Early VTE prophylaxis in severe traumatic brain injury: A propensity score weighted EAST multicenter study

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BACKGROUND: Patients with traumatic brain injury (TBI) are at high risk of venous thromboembolism events (VTE). We hypothesized that early chemical VTE prophylaxis initiation (≤24 hours of a stable head CT) in severe TBI would reduce VTE without increasing risk of intracranial hemorrhage expansion (ICHE).

METHODS: A retrospective review of adult patients 18 years or older with isolated severe TBI (Abbreviated Injury Scale score, ≥ 3) who were admitted to 24 Level I and Level II trauma centers from January 1, 2014 to December 31 2020 was conducted. Patients were divided into those who did not receive any VTE prophylaxis (NO VTEP), who received VTE prophylaxis ≤24 hours after stable head CT (VTEP ≤24) and who received VTE prophylaxis >24 hours after stable head CT (VTEP>24). Primary outcomes were VTE and ICHE. Covariate balancing propensity score weighting was utilized to balance demographic and clinical characteristics across three groups. Weighted univariate logistic regression models were estimated for VTE and ICHE with patient group as predictor of interest.

RESULTS: Of 3,936 patients, 1,784 met inclusion criteria. Incidences of VTE was significantly higher in the VTEP>24 group, with higher incidences of DVT in the group. Higher incidences of ICHE were observed in the VTEP≤24 and VTEP>24 groups. After propensity score weighting, there was a higher risk of VTE in patients in VTEP >24 compared with those in VTEP≤24 (odds ratio, 1.51; 95% confidence interval, 0.69–3.30; $p = 0.307$), however was not significant. Although, the No VTEP group had decreased odds

Submitted: November 30, 2022, Revised: March 2, 2023, Accepted: March 17, 2023, Published online: April 5, 2023.

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This study will be presented as a podium presentation at the 36th Annual EAST Scientific Assembly on January 19, 2023 in Orlando, FL.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jtrauma.com).

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DOI: 10.1097/TA.0000000000003985

of having ICHE compared with VTEP≤24 (odds ratio, 0.75; 95% confidence interval, 0.55–1.02, $p = 0.070$), the result was not statistically significant.

CONCLUSION: In this large multi-center analysis, there were no significant differences in VTE based on timing of initiation of VTE prophylaxis. Patients who never received VTE prophylaxis had decreased odds of ICHE. Further evaluation of VTE prophylaxis in larger randomized studies will be necessary for definitive conclusions. (*J Trauma Acute Care Surg.* 2023;95: 94–104. Copyright © 2023 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Therapeutic Care Management; Level III.

KEY WORDS: VTE prophylaxis; VTE; TBI; intracranial hemorrhage expansion.

Traumatic brain injury (TBI) leads to 50,000 deaths and nearly 300,000 hospitalizations annually in the United States.[1,2] Patients with TBI are at especially high risk of venous thromboembolism events (VTE) due to physiologic hypercoagulability and prolonged immobility, and at times lack of pharmacological prophylaxis,[3,4] even with appropriate mechanical and pharmacological prophylaxis.[5] According to the American College of Surgeons Trauma Quality Improvement Program (ACS TQIP) guidelines, the timing of VTE prophylaxis initiation is best determined by the severity of TBI, which is defined by a combination of clinical and radiographic findings.[6] Despite the existing recommendations, there is great variability in practice patterns of VTE prescription.[7]

Lesions, such as subdural (SDH) and epidural hematomas (EDH) greater than 8 mm, intraparenchymal contusions (IPH) or intraventricular hemorrhages (IVH) greater than 2 cm, multiple contusions per lobe, and subarachnoid hemorrhages (SAH) increase the risk of intracranial hemorrhage expansion (ICHE).[6] Deciding when to initiate pharmacologic prophylaxis requires balancing the risk of ICHE with preventing VTE. Although guidelines have advocated for early VTE prophylaxis initiation, there is conflicting evidence on the definition of "early," especially in the severe TBI population. Most guidelines suggest initiating VTE prophylaxis within 24 hours to 72 hours of stable head CT.[6,8–12] The Western Trauma Association advocates initiation of enoxaparin within 72 hours of the time of injury.[10] The American Association for the Surgery of Trauma Committee on Trauma guidelines recommend initiating VTE prophylaxis within 72 hours for high risk patients, without signs of progression on repeat imaging.[12] However, there is a lack of high quality evidence to suggest whether "early" initiation affects VTE and ICHE outcomes.

Therefore, we hypothesized that early (≤24 hours of stable head CT) initiation of pharmacologic VTE prophylaxis in patients with isolated severe TBI decreased risks of VTE without increasing risks of ICHE compared with patients with later or no chemical VTE prophylaxis.

METHODS

Study Design

We conducted an Eastern Association for the Surgery of Trauma (EAST) sponsored multicenter retrospective cohort study of 24 adult Level I and Level II trauma centers. Data were collected for the period of January 1 2014, to December 31, 2020, using Research Electronic Data Capture (REDCap) electronic data capture tool. REDCap is a secure, web-based software platform designed to support data capture for research studies. Patients with severe TBI, defined by Abbreviated Injury Scale (AIS) head score ≥3, were separated into three cohorts: those who did not receive pharmacological VTE prophylaxis (NO VTEP), those who had chemical VTE prophylaxis initiated within 24 hours of stable head CT (VTEP ≤ 24) and those who had chemical VTE prophylaxis initiated after 24 hours of stable head CT (VTEP > 24). The primary outcomes were incidences of VTE and ICHE. Secondary outcomes were hospital length of stay (LOS), intensive care unit (ICU) LOS, mortality, and neurosurgical interventions after VTE prophylaxis initiation.

Additional data collected included demographics, comorbidities, injury characteristics, admission laboratories and vitals, time to head CT stability, VTE prophylaxis and ICHE, incidences of DVT/PE, ICU LOS, hospital LOS, ventilator days, complications (urinary tract infection [UTI], pneumonia, myocardial infarction [MI], unplanned return to the operating room, and ICU), neurosurgical interventions, such as intracranial pressure monitor (ICP)/external ventricular drain (EVD) placement, craniotomy and craniectomy, discharge disposition, and mortality.

We confirm that this study complies with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Supplemental Digital Content Table 1, http://links.lww.com/TA/C959).[13]

Definitions

Isolated TBI was defined as any patient with only an AIS head classified as intracranial hemorrhage (SDH, SAH, EDH, IPH, IVH, and diffuse axonal injury). The diagnosis of VTE was confirmed with a venogram, duplex venous ultrasound or CT angiogram of the chest as defined by the National Trauma Data Bank. Of note, none of the 24 centers involved in the study screened for DVT. Intracranial hemorrhage expansion is defined as an increase in size of the existing bleed or presence of a new ICH as dictated by a radiologist, which may or may not have resulted in a neurosurgical intervention. A stable CT head was defined as being the first CT demonstrating no interval change or an improvement in ICH.

Inclusion and Exclusion Criteria

Patients 18 years or older who had an isolated TBI with an AIS ≥ 3 were included in this study. Patients who were only on Aspirin 81 mg in the preinjury period were also included. Patients who were excluded were those with concomitant injuries to the torso (AIS > 0), injuries to extremity and face with AIS ≥ 3, pregnant patients, prisoners, patient records with missing data for outcome variables, patients on anticoagulation, antiplatelet medications or higher doses of Aspirin in the preinjury period, transfer from an outside hospital, and patients who died or were discharged within 48 hours of admission (Fig. 1).

TABLE 1. Demographic and Clinical Characteristics in Patients With Severe TBI Before and After Propensity Score Weighing (N = 1,784)

	Before Weighting				After Weighting (for ICHE Outcome)			
	No VTEP Initiated (n = 782)	VTEP ≤ 24 (n = 273)	VTEP > 24 (n = 729)	*p**	No VTEP Initiated (n = 782)	VTEP ≤ 24 (n = 273)	VTEP > 24 (n = 729)	*p**
Age**, Median (Q1, Q3)	70 (54, 83)	66 (47, 81)	62 (46, 78)	<0.001*	66 (50, 81)	65 (52, 81)	65 (50, 80)	0.982
Sex**, n (%) Female	290 (37.1%)	101 (37.0%)	267 (36.6%)	0.982	291.43 (37.3%)	102.02 (37.4%)	271.21 (37.2%)	0.999
Race**, n (%)								
African American	165 (21.1%)	51 (18.7%)	170 (23.3%)	0.457	173.39 (22.2%)	60.26 (22.1%)	161.14 (22.1%)	>0.999
White	532 (68.1%)	191 (70.0%)	473 (64.9%)		521.10 (66.6%)	182.28 (66.8%)	485.89 (66.7%)	
Hispanic	40 (5.1%)	10 (3.6%)	33 (4.5%)		34.51 (4.4%)	11.95 (4.4%)	32.08 (4.4%)	
Asian	19 (2.4%)	6 (2.2%)	16 (2.2%)		18.54 (2.4%)	6.56 (2.4%)	17.23 (2.4%)	
Other	26 (3.3%)	15 (5.5%)	37 (5.1%)		34.47 (4.4%)	11.94 (4.4%)	32.67 (4.5%)	
AIS Head**, n (%)								
3	301 (38.5%)	121 (44.3%)	313 (42.9%)	0.075	319.67 (40.9%)	111.85 (41.0%)	297.73 (40.8%)	>0.999
4	233 (29.8%)	88 (32.2%)	206 (28.3%)		233.79 (29.9%)	81.98 (30.0%)	217.30 (29.8%)	
5	248 (31.7%)	64 (23.4%)	210 (28.8%)		228.55 (29.2%)	79.17 (29.0%)	213.96 (29.4%)	
Comorbidities**								
HTN, n (%)	440 (56.3%)	132 (48.4%)	350 (48.0%)	0.003*	401.55 (51.3%)	140.43 (51.4%)	372.79 (51.1%)	0.995
CAD, n (%)	104 (13.3%)	41 (15.0%)	76 (10.4%)	0.085	98.48 (12.6%)	34.63 (12.7%)	91.75 (12.6%)	0.999
COPD, n (%)	61 (7.8%)	19 (7.0%)	50 (6.9%)	0.761	60.34 (7.7%)	21.19 (7.8%)	56.25 (7.7%)	>0.999
DM, n (%)	154 (19.7%)	59 (21.6%)	136 (18.7%)	0.572	157.13 (20.1%)	55.02 (20.2%)	146.71 (20.1%)	>0.999
CKD, n (%)	77 (9.9%)	14 (5.1%)	39 (5.4%)	0.001*	53.01 (6.8%)	18.36 (6.7%)	49.55 (6.8%)	0.999
Coagulopathy, n (%)	77 (9.9%)	7 (2.6%)	16 (2.2%)	<0.001*	40.16 (5.1%)	13.40 (4.9%)	36.78 (5.0%)	0.989
Liver disease, n (%)	48 (6.1%)	3 (1.1%)	28 (3.8%)	<0.001*	34.27 (4.4%)	11.77 (4.3%)	32.39 (4.4%)	0.996
Cancer, n (%)	69 (8.8%)	10 (3.7%)	35 (4.8%)	<0.001*	46.71 (6.0%)	16.29 (6.0%)	43.17 (5.9%)	0.999
Mechanism of Injury**, n (%)								
Blunt	755 (96.5%)	267 (97.8%)	696 (95.5%)	0.124	754.73 (96.5%)	264.02 (96.7%)	703.12 (96.4%)	>0.999
Penetrating	20 (2.6%)	4 (1.5%)	30 (4.1%)		22.56 (2.9%)	7.38 (2.7%)	21.50 (2.9%)	
Other	7 (0.9%)	2 (0.7%)	3 (0.4%)		4.71 (0.6%)	1.60 (0.6%)	4.38 (0.6%)	
Mechanism of blunt injury, n (%)								
Fall	622 (82.5%)	198 (74.4%)	493 (70.8%)	<0.001*	596.61 (79.0%)	190.72 (71.6%)	521.24 (74.0%)	0.124
MVC	48 (6.4%)	25 (9.4%)	51 (7.3%)		57.18 (7.6%)	25.61 (9.6%)	44.89 (6.4%)	
MCC	6 (0.8%)	6 (2.3%)	13 (1.9%)		8.65 (1.1%)	6.06 (2.3%)	11.44 (1.6%)	
Assault	24 (3.2%)	12 (4.5%)	44 (6.3%)		27.70 (3.7%)	14.75 (5.5%)	40.58 (5.8%)	
Auto vs. Peds	19 (2.5%)	9 (3.4%)	40 (5.8%)		25.18 (3.3%)	13.36 (5.0%)	34.26 (4.9%)	
Other	35 (4.6%)	16 (6.0%)	55 (7.9%)		40.25 (5.3%)	15.96 (6.0%)	52.24 (7.4%)	
Mechanism of penetrating injury, n (%)								
GSW	18 (90.0%)	3 (100.0%)	30 (100.0%)	0.249	20.15 (89.3%)	6.09 (86.3%)	21.50 (96.2%)	0.588
Other	2 (10.0%)	0 (0.0%)	0 (0.0%)		2.41 (10.7%)	0.97 (13.7%)	0.84 (3.8%)	
Discharge disposition, n (%)								
Home	364 (46.6%)	110 (40.3%)	246 (33.7%)	<0.001*	370.95 (47.4%)	101.04 (37.0%)	246.22 (33.8%)	<0.001*
SNF	141 (18.0%)	41 (15.0%)	122 (16.7%)	0.502	127.47 (16.3%)	39.23 (14.4%)	131.64 (18.1%)	0.347
Rehab	139 (17.8%)	83 (30.4%)	242 (33.2%)	<0.001*	136.37 (17.4%)	83.37 (30.5%)	231.07 (31.7%)	<0.001*
LTAC	21 (2.7%)	5 (1.8%)	34 (4.7%)	0.032	21.89 (2.8%)	5.64 (2.1%)	35.30 (4.8%)	0.036
AMA	4 (0.5%)	2 (0.7%)	12 (1.7%)	0.082	5.49 (0.7%)	4.50 (1.6%)	9.80 (1.3%)	0.322

Admission vitals**, median (Q1, Q3)								
Heart rate	83 (71, 96) (n = 759)	81 (70, 93) (n = 263)	85 (72, 98) (n = 721)	0.012*	83 (71, 96) (n = 759)	82 (72, 97) (n = 263)	84 (71, 97) (n = 721)	0.999
SBP	146 (130, 166) (n = 760)	146 (130, 164) (n = 260)	143 (128, 160) (n = 725)	0.122	145 (130, 165) (n = 760)	144 (130, 166) (n = 260)	145 (130, 162) (n = 725)	0.985
GCS	15 (13, 15) (n = 779)	15 (13, 15) (n = 267)	14 (11, 15) (n = 722)	<0.001*	14 (12, 15) (n = 779)	14 (12, 15) (n = 267)	14 (12, 15) (n = 722)	0.988
Intracranial lesion on initial head CT								
Presence of SAH**, n (%)	137 (17.5%)	82 (30.0%)	190 (26.1%)	<0.001*	184.19 (40.4%)	64.26 (40.4%)	171.88 (40.4%)	>0.999
SDH bleed**, n (%)								
SDH bleed ≤8 mm	305 (39.0%)	142 (52.0%)	334 (45.8%)	<0.001*	346.55 (44.3%)	121.42 (44.5%)	322.18 (44.2%)	>0.999
SDH bleed >8 mm	271 (34.7%)	62 (22.7%)	184 (25.2%)		224.85 (28.8%)	78.40 (28.7%)	210.91 (28.9%)	
No SDH bleed	206 (26.3%)	69 (25.3%)	211 (28.9%)		210.61 (26.9%)	73.18 (26.8%)	195.91 (26.9%)	
EDH bleed**, n (%)								
EDH bleed ≤8 mm	17 (2.2%)	2 (0.7%)	27 (3.7%)	0.055	19.39 (2.5%)	6.65 (2.4%)	18.29 (2.5%)	>0.999
EDH bleed >8 mm	18 (2.3%)	7 (2.6%)	23 (3.2%)		21.51 (2.8%)	7.55 (2.8%)	20.02 (2.7%)	
No EDH bleed	747 (95.5%)	264 (96.7%)	679 (93.1%)		741.10 (94.8%)	258.80 (94.8%)	690.69 (94.7%)	
Presence of IVH**, n (%)	29 (3.7%)	5 (1.8%)	27 (3.7%)	0.292	26.60 (3.4%)	9.26 (3.4%)	25.13 (3.4%)	0.998
IPH bleed**, n (%)								
IPH bleed ≤2 cm	100 (12.8%)	32 (11.7%)	117 (16.1%)	0.003*	112.17 (14.3%)	38.68 (14.2%)	104.73 (14.4%)	>0.999
IPH bleed >2 cm	55 (7.0%)	22 (8.1%)	84 (11.5%)		71.89 (9.2%)	24.98 (9.1%)	66.97 (9.2%)	
No IPH bleed	627 (80.2%)	219 (80.2%)	528 (72.4%)		597.95 (76.5%)	209.34 (76.7%)	557.30 (76.4%)	
Multifocal contusions**, n (%)	136 (21.6%)	52 (23.6%)	193 (33.6%)	<0.001*	174.02 (27.5%)	59.85 (27.2%)	163.22 (27.7%)	0.989
Abnormal CTA head**, n (%)	21 (3.3%)	5 (2.3%)	22 (3.9%)	0.553	22.31 (3.6%)	7.73 (3.6%)	20.85 (3.6%)	>0.999
VTE prophylaxis								
Anti-Xa, n (%)	—	0 (0.0%)	4 (0.5%)	0.091	—	0 (0.0%)	5.04 (0.7%)	0.026
Type of VTE prophylaxis, n (%)				0.466				0.341
Heparin 5,000 U subcutaneous every 8 hours	—	132 (48.5%)	319 (43.9%)		—	119.15 (43.7%)	308.68 (42.5%)	
Heparin 5000 U subcutaneous every 12 hours	—	10 (3.7%)	21 (2.9%)		—	11.86 (4.4%)	22.26 (3.1%)	
Lovenox 0.5 mm/kg subcutaneous every 12 hours	—	0 (0.0%)	2 (0.3%)		—	0 (0.0%)	3.30 (0.5%)	
Lovenox 30 mg subcutaneous daily	—	12 (4.4%)	24 (3.3%)		—	15.36 (5.6%)	27.25 (3.7%)	
Lovenox 40 mg subcutaneous daily	—	35 (12.9%)	89 (12.2%)		—	35.25 (12.9%)	86.28 (11.9%)	
Lovenox 30 mg subcutaneous every 12 hours	—	76 (27.9%)	251 (34.5%)		—	84.04 (30.8%)	256.74 (35.3%)	
Lovenox 40 mg subcutaneous every 12 hours	—	2 (0.7%)	11 (1.5%)		—	1.17 (0.4%)	11.82 (1.6%)	
Other	—	5 (1.8%)	10 (1.4%)		—	5.59 (2.1%)	10.62 (1.5%)	
Medications/blood products given at admission								
Cryo-24 h**, mean (SD)	0.01 (0.12) (n = 702)	0.00 (0.00) (n = 269)	0.01 (0.11) (n = 703)	0.394	0.01 (0.12) (n = 702)	0.00 (0.00) (n = 269)	0.01 (0.14) (n = 703)	0.392
FFP-24 h**, mean (SD)	0.06 (0.42) (n = 703)	0.08 (0.55) (n = 269)	0.07 (0.49) (n = 704)	0.897	0.08 (0.50) (n = 703)	0.07 (0.45) (n = 269)	0.08 (0.50) (n = 704)	0.929
PCC-24 h**, mean (SD)	22.12 (234.14) (n = 678)	10.51 (168.42) (n = 257)	2.76 (71.96) (n = 679)	0.085	11.44 (164.21) (n = 678)	11.34 (171.98) (n = 257)	11.16 (144.63) (n = 679)	0.999
Platelets-24 h**, Mean (SD)	0.20 (0.84) (n = 703)	0.13 (0.51) (n = 269)	0.25 (1.31) (n = 704)	0.340	0.19 (0.81) (n = 703)	0.17 (0.57) (n = 269)	0.20 (1.01) (n = 704)	0.837
PRBC-24 h**, mean (SD)	0.13 (0.59) (n = 706)	0.11 (0.63) (n = 270)	0.10 (0.58) (n = 705)	0.195	0.13 (0.62) (n = 706)	0.11 (0.57) (n = 270)	0.12 (0.80) (n = 705)	0.939
TXA-24 h**, mean (SD)	0.01 (0.09) (n = 675)	0.00 (0.00) (n = 256)	0.00 (0.07) (n = 681)	0.567	0.00 (0.07) (n = 675)	0.00 (0.00) (n = 256)	0.00 (0.07) (n = 681)	0.639
MTP**, n (%)	6 (0.8%)	1 (0.4%)	7 (1.0%)	0.769	4.85 (0.6%)	1.24 (0.5%)	5.20 (0.7%)	0.898

Continued next page

TABLE 1. *(Continued)*

	Before Weighting				After Weighting (for ICHE Outcome)			
	No VTEP Initiated (n = 782)	VTEP ≤ 24 (n = 273)	VTEP > 24 (n = 729)	*p**	No VTEP Initiated (n = 782)	VTEP ≤ 24 (n = 273)	VTEP > 24 (n = 729)	*p**
Coagulation panel								
Hemoglobin**, median (Q1, Q3)	12.90 (11.40, 14.20) (n = 779)	13.10 (11.90, 14.40) (n = 262)	13.20 (12.00, 14.40) (n = 719)	0.004*	13.10 (11.60, 14.40) (n = 779)	13.20 (11.80, 14.40) (n = 262)	13.20 (11.80, 14.30) (n = 719)	0.960
International normalized ratio**, median (Q1, Q3)	1.10 (1.00, 1.10) (n = 716)	1.00 (1.00, 1.10) (n = 253)	1.00 (1.00, 1.10) (n = 693)	0.256	1.10 (1.00, 1.10) (n = 716)	1.00 (1.00, 1.10) (n = 253)	1.00 (1.00, 1.10) (n = 693)	0.999
Platelet**, median (Q1, Q3)	217.00 (169.00, 267.00) (n = 779)	216.00 (173.50, 265.00) (n = 260)	221.00 (174.00, 272.00) (n = 719)	0.362	220.00 (173.00, 269.00) (n = 779)	216.00 (170.00, 265.00) (n = 260)	219.00 (173.00, 272.00) (n = 719)	0.999

For comparisons involving continuous variables, nonparametric Wilcoxon Kruskal-Wallis tests or one-way ANOVA tests were used. For comparisons involving categorical variables, χ^2 or Fisher's exact tests were used, as appropriate.
*$p < 0.025$.
**Variables were included in the propensity score weighting model.
SBP, systolic blood pressure.

Institutional Review Board and Data Handling

Institutional review board approval was obtained at the primary institution and at each participating institution. Each institution was recruited via the EAST multicenter trial website and a data use agreement was secured. Data entered into REDCap were audited and validated on an ongoing basis by the primary investigators.

STATISTICAL ANALYSIS

Descriptive Statistics

Patient demographics and clinical characteristics were summarized in the overall sample and the three cohorts (NO VTEP vs. VTEP>24 vs. VTEP ≤24 hours) using descriptive statistics, including means, standard deviations, medians and interquartile ranges for continuous variables, and frequencies and percentages for categorical variables. For comparisons involving continuous variables, one-way analysis of variance (ANOVA) or nonparametric Kruskal-Wallis tests were used. Comparisons involving categorical variables relied on χ^2 or Fisher's exact tests, where appropriate.

Covariate Balancing Propensity Score Weighting

Covariate balancing propensity score (CBPS) weighting was performed on the total sample of 1,784 patients. Propensity scores (PS) represent the estimated probabilities of patients being in any one of the three cohorts, conditional upon the set of observed covariates, which included age, admission heart rate, systolic blood pressure, Glasgow Coma Scale (GCS), initial platelet count, hemoglobin, international normalized ratio, packed red blood cells, fresh frozen plasma, platelets, cryoprecipitate, tranexamic acid, Prothrombin complex concentrate given at admission, sex, race, AIS head, hypertension (HTN), coronary artery disease (CAD), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), coagulopathy, liver disease, cancer, mechanism of injury, massive transfusion given at admission, multiple contusions per lobe, presence of SAH, SAH with abnormal CTA, SDH, IVH, EDH and IPH for overall ICHE analysis. PS weighting for the VTE analysis included all of the above variables and ICHE. The percent of missing data of the variables included in the CBPS weighting ranged from 0.9% (GCS) to 20.4% (SAH with abnormal CTA head). Since large amounts of missing data in covariates would prevent the CBPS weighting methods to be performed properly, overall mean imputation of each continuous variable and recoding missing values for categorical variables as "Not Reported" was implemented. Absolute standardized mean differences (ASMDs) for covariates before and after weighting were used as model diagnostics. Absolute standardized mean differences estimates falling below 0.1 indicate good balance across groups.[14]

Weights were extracted for each patient after CBPS, and weighted logistic regression models were estimated for VTE and overall ICHE, with the three cohorts as the primary predictor. All weighted models were adjusted for cryoprecipitate given at admission, as this variable did not achieve good balance after weighting (ASMD >0.1) to reduce bias. Weighted odds ratios, along with their 95% confidence intervals and *p* values are reported.

Unweighted Bivariate and Multivariable Logistic Regression Modeling

Bivariate logistic regression models were used to examine the associated factors with VTE and overall ICHE for severe

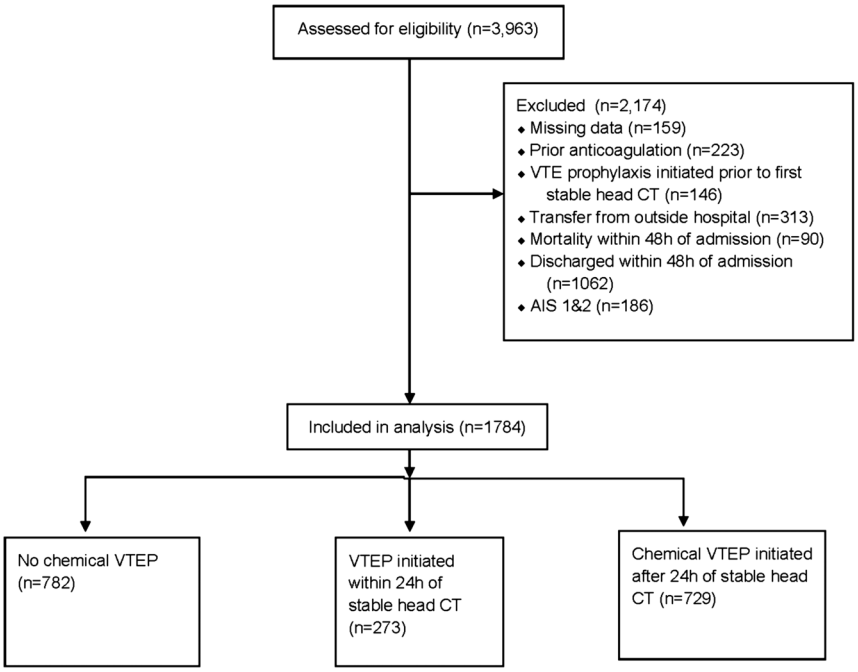

Figure 1. Flowchart for inclusion of patients in the study.

TBI patients. For bivariate models, each dichotomous outcome was regressed on each individual risk factor. Clinical factors demonstrating statistical significance at the $p < 0.20$ level in the bivariate models were included into a multivariable model for each outcome. Backwards elimination methods were then used to derive a final multivariable model for each outcome. Significance of predictors of interest were taken at the $p < 0.025$ level. All final multivariable models included patient cohort as a predictor regardless of statistical significance. Odds ratios and 95% confidence intervals were computed.

Statistical significance was taken at the $p < 0.025$ level to adjust for two the primary outcomes, VTE and overall ICHE. CBPS weighting methods were performed using the *WeightIt* package in R version 4.0.4[15] and all other analyses were done in SAS V9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Of the 3,963 total patients, 1,784 patients met inclusion criteria for an isolated severe TBI. There were 782 (43.8%) in the NO VTEP group, 273 (15.3%) in VTEP≤24, and 729 (40.9%) in VTEP>24 cohort. Table 1 summarizes demographic and clinical characteristics before and after implementing PS weighting, noting that weighted descriptive statistics reflect the model for overall ICHE. For weighted descriptive statistics of the model for VTE, see Supplemental Table 2, http://links.lww.com/TA/C960. Patients in VTEP>24 were significantly younger with a median age of 62 ($p < 0.001$) (Table 1), had longer hospital LOS, ICU stay and ventilator days ($p < 0.001$) compared with VTEP≤24 and NO VTEP groups (Table 2). This group also had more high-risk features on initial head CTs, including IPH and multifocal contusions. Furthermore, VTEP>24 group had a significantly higher incidence of complications (19.2%) compared with the other two groups with higher occurrences of unplanned admissions to the ICU and pneumonia (Table 2). The NO VTEP group had significantly higher incidences of HTN, CKD, coagulopathy, liver disease and malignancy. The majority of patients in all three groups had a blunt mechanism of injury secondary to falls. The NO VTEP group had a significantly higher number of patients discharged to home, however also had an increased mortality as compared with the other groups.

VTE and ICHE Events

The incidence of VTE in the entire cohort is 3.2% (n = 57). PE and DVT occurred in 0.9% and 2.5% of the patients, respectively (Table 2). Median time to first stable head CT was significantly lower in the VTEP>24 group at 12.2 hours. Median time to VTEP initiation from first stable head CT in the VTEP≤24 was 11.2 hours and 47 hours in the VTEP>24 group. Incidences of VTE were significantly higher in the VTEP>24 group.

Overall, ICHE occurred in 26.3% of all patients (n = 469). ICHE after VTEP initiation only occurred in 3.7% of patients in the VTEP≤24 and 3.4% of patients in VTEP>24 groups. Median times to ICHE from VTE prophylaxis initiation was 165.1 hours in VTEP≤24 and 51.8 hours in VTEP>24 group, with no significant differences identified (Table 2).

Neurosurgical Interventions

There were 500 (28.0%) patients with severe TBI who had neurosurgical interventions performed (Table 2). A higher number of patients in the VTEP>24 group had ICP monitors and EVDs placed, though not statistically significant. A higher number of patients in the NO VTEP group had craniotomies (18.7% NO VTEP vs. 12.1% in VTEP≤24 vs. 17.7% in VTEP>24, $p < 0.001$) and a lower number of craniectomies (4.5% NO VTEP vs. 6.6% VTEP≤24 vs. 10.7% VTEP>24, $p = 0.001$)

TABLE 2. Unweighted Outcomes and Neurosurgical Interventions in Patients With Severe TBI (n = 1,784)

	No VTEP (n = 782)	VTEP ≤ 24 (n = 273)	VTEP > 24 (n = 729)	*p**
ICU LOS (d), median (Q1, Q3)	2 (1, 4) (n = 742)	2 (1, 5) (n = 272)	3 (1, 8) (n = 723)	<0.001*
Hospital LOS, n (%)				<0.001*
48–72 h	234 (29.9%)	66 (24.2%)	85 (11.7%)	
>72 h	548 (70.1%)	207 (75.8%)	644 (88.3%)	
Ventilator LOS: median (Q1, Q3), d	0 (0, 0) (n = 713)	0 (0, 0) (n = 272)	0 (0, 4) (n = 715)	<0.001*
Mortality, n (%)	73 (9.3%)	13 (4.8%)	38 (5.2%)	0.002*
Complications, n (%)	65 (8.3%)	36 (13.2%)	140 (19.2%)	<0.001*
UTI, n (%)	22 (2.8%)	16 (5.9%)	35 (4.8%)	0.041
MI, n (%)	3 (0.4%)	0 (0.0%)	5 (0.7%)	0.395
Unplanned return to operating room, n (%)	16 (2.1%)	4 (1.5%)	12 (1.7%)	0.859
Unplanned readmission to the ICU, n (%)	15 (1.9%)	7 (2.6%)	35 (4.8%)	0.005*
Pneumonia, n (%)	16 (2.1%)	11 (4.0%)	55 (7.5%)	<0.001*
Time to 1st stable head CT (h), median (Q1, Q3)	15 (8.6, 26.9) (n = 699)	15 (9.0, 30.0) (n = 271)	12.2 (7.5, 23.0) (n = 719)	<0.001*
Time to VTEP from stable head CT (h), median (Q1, Q3)	—	11.2 (6.0, 17.0)	47.0 (33.6, 74.1)	<0.001*
Time to VTEP from admission (h), median (Q1, Q3)	—	30.23 (21.5, 45.7)	64.2 (46.1, 96.6) (n = 728)	<0.001*
VTE, n (%)	16 (2.1%)	7 (2.6%)	34 (4.7%)	0.012*
DVT, n (%)	14 (1.8%)	4 (1.5%)	26 (3.6%)	0.053
PE, n (%)	2 (0.3%)	5 (1.8%)	10 (1.4%)	0.010*
Time to VTE diagnosis (h), median (Q1, Q3)	132 (43.3, 167.6) (n = 12)	176.3 (29.0, 249.0) (n = 6)	175.0 (62.0, 283.0) (n = 33)	0.834
ICHE, n (%)	177 (22.6%)	80 (29.3%)	212 (29.1%)	0.008*
Time to ICHE from admission (h), median (Q1, Q3)	11.0 (7.0, 19.8) (n = 176)	9.2 (6.6, 18.9)	8.4 (6.1, 15.1) (n = 209)	0.040
ICHE after VTEP, n (%)	—	10 (3.7%)	25 (3.4%)	0.848
Time to ICHE from VTEP (h), median (Q1, Q3)	—	165.1 (71, 177.2) (n = 9)	51.8 (31.9, 99.0) (n = 24)	0.069
Neurosurgical interventions (n = 500)	(n = 201)	(n = 55)	(n = 244)	
Time to procedure from admission (h), median (Q1, Q3)	5.55 (2.00, 20.00) (n = 192)	4.39 (2.50, 10.84) (n = 52)	4.00 (2.00, 14.59) (n = 228)	0.298
ICP or EVD, n (%)	34 (4.3%)	8 (2.9%)	61 (8.3%)	0.055
ICP/EVD due to ICHE after VTEP, n (%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	0.601
Time to ICP/EVD after VTEP (h), median (Q1, Q3)	—	—	52.22 (49.9, 54.5)	
Craniotomy, n (%)	146 (18.7%)	33 (12.1%)	129 (17.7%)	<0.001*
Craniotomy due to ICHE after VTEP, n (%)	0 (0.0%)	0 (0.0%)	6 (0.8%) (n = 129)	0.348
Time to craniotomy after VTEP (h), median (Q1, Q3)	—	—	115.5 (71.0, 132.7) (n = 5)	
Craniectomy, n (%)	35 (4.5%)	18 (6.6%)	78 (10.7%)	0.001*
Craniectomy due to ICHE after VTEP, n (%)	0 (0.0%)	0 (0.0%)	3 (0.4%) (n = 78)	0.713
Time to craniectomy after VTEP (h), median (Q1, Q3)	—	—	49.9 (11.2, 54.5)	

For comparisons involving non-normally distributed continuous variables, non-parametric Wilcoxon Kruskal-Wallis tests were used. For comparisons involving categorical variables, χ^2 and Fisher's exact tests were used, as appropriate.

*$p < 0.025$.

performed. A total of 11 patients (0.6%) in the entire cohort required neurosurgical intervention after VTEP initiation and were all in the VTEP>24 group.

Propensity Score-Weighted Analysis

CBPS was chosen from a variety of weighting methods for having the best reduction of ASMD. (Supplemental Fig. 2a and 2b, http://links.lww.com/TA/C960). All variables, except for cryoprecipitate given on admission, had ASMD estimates falling below 0.1, which indicated a good balance (Supplemental Fig. 3a and 3b, http://links.lww.com/TA/C960). This is illustrated by Table 1 and Supplemental Table 2, http://links.lww.com/TA/C960, where variables included in the CBPS weighting were all balanced after weighting with *p*-values close to 1.

After PS weighting (Table 3), although there was a higher risk of VTE in VTEP >24 compared with those in VTEP≤24 (odds ratio [OR], 1.51; 95% confidence interval [CI], 0.69–3.30;

TABLE 3. Propensity Weighted Logistic Regression Models for VTE and Overall ICHE in Severe TBI Patients (n = 1,784)

Outcomes	Predictors	OR (95% CI)	*p*
VTE*	Patient cohort		
	No VTEP	0.62 (0.26–1.49)	0.282
	VTEP >24	1.51 (0.69–3.30)	0.307
	VTEP ≤24	Reference	
ICHE*	Patient cohort		
	No VTEP	0.75 (0.55–1.02)	0.070
	VTEP>24	0.81 (0.59–1.10)	0.178
	VTEP≤24	Reference	

*Outcomes being modeled are presence of VTE or ICHE and results are in reference to absence of these events. Models adjusted for cryoprecipitate given at admission, as this variable was imbalanced after weighting.

$p = 0.307$), the result was not statistically significant. The NO VTEP cohort had 38% decreased odds of having VTE compared to those receiving VTEP≤24 (OR, 0.62; 95% CI, 0.26–1.49; $p = 0.282$) but also was not statistically significant.

The No VTEP group had decreased odds of having ICHE compared to those in VTEP≤24 (OR, 0.75; 95%CI, 0.55–1.02, $p = 0.070$), although not statistically significant. VTEP >24 had 19% decreased odds of ICHE compared to VTEP≤24 (OR, 0.81; 95% CI, 0.59–1.10, $p = 0.178$), which was not significant.

Unweighted Multivariable Analysis for Risks of VTE and ICHE

A multivariable analysis using unweighted data to identify key risk factors for VTE and overall ICHE in the severe TBI population was performed. Bivariate logistic regression models showed that the following variables were significantly associated with VTE at the $p < 0.20$ level increased systolic blood pressure, lower GCS, increased INR, ICU LOS, additional ventilator days, VTEP>24, hospital LOS > 72 hours, higher AIS, DM, CKD, penetrating injury, unplanned return to the operating room, pneumonia, and SDH (data not shown). These variables were entered into a multivariable model using backwards elimination methods. ICU LOS remained the sole correlator of VTE at the $p < 0.025$ level (Table 4). The odds of VTE increased by 8% with each additional day spent in the ICU. Patient cohort was not a statistically significant predictor of VTE.

Bivariate logistic regression models showed that the following variables were significantly associated with ICHE: younger age, decreased GCS, increased ICU LOS, timing of VTEP, females, Asian race, hospital LOS >72 hours, HTN, COPD, CKD, coagulopathy, UTI, unplanned readmission to the ICU, unplanned return to the operating room, pneumonia, multiple parenchymal contusions per lobe, SAH, SDH, EDH, and IPH (data not shown). These variables were entered into a multivariable model using backwards selection elimination methods, males, UTI, pneumonia, hospital LOS >72 hours, multiple contusions per lobe, SDH ≤8 mm, IPH >2 cm, and SAH significantly correlated with overall ICHE at the $p < 0.025$ level. Female patients had 29% decreased odds of ICHE compared to male patients (OR, 0.71; 95% CI, 0.54–0.92; $p = 0.010$). Patients with UTI and pneumonia had a 96% and 91% increased odds of ICHE, respectively. Multiple contusions per lobe increased the risk of ICHE by 2.2 times (OR, 2.25; 95% CI, 1.70–2.98; $p < 0.001$) and SAH increased risk of ICHE by 1.55 times (OR, 1.55; 95% CI, 1.18–2.05; $p = 0.002$). Compared with patients with no SDH or IPH, those with SDH ≤ 8 mm and IPH > 2 cm had a 53% and 78% increased odds of ICHE, respectively (Table 5). There were no association with patient cohort and overall ICHE.

TABLE 4. Unweighted Backward Selection Multivariable Logistic Regression Model Results for VTE* (n = 1,737)

Variables	OR (95% CI)	p
Patient cohort		
No VTEP	0.97 (0.38, 2.47)	0.941
VTEP >24	1.78 (0.76, 4.17)	0.182
	Reference	
ICU LOS	1.08 (1.05, 1.11)	<0.001*

Outcomes being modeled are presence of VTE and results are in reference to absence of this event.
*$p < 0.025$.

TABLE 5. Unweighted Backwards Selection Multivariable Logistic Regression Model Results for Overall ICHE (n = 1,428)

Variables	OR (95% CI)	p
Patient cohort		
No VTEP	0.81 (0.57–1.17)	0.261
VTEP >24	0.86 (0.60–1.24)	0.427
VTEP ≤24	Reference	
Gender		
Female	0.70 (0.54–0.92)	0.009*
Male	Reference	
UTI		
Yes	1.96 (1.12–3.42)	0.019*
No	Reference	
Pneumonia		
Yes	1.91 (1.10–3.32)	0.022*
No	Reference	
Multiple contusions per lobe		
Yes	2.24 (1.69–2.97)	<0.001*
No	Reference	
Hospital LOS		
48–72 h	Reference	
>72 h	1.63 (1.17–2.28)	0.004*
Presence of SAH		
Yes	1.55 (1.18–2.04)	0.002*
No	Reference	
SDH bleed		
≤8 mm	1.54 (1.14–2.08)	0.005*
>8 mm	1.27 (0.88–1.84)	0.199
No bleed	Reference	
IPH bleed		
≤2 cm	1.20 (0.84–1.70)	0.313
>2 cm	1.79 (1.18–2.72)	0.006*
No bleed	Reference	

Outcomes being modeled are presence of ICHE and results are in reference to absence of these events.
*$p < 0.025$.

DISCUSSION

In this large multicenter retrospective study, we examined the effects of early VTEP initiation within 24 hours of a stable head CT in severe TBI patients. The incidence of VTE events in this patient cohort was 3.2%, which is consistent with previous studies.[16] Timing of VTE prophylaxis was not associated with VTE. A larger number of VTE events were noted in the VTEP>24 group compared with NO VTEP and VTEP≤24 groups; however, after adjusting for confounders, this difference disappeared. In a multivariable logistic regression model, VTE was significantly associated with prolonged ICU LOS. Prolonged immobilization and TBI-induced coagulopathic states have been shown to be significant risk factors for development of VTE in the TBI population.[17–20] Increased ICU LOS is significant for the underlying severity of TBI and its associated complications,

which further prolongs immobility, thereby increasing risk of VTE. Identification of such clinical factors is beneficial for VTEP implementation in severe TBI patients.

In the CBPS weighted logistic regression model, patients in NO VTEP group had 25% lower odds of developing ICHE compared to VTEP≤24 group; however, this was not a significant finding. Overall ICHE occurred in 26.3% of the patient cohort, which is consistent with available literature.[21–25] Further, male patients, hospital LOS >72 hours, complications, such as pneumonia and UTI, SAH, multiple contusions per lobe, SDH ≤ 8 mm and IPH >2 cm were associated with ICHE. Some of these clinical factors align with Berne Norwood Criteria which identifies high risk TBI patients and is consistent with reports from Carnevale et al.,[25] Chang et al.,[24] and Cepeda et al.[23] However, on the contrary to Carnevale et al., our study demonstrated a lower association of ICHE in female patients. Similar to our results, Oertel et al.[26] demonstrated a lower risk of ICHE in female patients and hypothesized the effects of estrogen and progesterone to have neuroprotective properties. Complications, such as UTI, pneumonia and hospital LOS >72 hours, were correlated with ICHE, though these findings are most likely secondary to the underlying severity of the TBI itself causing a prolonged hospital LOS and such complications. Chang et al. further demonstrated that the presence of SDH is a risk factor for ICHE. Similarly, our study demonstrated that presence of a SDH carried a higher association for ICHE. This finding is likely secondary to a combination of evolution of a SDH in relation to brain atrophy and cerebral volume, TBI induced coagulopathy and the presence of a concurrent ICH, which all carry a risk for expansion. Despite the overall incidence of ICHE, our study demonstrated low incidences of ICHE after VTEP (3.4% of the cohort who received VTEP) and neurosurgical interventions with no interventions in VTEP≤24 group after VTEP initiation, suggesting early VTEP is safe without a higher risk of ICHE leading to neurosurgical intervention. Further, ICHE occurred at median times of 165.1 and 51.8 hours after VTEP initiation in the VTEP≤24 and VTEP>24 cohorts respectively. Therefore, it is difficult to ascertain whether VTEP contributed to ICHE.

The VTEP>24 group was younger, had longer hospital LOS, and had higher complications compared to the other two groups. This group had a shorter time to the first stable head CT, however, did not receive VTEP until after 24 hours. It proved challenging to standardize the time periods to interval CTs since there were practice pattern variations amongst institutions to performing interval CTs at 6 hours, 12 hours, 24 hours or none at all. Patients in the VTEP>24 group also had high risk features according to Berne Norwood criteria and had a higher number of ICP/EVDs placed compared to the other groups. All of the above characteristics may have contributed to initiating VTEP after 24 hours. Eleven patients (1.5%) in the VTEP>24 group required neurosurgical interventions after VTEP initiation, though no significant differences were found compared to the other cohorts. It is unclear whether the delay in VTEP initiation in this group was related to the need for neurosurgical intervention or high-risk intracranial hemorrhage features, and ICHE, which may have played a role in a delay in initiation of VTEP. Given the small proportion of patients requiring neurosurgical interventions, the benefits of VTEP initiation in severe TBI patients may still outweigh the risk of neurosurgical interventions.

It is of interest to note that 43.8% of our patient cohort did not receive any VTEP. This group was more comorbid, had a higher mortality, and more craniotomies performed compared to the other two groups. There were no significant differences in VTE after CBPS weighting. This group may have a combination of the most severe and least severe patients. Although we excluded patients who were discharged or died within 48 hours of admission, the finding that the NO VTEP group did not have increased risk of VTE may reflect confounders that masked a true causal effect. The lack of VTEP initiation in this group may be due to an absence of a standard to initiate VTEP after a neurosurgical intervention and is largely dependent on neurosurgeon and trauma surgeon input. In their ACS TQIP study, Byrne et al.[27] demonstrated that while early VTE prophylaxis after neurosurgical intervention has a benefit in VTE, it does result in an increase in repeated neurosurgical interventions. We are unable to discern what the justification was for not initiating VTEP in this group, despite having similar other demographics. However, this finding highlights again the need for more standardization of VTEP initiation in the severe TBI group and the lack of VTEP initiation is likely more commonplace based on lack of clinical practice guidelines and evidence to support its use and represents an opportunity for process improvement in this patient population.

Timing to VTEP initiation in severe TBI patients is not addressed in current clinical guidelines practices available due to lack of strong evidence to support early VTE initiation. Current guidelines support 24–72 hours of VTEP initiation in TBI patients;[6,8–12] however, there are no clear guidelines on VTEP initiation in the event of hemorrhage progression or need for neurosurgical interventions.[12] Therefore, balancing risks of ICHE and VTE is the crux of the issue of VTEP initiation in severe TBI patients. This leads to several interinstitutional and interprofessional practice pattern variability based on local institutional policies or anecdotal experience.[28] Several studies have demonstrated reduced DVT events after early prophylaxis initiation within 24 hours without progression or need for neurosurgical intervention, however, are limited by single institution studies with a limited number of patients.[7,29–32] Byrne et al.[16] further report in a ACS TQIP based study that early VTEP <72 hours was safe without risks of ICHE and neurosurgical interventions. Yet, practice variability still exists in managing severe TBI patients.

This study has several limitations. Its retrospective nature carries inherent limitations. We did not capture neurologic status at discharge, long term mortality and VTE events and were not able to determine whether early prophylaxis had any effect on short term or long-term neurologic prognosis. Patients who were transitioned to hospice during the hospital stay were not excluded, which may impact incidences of mortality. Although we were able to capture ICHE in early CT scans and neurosurgical interventions, we were not able to discern rates of subclinical ICHE that may have caused delays in VTEP administration, which should be an area of further study in patients with severe TBI. Patients who had ICHE and clinical deterioration but were not amenable for surgical interventions were further not identified. We analyzed overall ICHE as an outcome in our PS model due to the low number of patients who had ICHE after VTEP initiation and the ability to compare across the three groups. There was an effort to examine detailed radiographic findings

including descriptors and dimensions of ICH by type of hemorrhage, however this would have required re-review of the CT scans which would have been impractical in this large study. The authors recognize that a low number of VTE (n = 57) events leads to low statistical power to detect differences across the cohorts. A post-hoc power analysis demonstrated that this study had 67% power to detect a small effect size (W) of 0.07 using a χ^2 test statistic and a type 1 error rate of 2.5% for the group sample sizes. Despite being underpowered, the actual comparison demonstrated a statistically significant difference, with $p = 0.012$ (Table 2). Given our analytical sample size (N = 1,784) and the number of VTE events (n = 57), we had sufficient power to detect approximately five predictors of VTE in the unweighted multivariable models. Only one predictor was observed at the $p < 0.025$ level (ICU LOS). However, risk factors for VTE, such as appropriate dosing and missed doses of chemoprophylaxis, were not accounted for, thus further confounding results of VTE.

Multiple imputation could not be used to resolve missing data points due to limitations of the *WeightIt* package in R.[15] As such, single mean imputation was used to address missing data points prior to implementing propensity score weighting. While this method may introduce bias, it allowed for the retainment of key covariates to balance the VTEP initiation groups.[33] However, this was a large multicenter cohort with extensive data validation utilized to ensure data accuracy. Its multicenter nature allows for generalizability of the severe TBI population. We only studied isolated TBI patients to reduce confounding from injuries to other body regions. We excluded patients on anticoagulation to further mitigate confounding factors for ICHE. However, this could have resulted in selection bias. Severe TBI patients were studied to focus on a patient population that lacks significant evidence to support VTEP initiation, but this does limit generalizability. However, we note that the NO VTEP group was included for comparison, a group that has been excluded from most studies.

CONCLUSION

In this large multicenter analysis, there were no significant differences in VTE based on timing of initiation of VTE prophylaxis. Patients who never received VTE prophylaxis had decreased odds of ICHE. Early VTEP initiation less than 24 hours of a stable head CT may be safe without a risk of need for neurosurgical intervention. Further evaluation of VTE prophylaxis in larger randomized studies will be necessary for definitive conclusions.

AUTHORSHIP

A.M.R., D.K., S.S.S. participated in the literature search. A.M.R., D.K., S.S.S. participated in the study design. A.M.R., D.K., S.S.S., C.J., E.J.K., L.L.P., C.M., I.S., A.J., V.S., A.M., E.T., M.R., L.L., W.Z., A.K., M.H., J.C., C.B., T.E., A.M.*, M.K., S.D., R.C., S.S., L.E.J., J.W., M.W., B.P., C.M.*, N.T., T.H., T.D., S.M., L.D.S., A.R., L.C.T., T.J.N., H.M.S., M.B.S., D.H., D.R., D.C., C.F., M.M., C.D., J.D., D.B. participated in the data collection. A.M.R., D.K., S.S.S., E.J.K. participated in the writing. A.M.R., D.K., S.S.S., C.J., E.J.K., J.C., T.E., L.C.T., M.R., K.S., P.F., W.J., A.L. participated in the critical revision.

ACKNOWLEDGMENTS

We are grateful to our colleagues from EAST TBI VTE research group for their contribution to the study. Without their work this article would not have been possible. Center for Biostatistics and Health Data Science: Alexandra Hanlon PhD, Danielle Sienko MS, Wenyan Ji MA, Alicia Lozano MS. Crozer Health: Sandra Durgin MSN RN CEN, Alexander Papa DO, Danielle Lapoint DO, Ammar Humayun MD; Loma Linda University: Georgi Mladenov MD, Xian Luo-Owen PhD, St. Mary's Medical Center: Alyha Benitez, John Sousa MD, Sarah Lee MD, Matthew Zinner MD; Promedica Toledo Hospital: Diane Philip MSN, RN, Tyler Wilbarger RN; Spartanburg Medical Center: Thomas J. Mack. University Hospitals Cleveland Medical Center: Angelica Bartholomew RN, Murathan Kahyaoglu. Research reported in this publication was supported by Eastern Association for the Surgery of Trauma, Junior Multicenter Investigator Award 2022.

DISCLOSURE

The authors declare no conflicts of interest.
The content is solely the responsibility of the authors and does not necessarily represent the official views of EAST.

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