

# Venous thromboembolism in children undergoing surgery: incidence, risk factors and related adverse events

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## ABSTRACT

**Background** Although less common in adults, venous thromboembolism (VTE) in children is a highly morbid, preventable adverse event. While VTE has been well studied among pediatric hospitalized and trauma patients, limited work has been done to examine postoperative VTE in children undergoing surgery.

**Methods** Using data from National Surgical Quality Improvement Project Pediatric database (NSQIP-P) from 2012 to 2016, a retrospective cohort analysis was performed to determine the incidence of, and risk factors for, VTE in children undergoing surgery. Additionally, the relationships between VTE and other postoperative adverse outcomes were evaluated.

**Results** Of 361 384 pediatric surgical patients, 378 (0.10%) were identified as experiencing postoperative VTE. After controlling for patient and surgical factors, we found that American Society of Anesthesiologists (ASA) class of II or greater, aged 16–18 years, non-elective surgery, general surgery (compared with several other surgical specialties), cardiothoracic surgery (compared with general surgery) and longer operative time were significantly associated with VTE in pediatric patients ( $p < 0.001$  for each comparison). Furthermore, a majority of adverse events were found to be associated with increased risk of subsequent VTE ( $p < 0.001$ ).

**Conclusion** In a large pediatric surgical population, an incidence of postoperative VTE of 0.10% was observed. Defined patient and surgical factors, and perioperative adverse events were found to be associated with such VTE events.

## INTRODUCTION

Venous thromboembolism (VTE) in children is a rare condition that includes deep vein thrombosis (DVT) and/or pulmonary embolism (PE). While there has been much written about VTE in the general hospitalized pediatric population (estimating an incidence between 0.18% and 0.58% of admissions),<sup>1–9</sup> and in children after trauma (estimated incidence between 0.02% and 0.33%<sup>10 11</sup>), there has been little investigation of VTE in children undergoing surgery.<sup>12–14</sup>

Several risk factors for VTE in children have been identified, including hematological malignancy (2.5-fold increased risk),<sup>7</sup>

## Key messages

### What is already known about this subject?

- ▶ Previous studies have described the incidence of venous thromboembolism (VTE) in children undergoing surgery as between 0.04% and 8.9%, depending on surgical specialty.
- ▶ Risk factors for VTE among pediatric surgical patients include: central venous lines, hematological malignancy, trauma/burns, prolonged ventilator use and longer hospital stay.
- ▶ Among children, neonates and adolescents are at greatest risk of developing VTE.

### What are the new findings?

- ▶ Children undergoing surgery are at higher risk of VTE if they are aged 16–18 years, have worse overall health status by the American Society of Anesthesiologists (ASA) classification and undergo longer, non-elective surgeries.
- ▶ Patients experiencing any adverse event after surgery, including medical and surgical adverse events, reoperation and readmission, are at increased risk of subsequent VTE.
- ▶ Children undergoing general surgery and cardiothoracic surgery are at higher risk of VTE compared with other surgical specialties.

### How might it impact on clinical practice in the foreseeable future?

- ▶ The current study adds to the limited literature characterizing risk factors for postoperative VTE among pediatric surgical patients.
- ▶ Weighing the risks and benefits of such an intervention, children identified to be at higher risk of VTE could potentially benefit from thromboprophylaxis when undergoing surgery.

orthopedic surgery (2.2-fold increased risk),<sup>7</sup> severe or critical injury (2.5-fold to 43.5-fold increased risk),<sup>11 15–18</sup> prolonged ventilator use (1.3-fold increased risk)<sup>19</sup> and longer hospital length of stay (1.03-fold increased risk).<sup>18</sup> Among children, VTE is most common in neonates and adolescents, with adolescents at highest risk.<sup>5–8 15 17–20</sup> Additionally, VTE occurs more commonly in tertiary care centers than in community hospitals.<sup>4 8</sup>



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In a study looking at surgical populations, Humes *et al* evaluate VTE in children in the year after general surgery and found the overall incidence to be 0.44% and risk factors to include at least one significant comorbidity.<sup>14</sup> Georgopoulos *et al* investigated VTE in children after elective pediatric orthopedic surgery and found the incidence to be 0.063% and risk factors to be older age, obesity and surgical complications.<sup>1</sup>

Additionally, Cairo *et al* and Ahn *et al* have recently identified risk factors for VTE among pediatric surgical patients, both using the National Surgical Quality Improvement Project Pediatric database (NSQIP-P).<sup>12 13</sup> Both studies used large numbers of patients to define demographic factors that predisposed to VTE in children, but did not take into account the factors that occurred postoperatively.

Although it is rare, the occurrence of VTE can be associated with significant morbidity in children. Complications occurring most commonly after VTE include post-thrombotic syndrome (estimated incidence of 26% after DVT in one systematic review),<sup>21 22</sup> and increased risk of mortality (relative risk of 6.27 compared with patients without VTE,<sup>8 21</sup> with mortality related to VTE estimated at 2.2%).<sup>2</sup> Furthermore, among pediatric patients treated after trauma, VTE has been linked to higher costs and longer hospital lengths of stay.<sup>10 16</sup>

Nonetheless, due to the low incidence of VTE in the pediatric population undergoing surgical intervention, prophylaxis is generally not used as it is in the adult population. As with any prophylactic regimen, the risks and benefits of any such intervention are used to derive recommendations to optimize outcomes. At present, few specific guidelines exist regarding VTE prophylaxis in children undergoing surgery.<sup>18 23 24</sup>

In the UK, the Association of Pediatric Anesthetists of Great Britain and Ireland (APAGBI) published guidelines for prevention of perioperative VTE in pediatric patients.<sup>24</sup> The guidelines suggest that all pediatric surgical candidates aged 13 years and older should be evaluated for their risk of VTE. In addition to non-pharmacological prophylactic measures (early mobilization, reduction of risk factors), in 'higher risk' adolescents (those with more than two risk factors) expected to have significantly reduced mobility for >48 hours, chemoprophylaxis with low molecular weight heparin could be considered. However, the authors note the limited nature of the existing evidence on the topic.

Similarly, citing a paucity of evidence on the efficacy of prophylactic anticoagulation in pediatric patients, the present guidelines from the British Society of Haematology for pharmacological thromboprophylaxis in children suggest that 'children, particularly adolescents, with multiple risk factors for VTE should be considered for thromboprophylaxis with (low molecular weight heparin)'.<sup>25</sup> The guidelines advocate for additional studies to elucidate risk factors for VTE in the pediatric population.

Attesting to the efficacy of thromboprophylaxis guidelines for reducing the risk of VTE, especially in critically ill children after trauma, a single center's VTE prophylaxis clinical practice guideline for pediatric trauma patients at high risk of VTE has shown prophylaxis to be associated with reductions in the incidence of VTE from 5.2% to 1.8% with no bleeding complications.<sup>23 26</sup> These findings suggest that thromboprophylaxis for high-risk patients can safely be applied.

It is hypothesized that patients' demographic, operative variables as well as perioperative events may influence the rate of VTE in pediatric surgical populations. However, due to the low incidence of such occurrences, a large national dataset is required to make such assessments. If risk factors for VTE could be better identified and quantified in the postoperative setting, the risk/benefit assessments for VTE prophylaxis could be better assessed in pediatric subpopulations.

## METHODS

### Study design and patient population

A retrospective cohort analysis was performed using data from the NSQIP-P database, aggregated from 2012 to 2016. This national database includes patients under 18 years of age undergoing surgery for non-traumatic indications (except for isolated limb section fractures) at multiple hospitals. The database included both inpatient and outpatient cases. Specifically trained nurses collected patient data perioperatively, and tracked patients for 30-postoperative days, regardless of discharge status.

All patients in the database from 2012 to 2016 with complete data were included in the analysis.

### Patient characteristics

Patient demographic variables were abstracted directly from the database, including: age, sex and American Society of Anesthesiologists (ASA) classification. Patient comorbidities were also assessed. While ASA class was used as a marker of overall health, individual and grouped comorbidities were also abstracted from the database. A number of comorbidity groupings were aggregated from defined variables in the database. Pulmonary comorbidities included: history of ventilator dependence, asthma, bronchopulmonary dysplasia/chronic lung disease, oxygen support, tracheostomy and structural pulmonary or airway abnormalities. Cardiac disease included: history of cardiac surgery, inotrope support, recent cardiopulmonary resuscitation and cardiac risk factors (major or minor as defined in the database). Neurological disease included cerebral palsy, neuromuscular disorder, seizure disorder, history of intraventricular hemorrhage, structural central nervous system abnormality and impaired cognitive status. Data on esophageal/gastric/intestinal disease, hematological disease, steroid use within 30 preoperative days and preoperative blood transfusion were also abstracted from the database.

## Surgical variables and 30-day outcomes

Data related to the operation performed were directly abstracted from the database. These included: operating surgeons' specialty and whether the operation was non-elective. Operative time in minutes, defined as the time from skin incision to closure, was directly abstracted from the database, as was length of stay in days (time from admission to discharge).

Thirty-day perioperative outcomes were directly abstracted from the database, and were classified into medical and surgical adverse events. Surgical adverse events were nerve injury, wound dehiscence (further subclassified as superficial or deep), flap failure, surgical site infection (SSI; superficial, deep or organ/space), and bleeding requiring transfusion. Medical adverse events were reintubation, renal failure and insufficiency, seizure, pneumonia, *Clostridium difficile* colitis, cardiac arrest, stroke, sepsis, septic shock, central line-associated bloodstream infection (CLABSI), urinary tract infection (UTI), coma and death. Any adverse event was noted when a patient experienced a medical or surgical adverse event.

Data on unplanned reoperation and readmission were also abstracted from the database. These were not categorized as medical or surgical adverse events but contributed to the total number of adverse events.

Patients were noted to have VTE if they experienced a DVT or PE. In calculating the cumulative incidence of adverse events, VTE contributed to the total number of adverse events (ie, 'any adverse event') and the number of medical adverse events. NSQIP-P includes variables which note the postoperative day on which adverse events occur. These variables were used to determine whether any of the perioperative adverse outcomes occurred before VTE.

## Statistical analysis

Chi-squared tests were used to compare categorical preoperative and intraoperative variables between patients who did and did not experience a postoperative VTE. These variables included comorbidities, categorical demographic variables (sex and ASA class), surgeons' specialty and whether a surgery was non-elective. Comparisons of continuous perioperative variables (operative time, length of stay) between patients who did and did not develop VTE, were performed using two-tailed t-tests after assessing for equality of variances using Levene's test.

Multivariable logistic regression analyses were performed. One logistic regression was used to determine the odds ratios (ORs) for VTE, for all demographic and operative variables. To reduce collinearity in the model, rather than including comorbidities, ASA class was included to represent patients' overall health status.

After controlling for patient age, sex and ASA class (ie, these variables were included as predictor variables in each model), a second set of 26 Firth logistic regressions was performed to determine the ORs of VTE, for

non-VTE adverse events that occurred before a VTE. Firth logistic regressions were used for these analyses, as this method is better suited to determining the odds of rare events than traditional multivariate regressions.<sup>27</sup>

Bonferroni corrections for multiple comparisons were performed for each group of univariate analyses. Statistical analysis was performed using Stata V.16.0 (StataCorp, College Station, Texas, USA).

## RESULTS

### Patient characteristics

In total, 361 384 patients were identified in the NSQIP-P database from 2012 to 2016 and included in the study after excluding patients with missing values. Patients' mean±SD age was 7.39±5.69 years (range 0–18 years), with 56.89% being male and 43.19% being female (table 1).

Regarding comorbidities, 24.54% of patients had an ASA class of III or greater (tables 1 and 2). The rates of individual and grouped comorbidities are given in table 2. The most common comorbidities in the dataset included neurological disease (23.82%), esophageal/gastric/intestinal disease (16.95%), pulmonary disease (14.80%) and cardiac disease (9.76%).

Of this population, 378 patients (0.10%) experienced a VTE within 30 postoperative days. Compared with patients without VTE, patients with VTE had a distribution of ages that included more older and younger patients ( $p<0.001$ ). However, groups were no different for sex ( $p=0.414$ ). Patients who developed VTE had a significantly higher overall ASA class and all seven types of comorbidities examined (table 2,  $p<0.001$  for all significant comparisons). Comorbidities most commonly seen among patients with VTE include esophageal/gastric/intestinal disease (46.30%), pulmonary disease (45.50%) and neurological disease (44.44%).

### Surgical variables and perioperative outcomes

From the overall cohort, general surgery was the most common treating specialty (137 181 patients, 37.96%), followed by orthopedic surgery (69,605, 19.26%) and otolaryngology (45 226, 12.51%; table 3). About a quarter of surgeries (26.65%) were non-elective, with patients who went on to have a VTE being more likely to undergo non-elective surgery ( $p<0.001$ ; table 3). Overall differences in surgeons' specialty (eg, general surgery vs orthopedic surgery) were noted between patients with and without VTE ( $p<0.001$ ).

Continuous operative variables are given in table 4. On average, operations lasted 95.57±93.27 min, with patients remaining in the hospital 4.61±13.53 days postoperatively. Patients with VTE had significantly longer operative times and lengths of hospital stay ( $p<0.001$  for both comparisons).

Temporally considering VTE relative to other postoperative adverse events, of the 378 patients who experienced a VTE, 221 (58.47% of patients with VTE) experienced an adverse event prior to VTE. The incidences of adverse

**Table 1** Demographic information for patients with and without postoperative VTE

Variables	Total		No VTE		VTE		P value*
	n=361 384		n=361 006 (99.90%)		n=378 (0.10%)		
	n	%	n	%	n	%	
Age, years (mean±SD)	7.39±5.69		7.39±5.69		7.27±6.77		<b>&lt;0.001</b>
≤1	71 227	19.71	71 107	19.70	120	31.75	
2–5	77 789	21.53	77 720	21.53	69	18.25	
6–10	81 015	22.42	80 980	22.43	35	9.26	
11–15	85 333	23.61	85 263	23.62	70	18.52	
16–18	46 020	12.73	45 936	12.72	84	22.22	
Sex							0.414
Male	205 424	56.89	205 217	56.85	207	54.76	
Female	155 960	43.19	155 789	43.15	171	45.24	
ASA class							<b>&lt;0.001</b>
I	116 379	32.23	116 369	32.23	10	2.65	
II	156 319	43.29	156 247	43.28	72	19.05	
III	79 763	22.09	79 568	22.04	195	51.59	
IV	8537	2.36	8446	2.34	91	24.07	
V	386	0.11	376	0.10	10	2.65	

\* $\chi^2$  test comparing patients with and without VTE. Bolding indicates statistical significance at  $p < 0.017$  (Bonferroni correction). ASA, American Society of Anesthesiologists; VTE, venous thromboembolism.

events in the overall study population, as well as adverse events preceding VTE, are given in [table 5](#). Considering patients who experienced an adverse event prior to VTE, 139 (36.77% of VTE) experienced a surgical adverse event, while 93 (24.60%) experienced a medical adverse event. Of the surgical adverse events experienced prior to VTE, bleeding requiring transfusion (117 patients, 30.95% of VTE), and organ/space SSI (19 patients, 5.03%) were most common. Of the medical adverse events experienced prior to VTE, unplanned reintubation was most common (40 patients, 10.58%), followed by sepsis (25, 6.61%) and pneumonia (20, 5.29%). Furthermore, 57

patients (15.08%) underwent reoperation prior to VTE, and 48 (12.70%) were readmitted before VTE.

### Logistic regression analysis

The first logistic regression analysis performed calculated the ORs of VTE for demographic and operative variables. Demographic variables significantly associated with VTE included: age 16–18 years relative to 11–15 years (OR 1.892, 95% confidence interval [CI] 1.374 to 2.606,  $p < 0.001$ ), age 6–10 years (OR 0.625, 95% CI 0.414 to 0.940,  $p = 0.024$ ) and ASA class II or higher ( $p < 0.001$  for each ASA class  $> I$ ). In the same model, operative variables

**Table 2** Comorbidities of patients with and without postoperative VTE

Comorbidities	Total		No VTE		VTE		P value*
	n=361 384		n=361 006 (99.90%)		n=378 (0.10%)		
	n	%	n	%	n	%	
ASA class $\geq$ III	88 686	24.54	88 390	2.45	296	78.31	<b>&lt;0.001</b>
Pulmonary disease	53 486	14.80	53 314	1.48	172	45.50	<b>&lt;0.001</b>
Cardiac disease	35 282	9.76	25 163	0.70	119	31.48	<b>&lt;0.001</b>
Esophageal/gastric/intestinal disease	61 259	16.95	61 084	1.69	175	46.30	<b>&lt;0.001</b>
Neurological disease	86 080	23.82	85 912	2.38	168	44.44	<b>&lt;0.001</b>
Hematological disease	10 984	3.04	10 916	0.30	68	17.99	<b>&lt;0.001</b>
Preoperative steroids	8319	2.30	8243	0.23	76	20.11	<b>&lt;0.001</b>
Preoperative transfusion	2948	0.82	2902	0.08	46	12.17	<b>&lt;0.001</b>

\* $\chi^2$  test comparing patients with and without VTE. Bolding indicates statistical significance at  $p < 0.006$  (Bonferroni correction for multiple corrections).

ASA, American Society of Anesthesiologists; VTE, venous thromboembolism.

**Table 3** Categorical perioperative factors in patients with and without postoperative VTE

Operative variable	Total n=361 384		No VTE n=361 006 (99.90%)		VTE n=378 (0.10%)		P value*
	n	%	n	%	n	%	
Surgical specialty							<b>&lt;0.001</b>
Cardiothoracic surgery	426	0.12	421	0.12	5	1.32	
Gynecology	848	0.23	846	0.23	2	0.53	
General surgery	137 181	37.96	136 950	37.94	231	61.11	
Neurosurgery	34 043	9.42	33 983	9.41	60	15.87	
Orthopedic surgery	69 605	19.26	69 557	19.27	48	12.70	
Otolaryngology (ENT)	45 226	12.51	45 207	12.52	19	5.03	
Urology	40 800	11.29	40 790	11.30	10	2.65	
Plastic surgery	33 255	9.20	33 252	9.21	3	0.79	
Non-elective surgery	96 306	26.65	96 162	26.64	144	38.10	<b>&lt;0.001</b>

\* $\chi^2$  test comparing patients with and without VTE. Bolding indicates statistical significance at  $p < 0.025$  (Bonferroni correction for multiple comparisons).

ENT, ear, nose and throat; VTE, venous thromboembolism.

significantly associated with higher risk of VTE were: non-elective surgery (OR 1.678, 95% CI 1.332 to 2.114,  $p < 0.001$ ) and longer operative time in minutes (OR 1.004, 95% CI 1.003 to 1.004,  $p < 0.001$ ). Compared with general surgery, cardiothoracic surgery was associated with a higher likelihood of VTE (OR 3.248, 95% CI 1.293 to 8.156,  $p = 0.012$ ). Furthermore, compared with general surgery, several surgical specialties were associated with lower odds of VTE. These were: neurosurgery (OR 0.622, 95% CI 0.463 to 0.837,  $p = 0.002$ ), orthopedic surgery (OR 0.496, 95% CI 0.341 to 0.704,  $p < 0.001$ ), otolaryngology (OR 0.465, 95% CI 0.288 to 0.749,  $p = 0.002$ ), urology (OR 0.310, 95% CI 0.162 to 0.594,  $p < 0.001$ ) and plastic surgery (OR 0.141, 95% CI 0.045 to 0.443,  $p = 0.001$ ). ORs and 95% CIs for this model are given in [table 6](#).

After controlling for patient age, sex and ASA class, 26 Firth logistic regression analyses were performed to calculate the ORs of VTE for postoperative adverse events that occurred before a VTE. Of the adverse events examined, any adverse event (OR 13.275, 95% CI 10.490 to 16.060,  $p < 0.001$ ), surgical adverse events (OR 12.358, 95% CI 9.559 to 15.156,  $p < 0.001$ ), medical adverse events (OR 11.750, 95% CI 8.957 to 14.543,  $p < 0.001$ ), reoperation (OR 11.479, 95% CI 8.668 to 14.290,  $p < 0.001$ )

and readmission (OR 11.741, 95% CI 8.931 to 14.551,  $p < 0.001$ ) were all associated with higher risk of a subsequent VTE.

In the same set of models, six of eight surgical adverse events studied were found to be associated with higher risk of subsequent VTE ( $p < 0.001$  for each significant association). Meanwhile, 8 of 13 medical adverse events were associated with increased risk of an ensuing VTE ( $p \leq 0.001$  for each significant comparison). The ORs for this set of regression analyses can be found in [table 7](#).

## DISCUSSION

Among hospitalized children, VTE is an adverse event which is highly morbid and potentially preventable. Previous work has investigated VTE in hospitalized children, as well as in children after trauma. However, few studies have examined VTE in pediatric patients undergoing surgery for other indications. Consequently, at present, children—including those at high risk for VTE—do not routinely receive prophylactic anticoagulation after non-trauma-related surgery.

To better identify which pediatric surgical patients are at risk of VTE and may benefit from pharmacological

**Table 4** Continuous perioperative variables in patients with and without postoperative VTE

Operative variable	Total n=361 384		No VTE n=361 006 (99.90%)		VTE n=378 (0.10%)		P value*
	Mean±SD	Mean±SD	Mean±SD	Mean±SD			
Operative time, min	95.57±93.27	95.50±93.20	163.52±129.07				<b>&lt;0.001</b>
Length of stay, days	4.61±13.53	4.58±13.48	30.92±29.04				<b>&lt;0.001</b>

\*Two-tailed t-test comparing patients with and without VTE, assuming unequal variances following the result of Levene's test. Bolding indicates significance at  $p < 0.025$  (Bonferroni correction for multiple comparisons).

SD, standard deviation; VTE, venous thromboembolism.

**Table 5** Total incidences of postoperative adverse events, adverse events occurring before a VTE

Adverse event	Total		Before VTE	
	n	%	n	% of VTE
	n=361 384		n=221 (58.47% of 378 VTE)	
Any adverse event	48 935*	13.54	221	58.47
Surgical adverse event	29284	8.10	139	36.77
Superficial SSI	3536	0.98	6	1.59
Deep SSI	766	0.21	4	1.06
Organ/Space SSI	2766	0.77	19	5.03
Superficial wound dehiscence	3514	0.97	8	2.12
Deep wound dehiscence	1250	0.35	–	0.00
Bleeding requiring transfusion	19454	5.38	117	30.95
Nerve injury	154	0.04	–	0.00
Flap failure	70	0.02	2	0.53
Medical adverse event	8,277*	2.29	93	24.60
Reintubation	1789	0.50	40	10.58
Pneumonia	1309	0.36	20	5.29
Sepsis	1680	0.46	25	6.61
Septic shock	299	0.08	12	3.17
CLABSI	271	0.07	9	2.38
<i>Clostridium difficile</i> colitis	281	0.08	–	0.00
UTI	1812	0.50	10	2.65
Renal failure	102	0.03	2	0.53
Renal insufficiency	143	0.04	1	0.26
Stroke	201	0.06	–	0.00
Seizure	584	0.16	11	2.91
Cardiac arrest	460	0.13	2	0.53
Coma	21	0.01	–	0.00
Death	1195	0.33	N/A	
Reoperation	9812	2.72	57	15.08
Readmission	17 835	4.94	48	12.70

\*Any adverse event and medical adverse events include all cases of VTE.

CLABSI, central line-associated bloodstream infection; N/A, not applicable; SSI, surgical site infection; UTI, urinary tract infection; VTE, venous thromboembolism.

thromboprophylaxis, using a national surgical database of over 360 000 children, the present study sought to characterize the incidence of VTE, and its risk factors, in children undergoing surgery across multiple surgical disciplines.

In a sample of 361 384 patients from the NSQIP-P database (2012–2016), the present study finds an incidence of VTE of 0.10%. This rate is consistent with previous

**Table 6** Multivariable ORs for VTE, controlling for demographic and operative variables

Variables	OR	95% CI	P value*
Age, years			
≤1	0.992	0.715 to 1.376	0.961
2–5	1.074	0.761 to 1.516	0.683
6–10	<b>0.625</b>	<b>0.414 to 0.940</b>	<b>0.024</b>
11–15	Referent		
16–18	<b>1.892</b>	<b>1.374 to 2.606</b>	<b>&lt;0.001</b>
Sex			
Female	Referent		
Male	0.977	0.797 to 1.199	0.827
ASA class			
I	Referent		
II	<b>4.502</b>	<b>2.317 to 8.745</b>	<b>&lt;0.001</b>
III	<b>19.715</b>	<b>10.316 to 37.677</b>	<b>&lt;0.001</b>
IV	<b>71.17</b>	<b>36.339 to 139.386</b>	<b>&lt;0.001</b>
V	<b>154.953</b>	<b>62.838 to 382.097</b>	<b>&lt;0.001</b>
Surgical specialty			
Cardiothoracic surgery	<b>3.248</b>	<b>1.293 to 8.156</b>	<b>0.012</b>
Gynecology	1.992	0.484 to 8.197	0.34
General surgery	Referent		
Neurosurgery	<b>0.622</b>	<b>0.463 to 0.837</b>	<b>0.002</b>
Orthopedic surgery	<b>0.496</b>	<b>0.341 to 0.704</b>	<b>&lt;0.001</b>
Otolaryngology (ENT)	<b>0.465</b>	<b>0.288 to 0.749</b>	<b>0.002</b>
Urology	<b>0.31</b>	<b>0.162 to 0.594</b>	<b>&lt;0.001</b>
Plastic surgery	<b>0.141</b>	<b>0.045 to 0.443</b>	<b>0.001</b>
Non-elective surgery	<b>1.678</b>	<b>1.332 to 2.114</b>	<b>&lt;0.001</b>
Operative time (min)	<b>1.004</b>	<b>1.003 to 1.004</b>	<b>&lt;0.001</b>

\*Logistic regression including all variables listed in this table.

Bolding indicates statistical significance at p<0.05.

ASA, American Society of Anesthesiologists; CI, confidence interval; ENT, ear, nose and throat; OR, odds ratio; VTE, venous thromboembolism.

reports of VTE in children, which find incidences of VTE of between 0.0629%<sup>1</sup> and 0.10%<sup>28</sup> in orthopedic surgery, 0.038% in general surgery<sup>14</sup> and 0.12%<sup>29</sup> to 8.9%<sup>30</sup> in trauma.<sup>6 18 31 32</sup>

Regarding risk factors for VTE, controlling for demographic and surgical variables, compared with patients aged 11–15 years, the present study identifies significantly increased risk of VTE among patients aged 16–18 years (OR=1.892, p<0.001), with children aged 6–10 years at lower risk (OR=0.625, p=0.024). This finding is consistent with previous studies, which suggests that adolescents are at higher risk for VTE.<sup>10 17 18 31 33</sup> As an example, a study of

**Table 7** Multivariable ORs for VTE, considering adverse events that occurred before a VTE

Adverse event	OR	95% CI	P value*
Any adverse event	<b>13.275</b>	<b>10.490 to 16.060</b>	<b>&lt;0.001</b>
Surgical adverse event	<b>12.358</b>	<b>9.559 to 15.156</b>	<b>&lt;0.001</b>
Superficial SSI	<b>9.134</b>	<b>6.115 to 12.152</b>	<b>&lt;0.001</b>
Deep SSI	<b>8.179</b>	<b>5.032 to 11.325</b>	<b>&lt;0.001</b>
Organ/Space SSI	<b>10.746</b>	<b>7.809 to 13.683</b>	<b>&lt;0.001</b>
Superficial wound dehiscence	<b>9.132</b>	<b>6.129 to 12.136</b>	<b>&lt;0.001</b>
Deep wound dehiscence	†		
Bleeding requiring transfusion	<b>12.009</b>	<b>9.207 to 14.810</b>	<b>&lt;0.001</b>
Flap failure	<b>6.448</b>	<b>3.386 to 9.511</b>	<b>&lt;0.001</b>
Nerve injury	†		
Medical adverse event	<b>11.750</b>	<b>8.957 to 14.543</b>	<b>&lt;0.001</b>
Reintubation	<b>10.597</b>	<b>7.773 to 13.420</b>	<b>&lt;0.001</b>
Pneumonia	<b>9.931</b>	<b>7.053 to 12.809</b>	<b>&lt;0.001</b>
Sepsis	<b>10.244</b>	<b>7.421 to 13.068</b>	<b>&lt;0.001</b>
Septic shock	<b>9.152</b>	<b>6.292 to 12.012</b>	<b>&lt;0.001</b>
CLABSI	<b>9.328</b>	<b>6.323 to 12.333</b>	<b>&lt;0.001</b>
<i>Clostridium difficile</i> colitis	†		
UTI	<b>9.616</b>	<b>6.709 to 12.524</b>	<b>&lt;0.001</b>
Renal failure	<b>7.172</b>	<b>3.947 to 10.396</b>	<b>&lt;0.001</b>
Renal insufficiency	<b>5.405</b>	<b>2.120 to 8.690</b>	<b>0.001</b>
Stroke	†		
Seizure	†		
Cardiac arrest	†		
Coma	†		
Reoperation	<b>11.479</b>	<b>8.668 to 14.290</b>	<b>&lt;0.001</b>
Readmission	<b>11.741</b>	<b>8.931 to 14.551</b>	<b>&lt;0.001</b>

\*Firth logistic regressions to determine the OR of VTE for preceding adverse events. Each regression controls variables of patient age, sex and ASA class. Bolding indicates statistical significance at  $p < 0.05$ .

†Insufficient number of observations for regression analysis.

ASA, American Society of Anesthesiologists; CI

, confidence interval; CLABSI, central line-associated bloodstream infection; OR, odds ratio; SSI, surgical site infection; UTI, urinary tract infection; VTE, venous thromboembolism.

hospitalized pediatric patients finds that compared with patients aged 1–4 years, those aged 15–17 years are at more than twice the risk of VTE.<sup>7</sup> Similarly, the APAGBI guidelines identify patients older than 13 years as being at higher risk for VTE.<sup>24</sup>

When separated from children aged 2–5 years, children aged 1 year or younger were not found to be at significantly increased risk for VTE, a finding that differs somewhat from previous studies, which have suggested that neonates are at increased risk for VTE.<sup>19</sup> The results of the present study could differ from those of prior analyses because of differences in the procedures and populations studied.

Regarding comorbidities, controlling for other factors, worse health status—as indicated by an ASA class >I—was significantly associated with VTE (compared with ASA class I, ASA class II OR=4.502, ASA class III OR=19.715, ASA

class IV OR=71.170, ASA class V OR=154.953;  $p < 0.001$  for all). Consistent with this finding, compared with patients who did not develop a postoperative VTE, patients with VTE had a significantly higher incidence of all seven types of comorbidities studied. Considered together, the finding that higher ASA class is associated with a higher risk of VTE, and the observation that multiple comorbidities are more common among patients with VTE, suggests that pediatric patients who are sicker are predisposed to postoperative VTE, with no single comorbidity driving this association. These findings aligned with previous work, which found that pediatric patients who developed VTE after surgery had at least one comorbid condition.<sup>5</sup> This is also consistent with the finding that, among adult patients, those with a higher comorbidity burden are at higher risk for VTE.<sup>34–36</sup>



Surgical specialty was another factor independently associated with patients' risk of VTE. Controlling for demographic and other operative factors, compared with general surgery (the specialty that treated the greatest number of patients in the study population), the present study found several surgical specialties to be independently associated with lower risk of VTE, including orthopedic surgery and plastic surgery (OR=0.496,  $p<0.001$  and OR=0.141,  $p=0.001$ , respectively). The result of plastic surgery was consistent with adult literature.<sup>37</sup> However, the result with orthopedic surgery was not expected and had not previously been reported.

Furthermore, neurosurgery, otolaryngology and urology were also found to have lower odds of VTE compared with general surgery. It is possible that this reflects a higher risk of VTE in the general surgical population rather than a reduction in risk conferred by other surgical specialties.

Patients undergoing cardiothoracic surgery, however, were found to be at higher risk of VTE when compared with patients receiving general surgery. This is consistent with previous literature in pediatric surgery, which finds higher rates of VTE after cardiothoracic procedures.<sup>38</sup>

Longer operative time was independently associated with VTE, while patients with VTE also had longer hospitalizations. An association between hospital length of stay and VTE risk in children had been reported previously,<sup>7 17 29</sup> as with operative time.<sup>12 13 38</sup> These findings are further corroborated in the literature around VTE in adults, where studies have found that longer operative times<sup>39</sup> and longer hospital stays<sup>39</sup> are associated with VTE.

Further relating to surgery, non-elective surgery was significantly associated with VTE. This finding is consistent with a study by Baker *et al*, which demonstrates a higher incidence of VTE in emergent surgery among pediatric patients undergoing orthopedic surgery.<sup>28</sup> These findings are consistent with the adult literature, which identifies non-elective surgery as a risk factor for thromboembolic events.<sup>40</sup>

Two recent studies have reported similar overall analyses. Ahn *et al* similarly used NSQIP-P to evaluate preoperative and perioperative factors associated with VTE in children undergoing surgery.<sup>13</sup> On multivariate analysis, the authors identify several risk factors for VTE: female sex, longer prehospital stay prior to surgery, current malignancy, preoperative mechanical ventilation, developmental delay, preoperative blood transfusion, preoperative infection and anesthesia time  $>2$  hours. Additionally, age of 2–9 years and Hispanic ethnicity were found to be negatively associated with VTE. The only variable associated with VTE consistently identified on multivariate analysis between the present study and that by Ahn *et al* is longer operative time, although all types of comorbidities examined in the current study are more common among patients with VTE. There are two reasons that potentially account for these differences. They focused

on comorbidities individually as opposed to grouped as ASA, and did not account for postoperative adverse events.

Similarly, Cairo *et al* identify risk factors for VTE in children undergoing abdominopelvic surgery.<sup>12</sup> In multivariate analysis, the authors found associations between VTE and age  $>15$  years, longer anesthesia time, preoperative renal failure, preoperative septic shock and ASA class  $>I$ . The present analysis similarly finds older age, longer operative time and ASA class  $>I$  to be associated with VTE.

Distinguishing the current study from these prior studies, to the authors' knowledge, the present study is the only study to date to consider postoperative adverse events and their relationship to VTE. Neither the studies by Ahn *et al* nor Cairo *et al* perform similar analyses.

In addition to identifying demographics, comorbidities and operative factors associated with postoperative VTE, the present study sought to identify postoperative adverse events that predisposed patients to VTE. In logistic regression analyses controlling for demographics and operative variables, a majority of adverse events studied were associated with VTE. Of the eight surgical adverse events examined, six were significantly associated with a subsequent VTE: SSI (superficial, deep and organ/space), superficial wound dehiscence, bleeding requiring transfusion, and flap failure. Additionally, medical adverse events were associated with a higher risk of VTE. Furthermore, reoperation was significantly associated with a subsequent VTE. In the adult literature, postoperative pneumonia has been found to be associated with VTE.<sup>41</sup> While not discernible from the dataset, it is likely that patients who sustain adverse events are less mobile after their complications, with stasis predisposing these patients to VTE.

Overall, the current study identified demographic, surgical and postoperative variables associated with the occurrence of VTE in children. Taken together, these findings suggest that children who are older, sicker (higher ASA class and comorbidity burden), who have longer, non-elective surgeries and who undergo general surgery or cardiothoracic surgery, are at higher risk of developing VTE. Furthermore, patients who develop any adverse event postoperatively, be it a surgical or medical complication, are at increased risk of an ensuing VTE.

The present study has several limitations. Foremost, the study faces the constraints of all retrospective analyses: namely, its limited ability to establish causal relationships between factors observed. Second, because NSQIP includes only the postoperative day on which an adverse event occurs, rather than the time, adverse events around a VTE can only be identified if they occur on different postoperative days from the VTE. This limitation somewhat blunted the study's ability to establish temporal relationships between adverse events. Third, the database does not include equal numbers of surgeries across surgical disciplines. Fourth, patients were only followed for 30 postoperative days. Therefore, adverse events occurring outside of this period were not captured. Fifth,

the present analysis is unable to identify which patients, if any, received chemoprophylaxis, or received postoperative anticoagulation. Sixth, there is not a universal screening protocol in place for VTE across the hospitals across the dataset. Therefore, interhospital variability in detection of VTE could affect the rate at which VTE was identified, likely leading to under-reporting.

With the above said, the current study clearly shows that certain pediatric subpopulations undergoing surgery are at elevated risks for VTE than the baseline postoperative VTE risk of 0.10%. The current study identified patient and surgery-related risk factors for postoperative VTE in children: older age, higher ASA class, non-elective surgery, general surgery and cardiothoracic surgery and longer operative time. Postoperatively, the study found that any adverse event, including medical and surgical adverse events, reoperation and readmission were associated with higher odds of an ensuing VTE.

Considering an illustrative example, according to the results of the current study, patients with ASA class III with at least one comorbidity who undergo non-elective surgery and experience a surgical postoperative adverse event would have a 19-fold higher incidence of VTE (overall incidence of 1.92%). These findings should clearly come into considerations when weighing the risks and benefits of VTE prophylaxis in pediatric postoperative patients.

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