported a VTE incidence of 19% in patients with pelvic and/or lower extremity fractures.[11] The frequency of VTE in our trauma population was 1.9%, which is in agreement with earlier reports.[5] This could also be explained by the fact that VTE incidence may be affected by diagnostic accuracy or screening patterns and the method of data collection.[12] In our cohort, only 30% of PE cases had a prior history of DVT diagnosed by lower-limb Doppler ultrasonography. This is consistent with the current guidance that routine screening may miss pelvic thrombi or upper-extremity DVT.[13] Worldwide, the victims of traumatic injuries are usually young individuals with male predominance.[14] Consistent with these observations, the average age of our patients was relatively young (46 years) and more than 50% were male.

The present study shows a frequent diagnosis of PE among hospitalized trauma patients and DVT at outpatient clinics. Our

findings are consistent with earlier reports which suggested that hospitalized patients, especially those who required major orthopedic or trauma surgery, had increased risk of developing PE. This is possibly due to prolonged immobilization, vascular injuries after surgery, elevation of thromboplastin agents, and hypercoagulability.[15,16] An earlier study from our center reported that the majority of DVT patients were diagnosed at outpatient clinics.[9]

The identification of associated risk factors for VTE in trauma patients is important for early diagnosis and management. The predisposing factors for VTE in our population are similar to those reported in the current literature. In particular, there is a significant association between the presence of a surgical event during the hospital admission, bedridden status, and prior PE, with subsequent development of PE after a traumatic event, as compared with DVT.

Notably, obesity, hypertension, diabetes mellitus, and hypercholesterolemia were frequent comorbidities associated with an increased predilection to VTE. In line with our findings, earlier studies have demonstrated a strong association with the development of PE and the frequency and magnitude of surgical interventions, recurrent VTE, hospital length of stay, cardiovascular diseases, and obesity.[17] Patients with anatomical distortion of the femoral vein due to posterior dislocation of the hip are particularly prone to developing VTE.[18] Considering the various risk factors and associated comorbidities, there is an increasing interest in considering early screening tools and the use of VTE prophylaxis in high-risk trauma patients.[19]

In our cohort, there was a nonsignificantly higher risk of developing PE in patients requiring neck vein central line placement. This is consistent with a high incidence of upper-limb DVTs found in other series of trauma patients.[20] Unfortunately, upper-limb DVT screening was not routine clinical practice in our institution during the period of study. Other authors have found an association between femoral catheters and the development of VTE.[21] This difference may reflect variations in the clinical practice when it comes to the selection of site for central venous access.

Interestingly, congestive heart failure was found significantly associated with the occurrence of PE in trauma patients. Gudipati *et al.*[17] conducted a cohort study of the incidence of PE in patients with acute trauma or who underwent elective orthopedic procedures. The authors reported cardiovascular disease, hypertension, and obesity as frequent risk factors for PE. Another study reported congestive heart failure, chronic pulmonary disease, and the presence of a neurological disorder as independent factors associated with poor outcome in VTE patients.[22] This could be attributed to hemodynamic instability in such patients.

Hereditary thrombophilia such as deficiency of protein C, protein S, and thrombin III has been proposed to be significant predisposing factors for VTE posttrauma.[2,23] A recent study by Cannon *et al*., however, reported no significant association between Factor V Leiden and prothrombin G20210A mutation, with the risk of VTE in trauma patients.[24] The present study identified a significant association between protein S deficiency and the development of PE. Identifying high-risk VTE families through screening could be a good strategy in trauma victims and may lead to more stringent thromboprophylaxis attempts.

Trauma itself is an established risk factor for provoked VTE, which makes the pretest probability of VTE high. The JCS Joint working group suggested a high negative predictive value of D-dimer for the development of acute PE.[25] However, a negative D-dimer result, particularly in suspected traumatic DVT patients, should not be used to rule out the diagnosis. In the current study, the median D-dimer value in patients with DVT was found to be higher than those with PE, but the rate of positive D-dimer result did not differ significantly between the groups. This suggests that D-dimer is not an accurate prognostic indicator of PE.[26] An earlier study evaluating suspected VTE in major trauma patients demonstrated moderate accuracy of D-dimer levels for predicting VTE after 10 days of ICU admission (AUROC of 0.785 (95% CI, 0.704-0.866; $P < 0.001$).[5] A further study reported on the implications of D-dimer testing to rule out VTE (100% negative predictive value) in severely injured patients. The authors observed a limited value of D-dimer before 48 h postinjury due to a high false-positive rate.[27] A negative D-dimer might thus have diagnostic potential to rule out PE and DVT in cases with negative CT and ultrasound findings, respectively.

It is interesting that the therapeutic approach to PE management in our patients included the use of unfractionated heparin (UFH) in almost 50% of cases. This probably reflects concerns about the reversal of bleeding in trauma victims. Although UFH poses a higher risk of heparin-induced thrombocytopenia, the inability to reverse LMWH quickly is considered by some to pose a greater risk. A prospective study from Tunisia showed that anticoagulant therapy was mainly used to treat PE in trauma patients, and the majority received UFH (93.1%).[28]

In contrast, a recent study by Khan *et al*. suggests that spinal trauma patients (considered a high-risk cohort) could be safely administered LMWH early posttrauma.[29] Current international guidelines recommend the use of LMWH therapy as a first-line treatment for VTE.[13] The management approach of acute PE over the past two decades has progressed from UFH to LMWH in many centers.

The use of anti-Xa assay (to measure plasma heparin; UFH and LMWH)-guided thromboprophylaxis is promising for reducing VTE occurrence in trauma patients.[30] Future studies of anti-Xa-directed therapy (as opposed to prophylaxis) may provide evidence for reassurance in terms of bleeding risk.

VTE-related complications and recurrence serve as good markers of morbidity. Considering this, more than 40% of our patients with VTE developed leg edema and over half of

them (regardless of confirmed presence of lower-limb DVT) complained of calf pain. Previous studies reported similar frequencies of postthrombotic syndrome (25%–50%) in DVT patients on clinical follow-up.[9,31] In the current study, 22 patients had recurrent DVT and 2 patients had recurrent PE. Consistent with our findings, an earlier meta-analysis demonstrated that the rate of recurrent DVT was higher than that of recurrent PE.[32]

The overall mortality rate in our cohort was 8.3%, and patients with either DVT or PE have similar death rates. Earlier studies have suggested a higher rate of mortality (18.7%) in trauma patients who developed VTE due to the detrimental impact of PE.[33] Similar estimates are shown by other studies.[34,35] In contrast, in treated PE patients, the 90-day mortality rate was found to be 0.5% in trauma patients not requiring surgical intervention.[36]

It remains unclear whether trauma itself is a specific predictor of a higher mortality in VTE or whether the VTE contributes to the cause of death in trauma victims; only three patients had echocardiographic evidence of RV dysfunction in our cohort. The similar rates of mortality in our DVT and PE patients support the notion that patients may not die from the underlying VTE but rather due to the severity of the injury and its associated complications.

There are certain limitations of the present study owing to the retrospective design. The incidence of trauma-associated VTE is lower in our series than reported in some series. This may be attributed to the widely different methods used in the previous literature in terms of capturing data. Furthermore, there are chances of underrepresentation of the disease burden, as a proportion of patients may have been diagnosed with VTE after discharge from the trauma service or may have presented later to ED as a clinical emergency. We lack information on the pattern, timing, severity of the injury, and the duration between trauma and occurrence of VTE, which could possibly have revealed more insight in terms of onset and presentation. We do not use specific risk-assessment tools in our practice, as these have at present not been validated in trauma patients. Notably, LMWH prophylaxis is ubiquitously used in our institution; still, the timing of, and compliance with prophylactic treatment is missing. It is possible that the lack of compliance with mechanical and chemoprophylaxis measures could have resulted in a higher incidence of trauma-related VTE than we would find today.

Conclusion

The coagulation profile plays an important role in posttrauma thromboembolism. A thorough assessment of the presence of thromboembolic events is warranted to avoid missing cases in trauma patients. D-dimer testing is promising for ruling out VTE in trauma patients. LMWH can be safely used in many patients with trauma-related VTE. The development of robust bleeding risk scores for trauma patients is warranted to guide the optimum anticoagulant therapy to treat VTE. Directed screening and interventions may be of benefit in selected trauma patients. Future studies should investigate PE and DVT as distinct entities with specific risk factors to aid the understanding and management of trauma-related VTE.

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Conflicts of interest

There are no conflicts of interest.

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