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Risks of venous thrombosis and bleeding in critically ill adolescents after trauma or major surgery☆

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ABSTRACT

Background: The risks of venous thromboembolism (VTE) and bleeding in critically ill adolescents based on interventions received and anatomic site of trauma or major surgery may identify a cohort eligible for enrollment in a trial of pharmacologic prophylaxis.
Methods: This retrospective cohort study using the Virtual Pediatric Systems database included adolescents admitted to pediatric intensive care units after trauma or major surgery between 2013 and 2017. Mixed effects logistic regression was used to determine the adjusted risks of VTE and bleeding with central venous catheterization (CVC), mechanical ventilation (MV) and anatomic site of trauma or major surgery. The adjusted risks were used to identify the cohort eligible for enrollment.
Measurements and Main Results: VTE developed in 212 (0.8%) of 27,647 adolescents. The adjusted risk of VTE was >2% with CVC and 2 or more of MV and trauma or major surgery to the brain or abdomen. Excluding those with bleeds present on admission or at high risk of bleeding, 375 (1.4%) adolescents would be eligible for enrollment.
Conclusions: VTE is generally uncommon in adolescents after trauma or major surgery. The small proportion of adolescents who are at high risk of VTE and at low risk of bleeding impacts the feasibility of a trial.
Level of Evidence: Prognostic Study Level II.

Venous thromboembolism (VTE) is a top contributor to harm in hospitalized children [1,2]. Initiatives are being undertaken to reduce its incidence in children based on the efficacy and safety of preventive strategies in adults [2,3]. Recently, the American Society of Hematology recommended that, in general, pharmacologic prophylaxis be used in adults after trauma or major surgery, i.e., surgical adults, who are at high risk of VTE with risk greater than 2%, but at low risk of bleeding with risk less than 2% [4–9]. Mechanical prophylaxis is recommended for surgical adults at high risk of both VTE and bleeding [4]. Despite the absence of definitive pediatric guidelines and paucity of pediatric-specific evidence, critically ill surgical adolescents are often targeted for pharmacologic prophylaxis because their coagulation system is comparable with adults [10]. Concerns regarding the lower risk and severity of VTE and unclear risk of bleeding with pharmacologic prophylaxis in adolescents compared with adults limit the extrapolation of adult guidelines to adolescents [11,12].

Multicenter randomized clinical trials (RCT) are the gold standard for establishing therapeutic efficacy. As we explore and design a RCT of pharmacologic prophylaxis against VTE in critically ill adolescents after trauma or major surgery, a key knowledge gap is the optimal study population that will maximize the benefit–risk ratio of pharmacologic prophylaxis. While studies in children and adults indicate that the risk of VTE is increased with central venous catheterization (CVC) or mechanical ventilation (MV) and after trauma or major surgery to the brain, pelvis or lower extremity, it is unclear which of these factors confer the highest risk of VTE in critically ill surgical adolescents [12–22]. Furthermore, trauma and major surgery, and MV are associated with increased risk of bleeding in critically ill adolescents [23]. These may limit the subjects who would be eligible to participate in a RCT.

This study aims to determine the risks of VTE and bleeding in critically ill surgical adolescents based on interventions received and

Abbreviations: CI, confidence interval; CVC, central venous catheter; DVT, deep venous thrombosis; ICD, International Classification of Diseases; ICU, intensive care unit; IQR, interquartile range; ISTH, International Society of Thrombosis and Hemostasis; MV, mechanical ventilation; OR, odds ratio; PIM2, Paediatric Index of Mortality 2; PRISM3, Pediatric Risk of Mortality 3; RCT, randomized controlled trial; VPS, Virtual Pediatric Systems; VTE, venous thromboembolism.

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anatomic site of trauma or major surgery. We hypothesized that an eligible population of critically ill adolescents after trauma or major surgery, i.e. at high risk of VTE but at low risk of bleeding, who could be enrolled in a RCT of pharmacologic prophylaxis against VTE can be identified based on these factors.

1. Methods

1.1. Study design

This is a retrospective cohort study of critically ill surgical adolescents using the Virtual Pediatric Systems (VPS, LLC) database of children admitted to the pediatric intensive care unit (ICU). VPS is a clinical database with prospective data collection using standardized clinical data definitions and quality control. The database contains de-identified patient and site information on consecutive admissions from >100 pediatric ICUs in the United States. Certified clinical staff collect and enter the data. The concordance in the database is consistently >95%. In addition, the VPS staff performs extensive quality validation before data are released for analysis. Diagnoses, procedures and other clinical data are collected in VPS, in addition to the codes from the International Classification of Diseases (ICD). Star codes are a VPS proprietary category of diagnostic conditions that group similar ICD codes into a more all-encompassing, clinically relevant grouping. For example, 5 ICD10 codes map to the star code Pulmonary embolus/infarction including 12.602 saddle pulmonary embolus of pulmonary artery with acute cor pulmonale, 12.692 saddle pulmonary embolus of pulmonary artery without acute cor pulmonale, 12.609 other pulmonary embolus with acute cor pulmonale, 12.609 other pulmonary embolus with acute cor pulmonale, and 12.782 chronic pulmonary embolism. Over 100 ICD-10 codes map to the Star code venous thrombosis/embolism. Star code and ICD code diagnoses include date of onset and date of resolution (if applicable), and if diagnosis was present on admission.

1.2. Study definitions

1.2.1. Prevalent VTE
Any diagnosis of VTE from VPS star codes or ICD-9/10 codes that were present on admission or with time of onset prior to admission.

1.2.2. Incident VTE
Any diagnosis of VTE from VPS star codes or ICD-9/10 codes after the day of admission to the pediatric ICU.

1.2.3. Adjusted risk of VTE
The risk of VTE while admitted to the pediatric ICU in critically ill surgical adolescents in the presence of the factors of interest and controlling for the confounders and ICU site. The adjusted risk of VTE was estimated from the full cohort, which is described below. Calculation of the adjusted risk of VTE is described in Section 1.6.

1.2.4. High risk of VTE
Patients with adjusted risk of VTE >2%.

1.2.5. Low risk of VTE
Patients with adjusted risk of VTE ≤2%.

1.2.6. Prevalent bleed
Any diagnosis of bleeding from VPS star codes or ICD-9/10 codes with onset time of 3 days before or on the day of admission to the pediatric ICU.

1.2.7. Incident bleed
Any diagnosis of bleeding from VPS star codes or ICD-9/10 codes with onset time after the day of admission to the pediatric ICU.

1.2.8. Adjusted risk of bleeding
The risk of bleeding after the day of admission to the pediatric ICU in critically ill surgical adolescents in the presence of the factors of interest and controlling confounders and ICU site. The adjusted risk of bleeding was estimated from the at-risk cohort, which is described below, after excluding those with prevalent bleeds. Calculation of the adjusted risk of bleeding is described in Section 1.6.

1.2.9. High risk of bleeding
Patients with adjusted risk of bleeding >2%.

1.2.10. Low risk of bleeding
Patients with adjusted risk of bleeding ≤2%.

1.3. Eligibility criteria

We analyzed 3 cohorts of surgical adolescents admitted to the pediatric ICU between January 1, 2013 and December 31, 2017 (Fig. 1).

1.3.1. Full cohort
This cohort included all adolescents 13–17 years old who were admitted after trauma or major surgery to a pediatric ICU participating in the VPS database. We excluded those with prevalent VTE.

1.3.2. At-risk cohort
This subset of the full cohort was at high risk of VTE who might benefit from pharmacologic prophylaxis. We excluded from the full cohort adolescents at low risk of VTE to derive the at-risk cohort.

1.3.3. Trial-eligible cohort
This subset of the at-risk cohort was at high risk of VTE and at low risk of bleeding and would form the population eligible for enrollment in a future pediatric RCT of pharmacologic prophylaxis. In our planned RCT, we anticipate enrolling critically ill surgical adolescents within a day of admission to the pediatric ICU to maximize the potential benefit of pharmacologic prophylaxis [24–26]. We showed in our prior survey that pediatric intensivists were willing to provide pharmacologic prophylaxis 3 days after a bleed in critically ill surgical patients [27]. Thus, we excluded from the at-risk cohort adolescents with prevalent bleeds to derive the trial-eligible cohort. The trial-eligible cohort also excluded those at high risk of bleeding.

1.4. Study variables

We abstracted variables from the VPS database including factors previously reported to be associated with VTE in critically ill and injured children [21]: patient age, sex, weight and height, severity of illness scores (Paediatric Index of Mortality 2 [PIM2] and Pediatric Risk of Mortality 3 [PRISM3]), presence of cancer or congenital heart disease, reason for admission (i.e., trauma or major surgery), anatomic site(s) of trauma or major surgery, CVC and MV. Adolescents who had trauma-related surgery were considered trauma admissions. Anatomic sites of trauma or major surgery that were of interest based on previously reported risk of VTE were categorized as brain, spine (including spinal cord), thorax (including heart), abdomen (including pelvic organs), or lower extremity/pelvis fracture [12–22]. Data regarding mechanical or pharmacologic prophylaxis is not available in VPS. Data was censored at ICU discharge or day 28, which represented 97.5%ile of length of stay in the pediatric ICU.

1.5. Outcome measures

Our primary outcome measure was development of VTE. VTE was either an extremity deep venous thrombosis (DVT) or pulmonary embolism given that the goal of pharmacologic prophylaxis is the prevention of these two manifestations of VTE. VPS does not collect information on

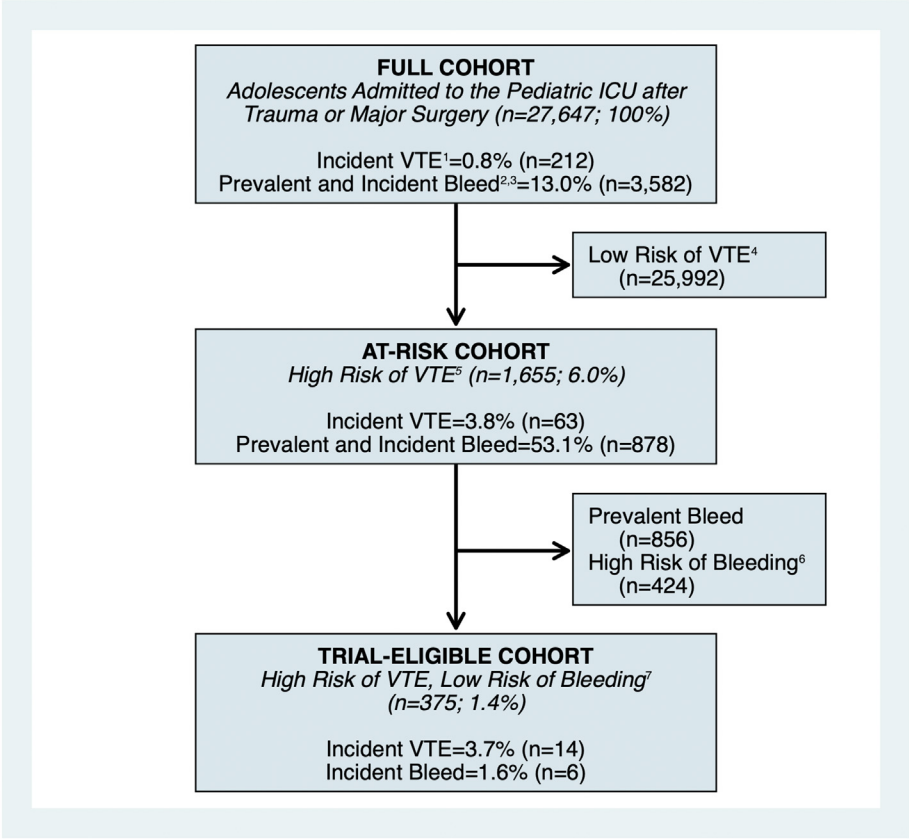

Fig. 1. Flow Diagram of Full, At-Risk and Trial-Eligible Cohorts. Figure Legend: ICU-intensive care unit; VTE- venous thromboembolism [1]Incident VTE: Any diagnosis of VTE from VPS star codes or ICD-9/10 codes after the day of admission to the pediatric ICU. [2]Prevalent bleed: Any diagnosis of bleeding from VPS star codes or ICD-9/10 codes with onset time of 3 days before or on the day of admission to the pediatric ICU. [3]Incident bleed: Any diagnosis of bleeding from VPS star codes or ICD-9/10 codes with onset time after the day of admission to the pediatric ICU. [4]Low risk of VTE: Patients with adjusted risk of VTE ≤2%. [5]High risk of VTE: Patients with adjusted risk of VTE >2%. [6]High risk of bleeding: Patients with adjusted risk of bleeding >2%. [7]Low risk of bleeding: Patients with adjusted risk of bleeding ≤2%.

the method of diagnosis of VTE. Our secondary outcome measures were DVT, composite outcome of VTE or death, and bleeding. DVT is the most common manifestation of VTE. The composite outcome of VTE or death addresses the competing risk problem in which a patient who dies will not develop VTE, unless the patient dies of pulmonary embolism, which is difficult to diagnose, even in adolescents [28]. We captured VPS star codes and ICD-9/10 codes recommended for bleeds by the Agency for Healthcare Research and Quality [29] (Supplemental Table 1). Both prevalent and incident bleeds captured by these codes were consistent with the definition used by the International Society of Thrombosis and Hemostasis (ISTH) for clinically relevant bleeding [30]. Clinically relevant bleeding included bleeds in specific anatomic sites, bleeds that resulted in physiologic compromise, and bleeds that required intervention to achieve hemostasis.

1.6. Statistical analysis

We compared the characteristics between adolescents with trauma or major surgery in the full cohort using Student's *t*-test for continuous variables and chi-squared test for categorical variables. Adolescents were excluded only in the comparisons for which they had missing data. To identify adolescents at high risk of VTE, mixed effects logistic regression was used to model the binary outcome of VTE from adolescents in the full cohort with CVC, MV and anatomic sites of trauma or major surgery as factors of interest. Given that trauma or major surgery could have occurred in multiple anatomic sites, each site was entered as a dichotomous variable in the model with each site compared with other sites. The regression model also included as confounders other patient characteristics that have been previously associated with VTE, i.e., age, male sex, severity of illness score using PIM2, obesity, reason for admission, and presence of cancer or congenital heart disease [21]. The appropriate VPS star codes and ICD-9/10 codes were used to identify obesity. To supplement these codes, we calculated the z-scores for body mass index and weight for age and sex with z-scores >2 used to define obesity [31]. The ICU site was entered in the regression model as a random effect variable to account for clustering within ICU. Variance inflation factor was calculated to detect collinearity [32]. From the regression model, we estimated the adjusted risk of VTE with CVC, MV and different sites of trauma or major surgery. The coefficients from the mixed effects logistic regression model were used to calculate the adjusted risk of VTE [33,34]. As sensitivity analyses, we performed similar regression analyses on the full cohort with DVT and VTE or death as outcomes.

We excluded adolescents with prevalent bleeds from the at-risk cohort to identify adolescents at high risk of bleeding after the day of admission to the pediatric ICU. Similar to VTE, we used mixed effects logistic regression to model incident bleeds with CVC, MV and anatomic sites of trauma or major surgery adjusting for patient characteristics considered for VTE and clustering within ICU site. We used the same patient characteristics as for VTE because we wanted to determine the effect of these characteristics on incident bleeds and infer their potential effects on the eligibility criteria of the planned RCT. Furthermore, our prior studies suggested that risk factors for VTE may also increase the risk of bleeding in critically ill children [23,35].

The frequencies of incident VTE and prevalent and incident bleeds were presented as percentages within each cohort. Adjusted risks of VTE or bleeding from the mixed effects logistic regression model were presented with 95% confidence intervals (CI). Associations between

outcome measures and factors of interest were expressed as odds ratios (OR; 95% CI). All statistical tests were performed using Stata 16 (StataCorp, Inc., College Station, TX). A *P*-value <0.05 was considered statistically significant.

2. Results

2.1. Full cohort

A total of 27,647 surgical adolescents from 165 pediatric ICUs were included in the full cohort after exclusion of 178 adolescents who had prevalent VTE (Table 1 and Fig. 1). Age was comparable between those with trauma or major surgery. Male sex and obesity were proportionately more common, while congenital heart disease and cancer were proportionately less common in those with trauma. Severity of illness by PIM2 and PRISM3 were higher in those with trauma. CVC was more common in those with major surgery, but MV was more common in those with trauma. Trauma to the brain, thorax, abdomen, and lower extremities were more common than major surgery to these sites. Major surgery to the spine was more common than spinal trauma. Those with trauma stayed longer in the ICU than those with major surgery.

Incident VTE occurred in 212 adolescents (0.8%), while 198 (0.7%) developed DVT, 21 (0.08%) developed PE and 835 (3.0%) developed VTE or died (Table 1). The incidence of VTE, DVT, and the composite outcome of VTE or death were higher in those with trauma at 1.1%, 1.1% and 6.4%, respectively, than those with major surgery at 0.6%, 0.6% and 1.9%, respectively. A total of 3582 (13.0%) adolescents after trauma or major surgery had prevalent or incident bleeds.

Of our factors of interest, CVC (OR: 8.16; 95% CI: 5.01, 13.26), MV (OR: 2.31; 95% CI: 1.61, 3.31), and trauma or major surgery to the brain (OR: 2.01; 95% CI: 1.41, 2.87) or abdomen (OR: 2.35; 95% CI: 1.55, 3.56) were associated with VTE (Table 2). Similar associations were found between our factors of interest and DVT and the composite outcome of VTE or death, except for trauma or major surgery to the abdomen, which was not associated with VTE or death. There were no missing data for all factors included in the regression models. The variance inflation factors for each factor in the models were at most 1.41 suggesting minimal collinearity.

2.2. At-risk cohort

The at-risk cohort consisted of the subset of adolescents from the full cohort where the adjusted risk of VTE exceeded 2% and was considered high risk of VTE. The adjusted risk exceeded 2% only in those with CVC and at least 2 of MV and trauma or major surgery to the brain or abdomen (Table 3). The adjusted risk of VTE ranged from 2.8% with CVC, MV and trauma or major surgery to the brain to 6.2% in the presence of all 4 factors. Thus, 1655 (6.0% of the full cohort) adolescents were considered at high risk of VTE and were included in the at-risk cohort (Fig. 1). A total of 63 (3.8%) adolescents in the at-risk cohort developed incident VTE, while 878 (53.1%) adolescents had a prevalent or incident bleed.

After excluding the 856 adolescents with prevalent bleeds, trauma or major surgery to the brain was marginally associated with incident bleeds (OR: 5.51; 95% CI: 0.95, 31.86) (Table 4). None of the other factors associated with VTE were associated with incident bleeds. In the presence of trauma or surgery to the brain, the adjusted risk of bleeding ranged from 3.5% to 10.0%, which would be considered high risk of bleeding (Table 3). Of the other factors of interest, again after excluding

Table 1
Patient variables and outcomes in adolescents admitted to the intensive care unit after trauma or major surgery.

	Full cohort		Trauma		Major surgery		
	n = 27,647		n = 6818		n = 20,829		
Variable	Mean/Freq	SD/%	Mean/Freq	SD/%	Mean/Freq	SD/%	p Value
Age (in years)	14.92	1.38	14.93	1.34	14.91	1.39	0.42
Weight (in kg)	59.57	21.01	66.55	17.98	57.28	21.43	<0.001
Height (in cm)*	161.12	15.96	168.74	12.02	158.49	16.31	<0.001
BMI (in kg/m2)*	22.85	11.68	23.46	6.22	22.64	13.04	<0.001
PIM2 (%)	3.22	9.84	6.97	16.36	2	5.9	<0.001
PRISM3 (%)	2.43	9.99	6.03	17.45	1.25	5.22	<0.001
Male	16,220	58.7	4591	67.3	11,629	55.8	<0.001
Race/ethnicity							0.004
White	13,654	49.4	3418	50.1	10,236	49.1	
African American	3296	11.9	880	12.9	2416	11.6	
Hispanic	4106	14.9	979	14.4	3127	15.0	
Others or mixed	2188	7.9	486	7.1	1702	8.2	
Unspecified	4358	15.8	1055	15.5	3303	15.9	
Obesity	4128	14.9	1119	16.4	3009	14.4	<0.001
Cancer	2271	8.2	38	0.6	2233	10.7	<0.001
Congenital heart disease	2954	10.7	67	1.0	2887	13.9	<0.001
Central venous catheterization	13,663	49.4	2925	42.9	10,738	51.6	<0.001
Mechanical ventilation	12,676	45.8	4020	59.0	8656	41.6	<0.001
Anatomic site							
Brain	3557	12.9	1852	27.2	1705	8.2	<0.001
Spine	3049	11.0	523	7.7	2526	12.1	<0.001
Thorax	4243	15.3	1366	20.0	2877	13.8	<0.001
Abdomen	1832	6.6	1253	18.4	579	2.8	<0.001
Lower extremity	1650	6.0	1231	18.1	419	2.0	<0.001
Outcomes							
VTE	212	0.8	78	1.1	134	0.6	<0.001
Deep vein thrombosis	198	0.7	75	1.1	123	0.6	<0.001
VTE or death	835	3.0	437	6.4	398	1.9	<0.001
Bleed	3582	13.0	2363	34.7	1219	5.9	<0.001
ICU length of stay**	5.48	5.5	6.51	6.4	5.14	5.12	<0.001
Death	633	2.3	363	5.3	270	1.3	<0.001

BMI, body mass index; PIM2, Paediatric Index of Mortality 2; PRISM3, Pediatric Risk of Mortality 3; VTE, venous thromboembolism; ICU, intensive care unit.
* n = 14,211 for full cohort, 3638 for trauma and 10,575 for major surgery.
** n = 26,046 for full cohort, 6646 for trauma and 19,600 for major surgery.

Table 2
Multivariable analysis of factors associated with venous thromboembolism in the full cohort (N = 27,647).

Variable	VTE				DVT				VTE/death			
	OR	95% CI		p Value	OR	95% CI		p Value	OR	95% CI		
Age (per 1-year increase)	1.11	1.00,	1.23	0.04	1.10	0.99,	1.22	0.07	1.06	1.00	1.13	0.046
Male	0.99	0.75,	1.32	0.95	1.04	0.77,	1.39	0.82	1.07	0.91	1.26	0.40
PIM2 (per 1% increase)	1.00	0.99,	1.01	0.95	1.00	0.99,	1.01	0.90	1.05	1.04	1.05	<0.001
Obesity	1.23	0.87,	1.76	0.25	1.31	0.91,	1.87	0.15	1.21	0.98	1.49	0.07
Trauma (vs. major surgery)	1.30	0.90,	1.88	0.16	1.39	0.95,	2.02	0.09	1.83	1.50	2.24	<0.001
Cancer	1.31	0.81,	2.13	0.27	1.31	0.79,	2.17	0.30	2.45	1.88	3.20	<0.001
Congenital heart disease	0.71	0.41,	1.21	0.21	0.72	0.41,	1.25	0.24	0.65	0.47	0.90	0.01
Central venous catheterization	8.16	5.01,	13.26	<0.001	8.27	4.96,	13.77	<0.001	6.53	4.91	8.67	<0.001
Mechanical ventilation	2.31	1.61,	3.31	<0.001	2.46	1.68,	3.61	<0.001	5.49	4.12	7.30	<0.001
Anatomic site												
Brain	2.01	1.41,	2.87	<0.001	1.98	1.37,	2.86	<0.001	1.24	1.00	1.54	0.046
Spine	0.73	0.40,	1.30	0.28	0.65	0.35,	1.23	0.19	0.46	0.31	0.69	<0.001
Thorax	0.92	0.62,	1.36	0.69	0.91	0.61,	1.37	0.66	0.81	0.65	1.02	0.08
Abdomen	2.35	1.55,	3.56	<0.001	1.94	1.24,	3.04	0.004	1.06	0.79	1.42	0.70
Lower extremity	0.64	0.36,	1.14	0.13	0.66	0.37,	1.20	0.17	0.54	0.38	0.77	0.001

VTE, venous thromboembolism; DVT, deep vein thrombosis; OR, odds ratio; CI, confidence interval; PIM2, Paediatric Index of Mortality.

the 856 adolescents with prevalent bleeds, trauma or major surgery to the thorax was associated with incident bleeds (OR: 3.30; 95% CI: 1.03, 10.61). The variance inflation factors for each factor in the regression model were at most 1.41.

2.3. Trial-eligible cohort

From the at-risk cohort, 856 adolescents were excluded due to prevalent bleeds and 424 were excluded due to high risk of bleeding, i.e., adjusted risk of bleeding >2% (Table 3), to form the trial-eligible cohort (Fig. 1). Adolescents in the trial-eligible cohort consisted of those with CVC, MV and trauma or major surgery to the abdomen. The 375 adolescents in the trial-eligible cohort represented 1.4% of the full cohort. Of these, 14 (3.7%) developed incident VTE and 6 (1.6%) had an incident bleed. The median times to diagnosis of incident VTE and incident bleed were 7 days (interquartile range [IQR]: 4, 8 days) and 4 days (IQR: 2, 9 days), respectively. A total of 2 adolescents developed incident VTE and incident bleed. One developed VTE at 7 days after admission to the pediatric ICU and bled at 12 days after admission. The other had missing data on times of diagnoses.

Table 3
Adjusted risks of venous thromboembolism and bleeding in the at-risk cohort (N = 1655).

CVC	MV	Brain	Abdomen	Adjusted risk of VTE	95% CI		Adjusted risk of bleeding	95% CI	
−	−	−	+	0.2%	0.1%	0.3%			
−	−	+	−	0.2%	0.1%	0.2%			
−	−	+	+	0.4%	0.1%	0.6%			
−	+	−	−	0.2%	0.1%	0.3%			
−	+	−	+	0.4%	0.2%	0.7%			
−	+	+	−	0.4%	0.2%	0.6%			
−	+	+	+	0.8%	0.3%	1.4%			
+	−	−	−	0.6%	0.4%	0.9%			
+	−	−	+	1.5%	0.7%	2.2%			
+	−	+	−	1.3%	0.7%	1.8%			
+	**−**	**+**	**+**	**2.9%**	**1.3%**	**4.5%**	**10.0%**	**−9.3%**	**30.2%**
+	+	−	−	1.4%	1.1%	1.8%			
+	**+**	**−**	**+**	**3.3%**	**1.9%**	**4.6%**	1.5%	0.3%	2.8%
+	**+**	**+**	**−**	**2.8%**	**1.8%**	**3.8%**	**3.5%**	**1.6%**	**5.4%**
+	**+**	**+**	**+**	**6.2%**	**3.3%**	**9.2%**	**7.6%**	**−2.9%**	**18.0%**

CVC, central venous catheterization; MV, mechanical ventilation; Brain, brain as anatomic site of trauma or major surgery; Abdomen, Abdomen and/or pelvic organs as anatomic site of trauma or major surgery; VTE, venous thromboembolism; CI, confidence interval. Risks of venous thromboembolism and bleeding were adjusted for age; sex; Paediatric Index of Mortality 2; obesity; reason for admission; cancer; congenital heart disease and other anatomic sites of trauma or major surgery.
+ indicates presence of factor; − indicates factor not present.
Bolded text = Factors associated with >2% risk of VTE or >2% risk of bleeding.

3. Discussion

Our retrospective cohort study of adolescents admitted to the pediatric ICU after trauma or major surgery evaluated the risks of VTE and bleeding in order to identify an optimal population for enrollment in a RCT of pharmacologic prophylaxis against VTE. We report that critically ill adolescents after trauma or major surgery, in general, are at low risk of VTE. Critically ill surgical adolescents at high risk of VTE are also at high risk of bleeding. Those at high risk of VTE but at low risk of bleeding who would be eligible for the RCT represent a small proportion of critically ill surgical adolescents. Our findings impact the feasibility of a future RCT of pharmacologic prophylaxis against VTE in critically ill surgical adolescents.

Despite similarities in the coagulation system between adolescents and adults, our findings suggest that recommendations for pharmacologic prophylaxis against VTE in adults should not be routinely extrapolated to adolescents. We observed lower risks of VTE at 0.8% among adolescents compared with the reported risks of VTE of at least 2% for adults who underwent similar procedures [6]. In particular, we did not find associations between VTE and trauma or major surgery to the lower extremities, which is an established risk factor for VTE in adults [6].

Table 4
Multivariable analysis of factors associated with bleeding in the at-risk cohort after excluding adolescents with prevalent bleeds (N = 799).

	Odds ratio	95% CI		p Value
Age (per 1-year increase)	0.97	0.70	1.36	0.87
Male	1.92	0.71	5.23	0.20
PIM2 (per 1% increase)	0.99	0.94	1.03	0.56
Obesity	1.84	0.70	4.84	0.21
Trauma (vs. major surgery)	0.52	0.18	1.50	0.22
Cancer	0.98	0.26	3.73	0.98
Congenital heart disease	2.79	0.33	23.61	0.35
Mechanical ventilation	0.69	0.05	10.24	0.79
Anatomic Site:				
Brain	5.51	0.95	31.80	0.06
Spine	0.69	0.09	5.49	0.73
Thorax	3.31	1.03	10.62	0.045
Abdomen	2.34	0.43	12.84	0.33
Lower extremity	0.21	0.03	1.82	0.16

PIM2, Paediatric Index of Mortality 2.

About half of the adolescents at high risk of VTE had prevalent bleeds. Given the concern of bleeding with pharmacologic prophylaxis, it is prudent to exclude these adolescents from a RCT in which the intervention would be started within a day of admission to the pediatric ICU to maximize the potential benefit of prophylaxis [25,26,36,37]. Consistent with recommendations for surgical adults, we opted to exclude trauma or surgery to the brain despite marginal association with bleeding because of the potential impact of bleeding to this site [4]. It is unclear whether delaying enrollment of these adolescents to increase available subjects would still provide benefit in reducing the risk of VTE as shown in observational studies in adults [38]. It is thought that the delay would reduce the risk of bleeding while the patient remains at high risk of VTE. This hypothesis is supported by our data in which half of the bleeds have occurred before VTE was diagnosed.

Adolescents with CVC, MV and trauma or major surgery to the abdomen, but not the brain, would be the ideal subjects for a RCT based on their high risk of VTE and low risk of bleeding. Unfortunately, this cohort of adolescents represent only 1.4% of adolescents admitted after trauma or major surgery to 165 pediatric ICUs over 5 years. Nearly 2500 subjects will be needed to detect a 50% reduction in the risk of VTE at 80% power, assuming a baseline VTE risk of 3.7% as seen in our study. A RCT of this magnitude will likely be infeasible. Systematic radiologic screening for VTE to inform the primary outcome as done in adults and recommended by ISTH will increase the baseline risk of VTE and reduce sample size [30]. However, concerns about the clinical significance of VTE detected on systematic radiologic screening may limit the use of this alternative approach [39]. Innovative study design, such as Bayesian RCT in which information will be borrowed from adult RCTs, may also reduce the sample size resulting in a feasible RCT [40]. Risk prediction models may better define the personalized risks of VTE and bleeding in critically ill surgical adolescents and result in a larger cohort of eligible patients. Unfortunately, no risk prediction models specific to critically ill surgical adolescents are currently available.

Our study was not designed to determine the efficacy and safety of pharmacologic prophylaxis. However, if the effect of pharmacologic prophylaxis in adolescents is similar to adults, adolescents with CVC, MV and trauma or major surgery to the abdomen but not to the brain may benefit from pharmacologic prophylaxis. In adults after trauma or major surgery, pharmacologic prophylaxis, in general, relatively reduces the risk of VTE by 50% and increases the risk of bleeding by 50% [4]. With incident VTE at 3.7% and incident bleed at 1.6% in our study, pharmacologic prophylaxis may be expected to absolutely reduce the risk of VTE by 1.9% and increase the risk of bleeding by 0.8% resulting in net benefit. At the minimum, surgical adolescents with CVC, MV and trauma or major surgery to the abdomen or brain may benefit from mechanical prophylaxis based on their high risk of VTE [4].

Our study has limitations. VPS does not collect information regarding the use of pharmacologic or mechanical prophylaxis. We previously showed that among patients admitted to the pediatric ICU after trauma, 62% of adolescents did not receive any prophylaxis, 30% received mechanical prophylaxis, 2.5% received pharmacologic prophylaxis and 6% received both [41]. While the rates of prophylaxis would likely be similarly low in our study population, their effect on the risks of VTE and bleeding are unclear and hence the need for a pediatric RCT. VPS also does not collect information on the method of diagnosis of VTE. This may have resulted in misclassification bias. Some adolescents may have developed VTE after discharge from the pediatric ICU, which may have underestimated the risks of VTE. We used anatomic sites of trauma or major surgery to define the risks of VTE and bleeding. The type of trauma or major surgery may have stronger associations with VTE or bleeding and could better characterize the trial-eligible cohort. However, based on the number of adolescents with VTE, we were limited to approximately 20 factors that can be entered in the regression models [42]. The trial-eligible cohort does not necessarily reflect adolescents currently receiving pharmacologic prophylaxis [10,41]. Some centers are comfortable prescribing pharmacologic prophylaxis to critically ill adolescents after trauma or major surgery as soon as bleeding is controlled [43]. However, for purposes of a RCT, the safety of the pharmacologic prophylaxis should be maximized until its efficacy is established in this patient population. Lastly, we defined the risk of bleeding regardless of the use of pharmacologic prophylaxis. More important would be the risk of recurrence of bleeding with pharmacologic prophylaxis. We may have inadvertently excluded adolescents with prevalent bleeds who would have been at low risk of recurrence of bleeding.

4. Conclusion

Adolescents admitted to the pediatric ICU after trauma or major surgery are, in general, at low risk of VTE. Those with CVC, MV and trauma or major surgery to the brain or abdomen are at high risk of VTE. However, pharmacologic prophylaxis may not be indicated for most of them given their high risk of bleeding, particularly in those who had trauma or major surgery to the brain. Critically ill adolescents with CVC, MV and trauma or major surgery to the abdomen, but not to the brain, have high risk of VTE and low risk of bleeding making them appropriate for enrollment in a RCT of pharmacologic prophylaxis against VTE. Given the small number of adolescents with this combination of factors, innovative techniques will be needed to design and successfully conduct a feasible and adequately powered RCT.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpedsurg.2020.06.037.

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References

[1] Goudie A, Dynan L, Brady PW, et al. Costs of venous thromboembolism, catheter-associated urinary tract infection, and pressure ulcer. Pediatrics. 2015;136(3):432–9 Epub 2015/08/12 https://doi.org/10.1542/peds.2015-138626260712.
[2] Lyren A, Brilli RJ, Zieker K, et al. Children's Hospitals' Solutions for Patient Safety Collaborative impact on hospital-acquired harm. Pediatrics. 2017;140(3). https://doi.org/10.1542/peds.2016-3494 Epub 2017/08/18 28814576.
[3] Children's Hospitals' Solutions for Patient Safety. SPS prevention bundles. [cited 2018 June 1]. Available from: http://solutionsforpatientsafety.org/for-hospitals/hospital-resources/.
[4] Anderson DR, Morgano GP, Bennett C, et al. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. Blood Adv. 2019;3(23):3898–944. https://doi.org/10.1182/bloodadvances.2019000975.
[5] Spyropoulos AC1, Hussein M, Lin J, et al. Rates of symptomatic venous thromboembolism in US surgical patients: a retrospective administrative database study. J Thromb Thrombolysis. 2009;28(4):458–64. https://doi.org/10.1007/s11239-009-0351-1.
[6] White RH, Zhou H, Romano PS. Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. Thromb Haemost. 2003;90(3):446–55.
[7] Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e227S 77S. Epub 2012/02/15 https://doi.org/10.1378/chest.11-229722315263. 3278061.
[8] Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e278S 325S. Epub 2012/02/15 https://doi.org/10.1378/chest.11-240422315265. 3278063.
[9] Byrne JP, Mason SA, Gomez D, et al. Timing of pharmacologic venous thromboembolism prophylaxis in severe traumatic brain injury: A propensity-matched cohort study. J Am Coll Surg. 2016;223(4):621–31 e5. Epub 2016/07/28 https://doi.org/10.1016/j.jamcollsurg.2016.06.38227453296.
[10] Faustino EV, Hanson S, Spinella PC, et al. On behalf of the PROphylaxis against ThRombosis prACTice study investigators of the PALISI BloodNet. A multinational study of thromboprophylaxis practice in critically ill children. Crit Care Med. 2014;42(5):1232–40 Epub 2013/12/20 https://doi.org/10.1097/CCM.0000000000000014724351371.
[11] Amos LE, Silvey M, Hall M, et al. Primary thromboprophylaxis in hospitalized children: a multi-center retrospective analysis. Thromb Res. 2019 Apr;176:1–7. https://doi.org/10.1016/j.thromres.2019.02.001.

[12] Faustino EV, Shabanova V, Pinto M, et al. Epidemiology of lower extremity deep venous thrombosis in critically ill adolescents. J Pediatr. 2018. https://doi.org/10.1016/j.jpeds.2018.05.006 Epub 2018/06/13 29891258.
[13] Hanson SJ, Punzalan RC, Greenup RA, et al. Incidence and risk factors for venous thromboembolism in critically ill children after trauma. J Trauma. 2010;68(1):52–6 Epub 2010/01/13 https://doi.org/10.1097/TA.0b013e3181a7465220065757.
[14] Leeper CM, Vissa M, Cooper JD, et al. Venous thromboembolism in pediatric trauma patients: Ten-year experience and long-term follow-up in a tertiary care center. Pediatr Blood Cancer. 2017;64(8). https://doi.org/10.1002/pbc.26415 Epub 2017/01/10 28067012.
[15] Connelly CR, Laird A, Barton JS, et al. A clinical tool for the prediction of venous thromboembolism in pediatric trauma patients. JAMA Surg. 2016;151(1):50–7 Epub 2015/10/01 https://doi.org/10.1001/jamasurg.2015.267026422678.
[16] Greenwald L, Yost M, Sponseller P, et al. The role of clinically significant venous thromboembolism and thromboprophylaxis in pediatric patients with pelvic or femoral fractures. J Pediatr Orthop. 2012;32(4):357–61. https://doi.org/10.1097/BPO.0b013e31824b2a072012296919.
[17] Guzman D, Sabharwal S, Zhao C, et al. Venous thromboembolism among pediatric orthopedic trauma patients: a database analysis. J Pediatr Orthop B. 2018;27(2):93–8 Epub 2017/01/13 https://doi.org/10.1097/bpb.0000000000000042428079740.
[18] Murphy RF, Heyworth B, Kramer D, et al. Symptomatic venous thromboembolism after adolescent knee arthroscopy. J Pediatr Orthop. 2016. https://doi.org/10.1097/BPO.0000000000000894 Epub 2016/11/20 27861210.
[19] Mahajerin A, Branchford BR, Amankwah EK, et al. Hospital-associated venous thromboembolism in pediatrics: a systematic review and meta-analysis of risk factors and risk assessment models. Haematologica. 2015;100(8):1045–50 Epub 2015/05/24 https://doi.org/10.3324/haematol.2015.123455. PubMed 26001789.
[20] Higgerson RA, Lawson KA, Christie LM, et al. Incidence and risk factors associated with venous thrombotic events in pediatric intensive care unit patients. Pediatr Crit Care Med. 2011;12(6):628–34 Epub 2011/11/10.
[21] Chima RS, Hanson SJ. Venous thromboembolism in critical illness and trauma: pediatric perspectives. Front Pediatr. 2017;5. https://doi.org/10.3389/fped.2017.00047 Available at: https://www.frontiersin.org/article/10.3389/fped.2017.00047.
[22] Faustino EVS, Shabanova V, Pinot MG, et al. Epidemiology of lower extremity deep venous thrombosis in critically ill adolescents. J Pediatr. 2018;201:176–83.
[23] Pinto MG, Shabanova V, Li S, et al. Epidemiology of clinically relevant bleeding in critically ill adolescents. Pediatr Crit Care Med. 2019 Oct;20(10):907–13. https://doi.org/10.1097/PCC.0000000000002018.
[24] Faustino EV, Patel S, Thiagarajan RR, et al. Survey of pharmacologic thromboprophylaxis in critically ill children. Crit Care Med. 2011;39(7):1773–8 Epub 2011/03/23 https://doi.org/10.1097/CCM.0b013e3182186ec021423003.3118917.
[25] Skarupa D, Hanna K, Zeeshan M, et al. Is early chemical thromboprophylaxis in patients with solid organ injury a solid decision? J Trauma Acute Care Surg. 2019;87(5):1104–12. https://doi.org/10.1097/TA.0000000000002438.
[26] Sumislawski JJ, Kornblith LZ, Conroy AS, et al. Dynamic coagulability after injury: is delaying venous thromboembolism chemoprophylaxis worth the wait? J Trauma Acute Care Surg. 2018 Nov;85(5):907–14. https://doi.org/10.1097/TA.0000000000002048.
[27] Mesa Galan LA, Egea-Guerrero JJ, Quintana Diaz M, et al. The effectiveness and safety of pharmacological prophylaxis against venous thromboembolism in patients with moderate to severe traumatic brain injury: a systematic review and meta-analysis. J Trauma Acute Care Surg. 2016 Sep;81(3):567–74. https://doi.org/10.1097/TA.0000000000001134.
[28] Bliss S, Weinberger S, Meier M, et al. The unusual suspect. N Engl J Med. 2002;347:1876–81. https://doi.org/10.1056/NEJMcps021566.
[29] Maynard G. Preventing hospital-associated venous thromboembolism: a guide for effective quality improvement. 2nd ed.. Rockville, MD: Agency for Healthcare Research and Quality; 2016 AHRQ publication no. 16–0001-EF Available at https://wwwahrqgov/patient-safety/resources/vtguide/appchtml Accessed January 30, 2020.
[30] Schulman S, Angerås U, Bergqvist D, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost. 2010;8(1):202–4. https://doi.org/10.1111/j.1538-7836.2009.03678.x. PMID 19878532.
[31] Kêkê LM, Samouda H, Jacobs J, et al. Body mass index and childhood obesity classification systems: a comparison of the French, international obesity task force (IOTF) and World Health Organization (WHO) references. Rev Epidemiol Sante Publique. 2015;63(3):173–82. https://doi.org/10.1016/j.respe.2014.11.003.
[32] Johnston R, Jones K, Manley D. Confounding and collinearity in regression analysis: a cautionary tale and an alternative procedure, illustrated by studies of British voting behaviour. Qual Quant. 2018;52:1957–76. https://doi.org/10.1007/s11135-017-0584-6.
[33] Bland JR, Cook AC. Random effects probit and logit: understanding predictions and marginal effects. Applied Economics Letters. 2019;26(2):116–23. https://doi.org/10.1080/13504851.2018.1441498.
[34] Hedeker D, du Toit SHC, Demirtas H, et al. A note on marginalization of regression parameters from mixed models of binary outcomes. Biometrics. 2018;74(1):354–61. https://doi.org/10.1111/biom.12707.
[35] White LJ, Fredericks R, Mannarino CN, et al. Epidemiology of bleeding in critically ill children. Journal of Pediatrics. 2017;184:114–9 e6.
[36] Decousus H, Tapson VF, Bergmann JF, et al. Factors at admission associated with bleeding risk in medical patients: findings from the IMPROVE investigators. Chest. 2011 Jan;139(1):69–79. https://doi.org/10.1378/chest.09-3081.
[37] Chang R, Scerbo MH, Schmitt KM, et al. Early chemoprophylaxis is associated with decreased venous thromboembolism risk without concomitant increase in intraspinal hematoma expansion after traumatic spinal cord injury. J Trauma Acute Care Surg. 2017;83(6):1088.
[38] Abdel-Aziz Hiba, Dunham C Michael, Malik Rema J, et al. Timing for deep vein thrombosis chemoprophylaxis in traumatic ybrain injury: an evidence-based review. Crit Care. 2015;19(1):96 Published online 2015 Mar 24 https://doi.org/10.1186/s13054-015-0814-z.
[39] Sharathkumar AA, Biss T, Kulkarni K, et al. Epidemiology and outcomes of clinically unsuspected venous thromboembolism in children: a systematic review. J Thromb Haemost. 2020 Jan 27. https://doi.org/10.1111/jth.14739.
[40] Broglio KR, Connor JT, Berry SM. Not too big, not too small: a goldilocks approach to sample size selection. J Biopharm Stat. 2014;24(3):685–705. https://doi.org/10.1080/10543406.2014.888569.
[41] Bigelow AM, Flynn-O'Brien KT, Simpson PM, et al. Multicenter review of current practices associated with venous thromboembolism prophylaxis in pediatric patients after trauma. Pediatr Crit Care Med. 2018 Sep;19(9):e448–54. https://doi.org/10.1097/PCC.0000000000001614.
[42] Peduzzi P, Concato J, Kemper E, et al. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996 Dec;49(12):1373–9.
[43] Landisch RM, Hanson SJ, Cassidy LD, et al. Evaluation of guidelines for injured children at high risk for venous thromboembolism: a prospective observational study. J Trauma Acute Care Surg. 2017 May;82(5):836–44. https://doi.org/10.1097/TA.0000000000001404.