

# The association of timing of pharmacological prophylaxis and venous thromboembolism in patients with moderate-to-severe traumatic brain injury: A retrospective cohort study

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## Abstract:

**OBJECTIVES:** Patients with traumatic brain injury (TBI) have an increased risk for venous thromboembolism (VTE). The current guidelines recommend pharmacologic prophylaxis, but its timing remains unclear.

**METHODS:** In this retrospective cohort study, patients with moderate-to-severe TBI admitted to a tertiary care intensive care unit between 2016 and 2019 were categorized into two groups according to the timing of pharmacologic prophylaxis: early if prophylaxis was given within 72 h from hospital admission and late if after 72 h.

**RESULTS:** Of the 322 patients in the cohort, 46 (14.3%) did not receive pharmacological prophylaxis, mainly due to early brain death; 152 (47.2%) received early pharmacologic prophylaxis and 124 (38.5%) received late prophylaxis. Predictors of late pharmacologic prophylaxis were lower body mass index, intracerebral hemorrhage (odds ratio [OR], 3.361; 95% confidence interval [CI], 1.269–8.904), hemorrhagic contusion (OR, 3.469; 95% CI, 1.039–11.576), and lower platelet count. VTE was diagnosed in 43 patients on a median of 10 days after trauma (Q1, Q3: 5, 15); 6.6% of the early prophylaxis group and 26.6% of the late group ( $P < 0.001$ ). On multivariable logistic regression analysis, the predictors of VTE were Acute Physiology and Chronic Health Evaluation II score, subarachnoid hemorrhage, and late versus early pharmacologic prophylaxis (OR, 3.858; 95% CI, 1.687–8.825). The late prophylaxis group had higher rate of tracheostomy, longer duration of mechanical ventilation and stay in the hospital, lower discharge Glasgow coma scale, but similar survival, compared with the early group.

**CONCLUSIONS:** Late prophylaxis (>72 h) was associated with higher VTE rate in patients with moderate-to-severe TBI, but not with higher mortality.

## Keywords:

Heparin, thromboprophylaxis, traumatic brain injury, venous thromboembolism

Patients with traumatic brain injury (TBI) have an increased risk for the development of venous thromboembolism (VTE), encompassing pulmonary embolism (PE)

and deep vein thrombosis (DVT).<sup>[1-3]</sup> This is due to multiple factors that include associated injuries such as lower extremity fractures, lack of mobilization, and presence

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of a hypercoagulable state, related to TBI-mediated release of tissue factor from the brain, which activates the extrinsic pathway of coagulation.<sup>[2-4]</sup> The VTE rate ranges between 5% and 10% if VTE prophylaxis is provided and between 11% and 30% if prophylaxis is not given.<sup>[5]</sup> The Brain Trauma Foundation guidelines suggest a combination of mechanical and pharmacological prophylaxis, using either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH), in severe TBI with level III supporting evidence.<sup>[6]</sup> Mechanical prophylaxis is widely used as it is associated with a lower risk of bleeding and is easy to use.<sup>[3,7]</sup> Even though pharmacologic prophylaxis is thought to be more effective for VTE prevention, its use is often delayed in these patients beyond 72 h due to concerns of increased risk of intracranial hemorrhage.<sup>[3,5,8,9]</sup> However, VTE can occur early after TBI. A study of 603 patients with moderate-to-severe TBI who had screening by lower limb ultrasound twice-weekly found that the median time to DVT diagnosis was 6 days (interquartile range, 2–11) and to PE diagnosis was 6.5 days (interquartile range, 2–16.5).<sup>[3]</sup>

The current evidence on the timing of initiating pharmacologic VTE prophylaxis for patients with TBI is limited and controversial. A 2013 systematic review found insufficient evidence to comment on the effectiveness of chemoprophylaxis for DVT started < 72 h versus > 72 h as included studies showed conflicting results.<sup>[10]</sup> A 2015 review found that the rate of DVT was 2.6% when chemoprophylaxis was started on days 1–3, 2.2% when started on days 4 or 5, and 14.1% when started on day 8.<sup>[11]</sup> The study concluded that chemoprophylaxis should not be given within 3 days of injury if intracranial hemorrhage was moderate or high risk for expansion, was reasonable when low-risk patients had not developed expansion of intracranial hemorrhage within 48 h of injury and was acceptable after day 3 when low-risk patients develop an expansion of intracranial hemorrhage within 48 h postinjury.<sup>[11]</sup> A more recent large retrospective study of 2468 TBI patients found that early (<72 h) versus late prophylaxis was associated with lower VTE on adjusted multivariable logistic regression analysis.<sup>[12]</sup> The current Brain Trauma Foundation guidelines do not specify the optimal pharmacologic prophylaxis timing but suggest its use when the brain injury is stable and the benefit outweighs the bleeding risk.<sup>[6]</sup> On the other hand, the Neurocritical Care Society recommends initiating LMWH or UFH for VTE prophylaxis within 24–48 h of presentation in patients with TBI and intracranial hemorrhage.<sup>[13]</sup> This leads to variability in the clinical practice of VTE prophylaxis in TBI patients.<sup>[14]</sup>

VTE during hospitalization is a preventable adverse event. It is associated with increased cost, morbidity, and

mortality.<sup>[15-17]</sup> Data on the importance of pharmacologic prophylaxis timing in patients of TBI are relatively scarce. The main objective of this study was to identify the association of the timing of VTE pharmacologic prophylaxis with VTE events in patients with moderate-to-severe TBI.

## Methods

### Study design, patients, and settings

This was a retrospective cohort study conducted in the adult intensive care units (ICUs) of King Abdulaziz Medical City, 1000-bed tertiary care and level I trauma center in Riyadh, Saudi Arabia. The units were staffed with onsite consultants, staff physicians or fellows, and rotating residents 24 h per day, 7 days per week. The study subjects were patients with moderate-to-severe TBI admitted between February 1, 2016, and December 31, 2019. Head injury severity was defined according to the best postresuscitation preintubation Glasgow coma scale (GCS). Severe TBI is being defined as a GCS of <9, and moderate TBI is being defined as a GCS of 9–12. We excluded patients aged <14 years, had VTE within 6 months before admission, used systemic anticoagulation for reasons other than VTE during ICU admission, or were transferred from other hospitals. Severe TBI patients were usually managed with standardized evidence-based Head Injury Protocol.<sup>[18]</sup> Mechanical prophylaxis using pneumatic compression devices was usually implemented on ICU admission. The timing of pharmacological VTE prophylaxis was usually decided by the ICU team after discussion with the trauma and neurosurgery teams. This study was approved by the Institutional Review Board of the Ministry of National Guard Health Affairs.

### Data collection

The collected data included demographics, comorbidities, Acute Physiology and Chronic Health Evaluation (APACHE) II<sup>[19]</sup> and Injury Index Scale at admission,<sup>[20]</sup> admission GCS, description of TBI based on computed tomography (CT) findings, details of other injuries, presence of active bleeding, use of invasive mechanical ventilation, central venous catheter, and vasopressors, TBI management including craniotomy, intracranial pressure monitoring, and the hospital Head Injury Protocol, and details of VTE prophylaxis (type and timing). The primary outcome was the occurrence of VTE during the hospital stay. The diagnosis of VTE was made based on clinical suspicion of the treating team. Other studied outcomes were tracheostomy, length of ICU and hospital stay, discharge, ICU and hospital mortality, and GCS discharge for hospital survivors.

### Statistical analysis

Statistical analysis was performed using SPSS version 15 (SPSS Inc., Chicago, IL, USA). Frequencies

and percentages were used to describe categorical variables, while means and standard deviations or medians with the first and third quartiles were used to describe continuous variables. Chi-square test or Fisher's exact test was used to compare the categorical variables of patients who developed VTE and those who did not. Student's *t*-test was used to compare the continuous variables between the two groups. As it is recommended to consider pharmacologic prophylaxis in patients with significant TBI within 72 h,<sup>[21]</sup> we categorized patients into two groups: early pharmacologic prophylaxis if a heparin was ordered and administered within 72 h from hospital admission and late if heparin was ordered after 72 h.

Multivariable logistic regression analysis was performed to assess the predictors of early ( $\leq 72$  h) versus late ( $>72$  h) pharmacologic prophylaxis. The variables with  $P < 0.2$  between the two groups were entered in the model and were body mass index (BMI), APACHE II score, intracerebral hemorrhage or hemorrhagic contusion, subdural hematoma, subarachnoid hemorrhage, abdomen/pelvis injury, bone fracture, presence of active bleeding on admission, use of vasopressors, use of Head Injury Protocol, and platelet count. It was also performed to assess the predictors of VTE. The variables with  $P < 0.2$  between the patients who were diagnosed to have VTE and those who did not were entered in the model and were age, admission GCS, active bleeding on admission, intracerebral hemorrhage or contusion, subarachnoid hemorrhage, subdural hematoma, early versus late pharmacologic prophylaxis, platelet count, red blood cell and fresh frozen plasma transfusion, and use of Head Injury Protocol. The results would be presented as an odds ratio (OR) with a 95% confidence interval (CI). A two-sided  $P < 0.05$  was considered statistically significant.

## Results

### Baseline characteristics

The study cohort consisted of 322 patients. The mean age was  $31.3 \pm 12.6$  years, and the admission GCS was  $6.0 \pm 2.9$ . All patients required mechanical ventilation. The most common TBI was intracerebral hemorrhage/hemorrhagic contusions (80.4%). Most patients had other associated injuries, with only 76 (23.6%) having isolated head injury. Craniotomy was performed in 68 (21.1%) patients, and most (70.9%) were managed with our Head Injury Protocol.

### Practices of thromboprophylaxis

The vast majority (87%) of the patients received mechanical prophylaxis after ICU admission, mostly in the form of pneumatic compression devices, as only 2% received elastic stockings. Of the 322 patients,

46 (14.3%) did not receive pharmacological prophylaxis during the ICU stay (20 patients with severe injuries and significant active bleeding and 18 with early brain death). The median time between presentation and starting pharmacologic prophylaxis was 64.5 h (Q1, Q3: 38, 108 h); 152 (47.2%) received early pharmacologic prophylaxis and 124 (38.5%) received late prophylaxis. Figure 1 shows which day pharmacologic prophylaxis was started after hospital admission. Almost one-third of the patients received pharmacologic prophylaxis within the first 48 h and 55.1% within 72 h. Approximately 10% of the patients received pharmacologic prophylaxis after 7 days.

Table 1 shows the baseline characteristics of the patients in the cohort. Late prophylaxis was associated with lower BMI and platelet count, higher prevalence of active bleeding, bone fracture injuries, and subarachnoid hemorrhage on admission, and more use of Head Injury Protocol. There was no significant relationship between the increase of hemorrhage on brain CT and early versus late pharmacologic prophylaxis ( $P = 0.13$ ). UFH was more commonly used than LMWH for pharmacologic prophylaxis, more particularly in the late prophylaxis group (65.8% of early prophylaxis and 77.4% of late prophylaxis,  $P = 0.03$ ). The timing of prophylaxis was  $39.6 \pm 20.2$  h for the early group and  $143.5 \pm 107.1$  h for the late group ( $P = 0.01$ ). Retrievable vena cava filters were inserted in 30 patients on a median of 5 days (Q1, Q3: 3, 13) from admission and were more frequently used in the late group (16.9 vs. 6.0%,  $P = 0.004$ ).

On multivariable logistic regression analysis, the predictors of late pharmacologic prophylaxis were BMI (OR per unit increment, 0.928; 95% CI, 0.877–0.982), bone fracture (OR, 2.616; 95% CI, 1.179–5.803), intracerebral hemorrhage versus none (OR, 3.361; 95% CI, 1.269–8.904), hemorrhagic contusion (OR, 3.469; 95% CI, 1.039–11.576), combination of intracerebral hemorrhage and contusions (OR, 3.469; 95% CI, 1.039–11.576), and platelet count (OR per  $10^9/L$ , 0.996; 95% CI, 0.992–0.999).

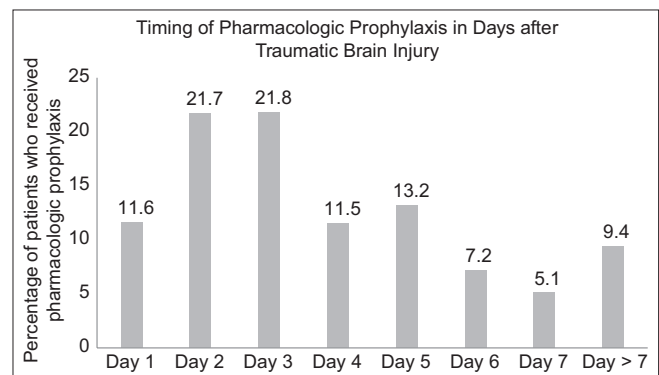


Figure 1: Timing of pharmacologic prophylaxis after hospital admission

**Table 1: Characteristics of the three groups of the study cohort (no pharmacologic prophylaxis and early and late pharmacologic prophylaxis)**

	No prophylaxis (n=46)	Early prophylaxis (n=152)	Late prophylaxis (n=124)	P*
Age (years), mean±SD	27.1±7.5	31.5±13.2	32.7±13.1	0.44
Male gender, n (%)	43 (93.5)	144 (94.7)	119 (96.0)	0.63
BMI (kg/m <sup>2</sup> ), mean±SD	25.9±7.1	24.3±5.5	22.7±4.8	0.01
Previous VTE, n (%)	0	0	0	
GCS on admission, mean±SD	4.5±2.6	6.4±2.9	6.2±2.8	0.56
GCS<9, n (%)	41 (89.1)	118 (77.6)	103 (83.1)	0.26
APACHE II score, mean±SD	17.6±12.1	17.9±2.3	18.3±2.5	0.10
Injury severity score, mean±SD	30.7±8.0	28.8±7.6	28.5±7.1	0.75
Requirement for mechanical ventilation, n (%)	46 (100)	152 (100)	124 (100)	
Vasopressor use, n (%)	43 (93.5)	126 (82.9)	111 (90.2)	0.08
Active bleeding on admission, n (%)	30 (65.2)	74 (49.0)	76 (61.8)	0.03
Isolated TBI, n (%)	9 (19.6)	42 (27.6)	25 (20.2)	0.15
Associated injuries, n (%)				
Chest injury	10 (27.7)	25 (16.4)	22 (17.7)	0.78
Abdomen or pelvis injury	4 (8.7)	12 (7.9)	16 (12.9)	0.17
Vascular injury	5 (10.9)	13 (8.6)	12 (9.7)	0.75
Bone fracture injury	19 (41.3)	32 (21.1)	43 (34.7)	0.01
Type of TBI on brain CT imaging, n (%)				
Epidural hemorrhage	5 (10.9)	13 (8.6)	16 (12.9)	0.24
Subdural hemorrhage	23 (50.0)	49 (32.2)	54 (43.5)	0.05
Subarachnoid hemorrhage	27 (58.7)	44 (28.9)	51 (41.1)	0.03
Intracerebral hemorrhage/hemorrhagic contusion	39 (84.8)	107 (70.4)	113 (91.1)	0.17
Increase in hemorrhage on repeated brain CT within 3 days, n (%)**	10 (28.6)	49 (33.8)	51 (42.9)	0.13
Laboratory findings on admission				
Creatinine µmol/L, mean±SD	104.3±101.8	90.5±63.4	86.9±22.6	0.55
Admission hemoglobin g/L, mean±SD	137±28	142±23	138±25	0.25
Admission platelets×10 <sup>9</sup> /L, mean±SD	249±87	289±84	258±78	0.002
PTT in seconds, mean±SD	30.9±6.3	29.1±3.6	28.8±4.6	0.52
INR, mean±SD	1.2±0.1	1.2±0.3	1.2±0.3	0.91
Interventions				
Tranexamic acid in the emergency department, n (%)	22 (52.2)	33 (21.7)	31 (25.4)	0.47
Blood transfusion, n (%)				
Red blood cells	24 (52.2)	53 (34.9)	63 (50.8)	0.08
Platelets	8 (17.4)	23 (15.1)	21 (16.9)	0.68
Fresh frozen plasma	11 (23.9)	27 (17.8)	24 (19.4)	0.74
Insertion of central venous line, n (%)	35 (76.1)	129 (84.9)	116 (93.5)	0.02
Internal jugular	17 (37.0)	82 (53.9)	60 (48.4)	0.36
Subclavian	10 (21.7)	27 (17.8)	31 (25.0)	0.14
Femoral	26 (56.5)	102 (67.1)	84 (67.7)	0.91
Head injury protocol, n (%)	34/44 (77.3)	97/152 (63.8)	105/123 (85.4)	<0.001
ICP monitoring, n (%)	10 (22.2)	20 (14.0)	29 (26.1)	0.02
Craniotomy, n (%)	13 (28.3)	24 (15.8)	31 (25.0)	0.06
Pharmacological prophylaxis timing (h), mean±SD	-	39.6±20.2	143.5±107.1	<0.001

\*For the difference between the early prophylaxis and late prophylaxis groups. \*\*CT scan was not repeated within 3 days in 28 patients in the early prophylaxis group and 7 patients in the late prophylaxis group. Early prophylaxis was defined as receiving pharmacologic prophylaxis within 72 h from hospital admission. APACHE=Acute physiology and chronic health evaluation, CT=Computed tomography, GCS=Glasgow Coma Scale, ICP=Intracranial pressure, INR=International normalized ratio, PTT=Partial thromboplastin time, SD=Standard deviation, VTE=Venous thromboembolism, TBI=Traumatic brain injury, BMI=Body mass index

### Venous thromboembolism and other outcomes

Limb Doppler ultrasound was performed for 125 (38.8%) patients and spiral chest CT for 29 (9%). VTE was diagnosed in 15.6% of the patients who received pharmacologic prophylaxis on a median of 10 days after trauma (Q1, Q3: 5, 15); 10 (6.6%) patients were in the

early prophylaxis group and 33 (26.6%) patients in the late group ( $P < 0.001$ ) [Table 2]. A vast majority (88.3%) of VTE cases were DVTs; 22 patients had lower limb DVT and 20 patients had upper limb DVT. For the eight PE cases, two involved the main pulmonary artery, one was lobar, four segmental, and one subsegmental.



**Table 2: Outcomes of the three groups of the study cohort (no pharmacologic prophylaxis and early and late pharmacologic prophylaxis)**

Variables	No prophylaxis (n=46)	Early prophylaxis (n=152)	Late prophylaxis (n=124)	P*
Any VTE, n (%)	3 (6.5)	10 (6.6)	33 (26.6)	<0.001
Deep vein thrombosis, n (%)	3 (6.5)	10 (6.6)	28 (22.6)	<0.001
Pulmonary embolism, n (%)	0	1 (0.7)	6 (4.8)	0.03
Tracheostomy, n (%)	2 (4.5)	29/143 (20.3)	55/119 (46.2)	<0.001
MV duration (days), mean±SD	7.6±4.0	9.9±6.4	12.9±8.0	0.001
ICU LOS (days), mean±SD	17.8±32.1	20.2±31.1	23.9±38.5	0.39
Hospital LOS (days), mean±SD	27.2 56.7	57.6±76.2	87.3 13±0.7	0.03
ICU Mortality, n (%)	38 (82.6)	14 (9.2)	11 (8.9)	0.92
Hospital mortality, n (%)	38 (82.6)	14 (9.2)	11 (8.9)	0.92
GCS at discharge for survivors, mean±SD	5.9±5.0	13.6±2.8	12.7±3.2	0.04

\*For the difference between the early prophylaxis and late prophylaxis groups. Early prophylaxis was defined as receiving pharmacologic prophylaxis within 72 h from hospital admission. GCS=Glasgow coma scale, ICU=Intensive care unit, LOS=Length of stay, MV=Mechanical ventilation, VTE=Venous thromboembolism, SD=Standard deviation

VTE was also more common with the following variables on univariate analysis: intracerebral hemorrhage (13.9%), hemorrhagic contusion (13.8%), combined intracerebral hemorrhage and hemorrhagic contusion (24.1%;  $P = 0.048$  in between the groups), presence of injuries beside TBI (18.2% vs. 7.5% for isolated TBI,  $P = 0.04$ ), and use of head injury protocol (18.8% vs. 6.8% for other patients,  $P = 0.02$ ). Severe versus moderate TBI, use of tranexamic acid on admission, central venous catheter in the femoral vein, and unfractionated versus LMWH were not associated with VTE. On multivariable logistic regression analysis, the predictors of VTE were APACHE II score (OR per unit increment, 1.210; 95% CI, 1.018–1.437), subarachnoid hemorrhage (OR, 2.282; 95% CI, 1.037–5.022), and late versus early pharmacologic prophylaxis (OR, 3.858; 95% CI, 1.687–8.825).

The late prophylaxis group had higher rate of tracheostomy, longer duration of mechanical ventilation and stay in the hospital, and lower GCS at hospital discharge [Table 2]. The mortality rates were similar in the early and late prophylaxis groups. Similarly, the patients who developed VTE had more tracheostomy and longer duration of mechanical ventilation and stay in the hospital [Table 3]. VTE was not associated with hospital mortality (APACHE II-adjusted OR, 1.695; 95% CI, 0.453–6.341;  $P = 0.43$ ).

## Discussion

The main findings of this study were that pharmacologic prophylaxis was frequently given after 72 h from presentation in patients with moderate-to-severe TBI; late prophylaxis >72 h was associated with a higher rate of VTE, longer duration of mechanical ventilation but similar mortality compared with early prophylaxis; and the mortality of patients who were diagnosed to have VTE was similar to that of those who were not.

TBI is associated with increased VTE risk. Guidelines recommend the application of mechanical prophylaxis as soon as possible in TBI patients.<sup>[6,13]</sup> Pneumatic compression devices seem to be more effective than elastic stockings.<sup>[22,23]</sup> In the current study, 87% of the patients received pneumatic compression device and only 2% elastic stockings. Lower extremity fractures or injuries may prevent the application of mechanical prophylaxis. Pharmacologic prophylaxis is also recommended in TBI patients, especially if bleeding is not ongoing.<sup>[6,13]</sup> However, high-quality evidence is lacking. A trial randomized 62 patients with small TBI patterns and stable brain CT scans at 24 h after injury to receive enoxaparin 30 mg bid or placebo 24 to 96 h after injury.<sup>[24]</sup> The rates of radiographic progression of TBI on CT scans performed 24 h after the start of treatment were 5.9% (95% CI, 0.7%–19.7%) for enoxaparin and 3.6% (95% CI, 0.1%–18.3%) for placebo.<sup>[24]</sup> In an observational study where 49.5% of 812 TBI patients received pharmacologic prophylaxis, lower VTE risk was found in the pharmacologic prophylaxis group (risk ratio, 0.194; 95% CI, 0.049–0.760).<sup>[25]</sup>

The lack of clear recommendations on the timing of pharmacologic prophylaxis in TBI leads to inconsistent and variable prophylaxis practices. Pharmacologic prophylaxis is often delayed due to the feared complication of increasing intracranial hemorrhage. In a survey of 391 members of the Eastern Association for the Surgery of Trauma, a significant variation in VTE prophylaxis practices in TBI was observed with 50% of respondents reporting that their practice was conservative.<sup>[14]</sup> A *post hoc* analysis of the erythropoietin in TBI trial (603 patients) found that pharmacological prophylaxis was given in 5% of patients on day 1, 30% of patients on day 3, and 57% of patients on day 7.<sup>[3]</sup> In the current study, we found that the median time to receive pharmacologic prophylaxis from the presentation was 65 h, with less than one-third of patients receiving

**Table 3: Management and outcomes of patients who developed and did not develop venous thromboembolism**

	VTE (n=43)	No VTE (n=233)	P
Pharmacologic prophylaxis before VTE event, n (%)			
Unfractionated heparin	33 (76.7)	163 (70.1)	0.37
Low molecular weight heparin	10 (23.3)	70 (30.0)	
Pharmacological prophylaxis timing (h), mean±SD	140.1±158.9	76.4±65.67	0.01
Tracheostomy, n (%)	20/40 (48.7)	64/222 (28.8)	0.008
MV duration (days), mean±SD	17.7±10.6	10.0±5.8	<0.001
ICU LOS (days), mean±SD	27.1±37.1	21.1±34.1	0.29
Hospital (days), mean±SD	129.2±178.5	60.2±82.0	0.02
ICU mortality, n (%)	3 (7.0)	22 (9.4)	0.61
Hospital mortality, n (%)	3 (7.0)	22 (9.4)	0.61
GCS at discharge for survivors, mean±SD	13.5±2.2	13.1±3.1	0.52

Analysis was limited to the patients who received pharmacologic prophylaxis. GCS=Glasgow Coma Scale, ICU=Intensive care unit, LOS=Length of stay, MV=Mechanical ventilation, SD=Standard deviation, VTE=Venous thromboembolism

pharmacologic prophylaxis within 48 h. Factors associated with time to VTE were age (hazard ratio per year, 1.02; 95% CI, 1.01–1.03), patient weight, and TBI severity.<sup>[3]</sup> In our study, the absence of intracranial hemorrhage on admission brain CT was the only significant factor associated with early pharmacologic prophylaxis. There was a trend for late prophylaxis with the use of Head Injury Protocol, which is usually used in patients with severe TBI.

We found that VTE events were more common in patients with late pharmacologic prophylaxis, increasing the risk by almost fourfold on the multivariable logistic regression analysis. Studies that evaluated timings of pharmacologic prophylaxis showed conflicting results. One study found that TBI was independently associated with DVT, irrespective of the time of initiation of pharmacologic prophylaxis (<24 h, 24–48 h, and >48 h).<sup>[26]</sup> A review of literature from 2003 till 2012 found that the rates of DVT were similar (<3%) when pharmacologic prophylaxis was started on days 1–3 or on days 4 or 5.<sup>[11]</sup> The rate was significantly higher (14.1%) when started on day 8.<sup>[11]</sup> A more recent large retrospective study of 2468 TBI patients found that early (<72 h) versus late prophylaxis was associated with lower VTE (OR, 0.48; 95% CI, 0.25–0.91 for PE and OR, 0.51; 95% CI, 0.36–0.72 for DVT) on propensity score-adjusted multivariable logistic regression analysis.<sup>[12]</sup> In a before (no routine administration of chemoprophylaxis)–after (chemoprophylaxis with either 30 mg of enoxaparin twice daily or 5000 units of UFH 3 times a day initiated 24 h after a stable brain CT) study, DVT rate was 5.6% in the before versus 0% in the after group ( $P = 0.008$ ). PE occurred in 3.7% and 0.8%, respectively ( $P = 0.18$ ).<sup>[27]</sup> There was no difference in the progression of intracranial hemorrhage (2.8% vs. 0.7%;  $P = 0.33$ ).<sup>[27]</sup> Another study of 669 TBI patients found that early (<72 h) versus late pharmacologic

prophylaxis was associated with neither VTE nor progression of intracranial hemorrhage.<sup>[28]</sup>

Guidelines recommend either UFH or LMWH for VTE prophylaxis in TBI patients. A prospective observational study of 525 patients with TBI who received enoxaparin within 48 h after admission found a low rate (18 patients, 3.4%) of progression of intracranial hemorrhage with six patients (1.1%) having a change in treatment including three patients who required craniotomy.<sup>[29]</sup> In a retrospective study of 386 TBI patients who received pharmacologic prophylaxis, the UFH group had a significantly higher rate of PE than the LMWH group (4% vs. 0%,  $P < 0.05$ ) as well as a higher rate of expansion of intracranial hemorrhage.<sup>[30]</sup> However, the analysis was not adjusted for injury severity.<sup>[30]</sup> A recent retrospective study of 20,417 TBI patients, 49.1% receiving LMWH, and 50.9% UFH, found that LMWH was associated with VTE and mortality risk on multivariable logistic regression analysis, regardless of the timing of prophylaxis initiation.<sup>[31]</sup> UFH was more commonly used than LMWH in our study, likely because guidelines do not prefer one over the other.<sup>[6]</sup>

Placement of vena cava filters has been suggested to prevent PE in TBI patients.<sup>[32]</sup> A clinical trial randomized 240 severely injured patients who had a contraindication to receiving pharmacologic prophylaxis to early vena cava filter placement and found no difference in symptomatic PE incidence (13.9% in the vena cava filter group and 14.4% in the control group).<sup>[33]</sup> Among the patients who received prophylactic anticoagulation after 7 days of injury, the PE incidence was 0% in the vena cava filter group and 14.7% in the control group.<sup>[33]</sup> In our study, vena cava filters were more commonly used in the pharmacologic prophylaxis groups.

VTE may be associated with increased morbidity and mortality. In our study, late pharmacologic prophylaxis

and VTE were associated with a longer duration of mechanical ventilation. Acute PE may lead to hypoxia, which may delay the discontinuation of mechanical ventilation.

The findings of our study should be interpreted in the light of their strengths and limitations. The strengths include retrieving detailed data about injuries, thromboprophylaxis, and outcomes. The limitations include a small sample size, retrospective design, and being a single-center study. The findings may have been affected by unmeasured confounders. However, our findings are in line with other studies and address an important clinical practice that is frequently suboptimal.

## Conclusions

We found that pharmacologic prophylaxis was often delayed in patients with moderate-to-severe TBI, which was associated with an almost fourfold increase in VTE risk. Late prophylaxis was also associated with a longer duration of mechanical ventilation, but not with mortality.

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## Conflicts of interest

There are no conflicts of interest.

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