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Risk of venous thromboembolism in pediatric hospitalized patients undergoing noncardiac surgery: A report from the Children's Hospital-Acquired Thrombosis consortium

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Abstract

Background: Surgery is a known risk factor for hospital-acquired venous thromboembolism (HA-VTE) in children.

Objectives: To assess whether the odds of HA-VTE differs across six anatomic sites of noncardiac surgery and to identify risk factors for HA-VTE in these children.

Methods: This was a multicenter, case–control study. Anatomic sites of surgery and risk factors for HA-VTE were collected on hospitalized pediatric patients who had undergone a single noncardiac surgery and developed HA-VTE (cases), and those who did not develop HA-VTE (controls), via the Children's Hospital-Acquired Thrombosis (CHAT) Registry. Logistic regression estimated the odds ratio (OR) and 95% confidence intervals (CIs) between six anatomic sites of surgery and 16 putative HA-VTE risk factors. Variables with a *p* value of 0.10 or less in unadjusted analyses were included in

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adjusted models for further evaluation. The final model used backward selection, with a significance level of 0.05.

Results: From January 2012 to March 2020, 163 cases (median age, 5.7 years; interquartile range [IQR], 0.3–14.2) and 208 controls (median age of 7.5 years; IQR, 3.7–12.9) met our criteria. There was no statistically significant increased odds of VTE among the types of noncardiac surgery. In the final adjusted model, central venous catheter (CVC; OR, 14.69; 95% CI, 7.06–30.55), intensive care unit (ICU) stay (OR, 5.31; 95% CI, 2.53–11.16), and hospitalization in the month preceding surgery (OR, 2.75; 95% CI, 1.24–6.13) were each independently significant risk factors for HA-VTE.

Conclusion: In children undergoing noncardiac surgery, placement of CVCs, admission/transfer to the ICU, or hospitalization in the month prior to surgery were positively associated with HA-VTE.

KEYWORDS

Hospitals, Pediatric, Surgery, Thrombosis, Venous thromboembolism

Essentials

- Surgery is a risk factor for venous thromboembolism in hospitalized children.
- We conducted a case–control study using the Children's Hospital-Acquired Thrombosis Consortium Registry.
- There was an increase in hospital-acquired venous thromboembolism in children undergoing noncardiac surgery.
- The risk was highest in those with a central venous catheter, intensive care unit stay, or hospitalization 1 month prior.

1 | BACKGROUND

Venous thromboembolism (VTE) is rare in hospitalized children. However, the incidence of VTE in children has increased from 5.3 to 37–58 cases per 10,000 hospital admissions.[1,2] This increase is likely multifactorial. As medicine becomes more advanced, providers are treating more chronic medical conditions and clinicians are more aware of and diagnostic imaging is more sensitive at detecting pediatric VTE.[1,3] The increased VTE prevalence is relevant because VTE in children can cause significant morbidity and mortality.[4,5] Postthrombotic syndrome, a common long-term complication of a VTE, develops in up to 26% of pediatric patients with a VTE, impacting quality of life.[1,4,6,7] Additional complications include progressive thrombosis, pulmonary embolism, and recurrent VTE. Mortality related to VTE in children has been reported to be up to 2.2%.[4,5]

Hospitalized children are at the greatest risk for VTE. They are up to 100-fold more likely to develop a VTE than the general population.[8] Up to 43% of pediatric patients undergoing surgery will develop a VTE.[9] Hospitalized children undergoing surgery are at increased risk of developing VTE compared to outpatient children undergoing surgery and have a ninefold increased risk compared to the general population.[10] Risk factors that have been associated with pediatric surgical VTE include an American Society of Anesthesiologists (ASA) classification greater than 2, nonelective surgery, operation time greater than 2 h, age greater than 15 years, adverse events surrounding surgery, and cardiothoracic surgery.[11,12] In addition, other factors besides surgery, including presence of a central venous catheter (CVC),

intensive care unit (ICU) admission or stay, prolonged hospital length of stay, immobility, and thrombophilia have been associated with VTE in children.[1,9,13-21] Less is known about their effect on postoperative hospital-acquired VTE (HA-VTE) risk.

Children undergoing cardiac surgery are known to have an increased prevalence of VTE and higher mortality compared to all hospitalized children having surgery.[13,22,23] The relative increase in pediatric cardiac surgery–associated HA-VTE has been shown to be up to 253%.[22] Pediatric cardiac surgery affects physiology of children differently.[23,24] Less is known about risk of HA-VTE in children undergoing noncardiac surgery.

The Children's Hospital-Acquired Thrombosis (CHAT) Registry is a multi-institutional registry of pediatric HA-VTE participants designed to address the risk for, and prevention of, VTE in hospitalized children.[9] Using the CHAT Registry, our objective was to assess whether the odds of HA-VTE differs across six anatomic sites of noncardiac surgery and identify HA-VTE risk factors in children undergoing noncardiac surgery.

2 | METHODS

2.1 | Study design

We conducted a multicenter, case–control study using data from the CHAT Registry. The CHAT Registry has been previously described in detail.[9] Briefly, the Registry consists of HA-VTE cases diagnosed

since January 1, 2012, and institution and year of admission matched controls from eight US pediatric hospitals. These hospitals are all large, tertiary care centers for children. Each participating hospital was granted a waiver of informed consent by its institutional review board. The study was performed with prior approval and was considered exempt by the research and ethic institutional board at Akron Children's Hospital.

2.2 | Eligibility

Eligible patients were hospitalized children aged 0–21 years of age. For this analysis, a data cutoff of March 2020 was used. All HA-VTE cases were hospitalized participants who had a radiologic imaging-confirmed VTE during their admission. Non-VTE controls were hospitalized participants without a VTE diagnosis on admission or during their hospitalization and were matched to cases based on institution and admission year. All participants had a single noncardiac surgery during their hospitalization. Cases were excluded if their VTE was diagnosed prior to their surgery, if they had a cardiac surgery during their hospitalization, or if they had multiple surgeries during their hospitalization. As this analysis was restricted to participants who had noncardiac surgery, the original 1:1 case–control matching scheme of the CHAT Registry is not guaranteed.

2.3 | Data collection, management, and quality assurance

Multiple variables during admission were evaluated from the data elements within the CHAT Registry, as has been previously published.[9] Demographic data included age at admission, sex, race, and ethnicity. History of cancer, autoimmune and inflammatory disorders, history of VTE, thrombophilia, and other conditions were collected. Variables during admission included admission or transfer to the ICU, length of hospital admission, CVC placement, and measurement of mobility using the Braden Q mobility score.[25] Variables were captured prior to the HA-VTE diagnosis date for cases and discharge date for controls.

Data were collected using standardized data collection forms that were provided to each participating hospital within Research Electronic Data Capture.[26,27] Each month, reports were sent to participating sites' research staff and principal investigator to identify missing or flagged data. Despite this review, there were high counts of missing/unknown values provided for race, thrombophilia, and Braden Q mobility score.

2.4 | Definitions

A diagnosis of a HA-VTE was confirmed by radiologic imaging, which consisted of Doppler ultrasonography, computed tomography scan, venography, echocardiogram, or magnetic resonance imaging.

CVC catheters included Broviac and Hickman catheters; implanted port; and internal jugular, subclavian, and femoral CVC.

A history of autoimmune/inflammatory disorders was specified by the individual institutional sites and included not specified, systemic lupus erythematosus, celiac disease, inflammatory bowel disease, and juvenile rheumatoid arthritis.

Immobility was defined as a Braden Mobility score of 1 or 2 (completely immobile or very limited mobility).[26]

Thrombophilia testing included antiphospholipid syndrome, antithrombin deficiency, factor V Leiden, homocysteine level, factor VIII levels, lipoprotein A, plasminogen activator inhibitor-1 mutation, protein C or S deficiency, prothrombin gene mutation, and von Willebrand antigen and activity. The diagnosis of thrombophilia was determined by the individual institutional providers.

For those with a history of VTE, other conditions included protein-losing enteropathy, unstable hemoglobin, and parenteral nutrition dependence.

Intensive care unit was defined as any subject admitted or transferred to either the neonatal ICU (NICU) or pediatric ICU.

The types of surgery included thoracic; abdominal/genitourinary; ear, nose, and throat (ENT); neurosurgery; orthopedic; and other. The surgical category was determined by the participating institution within the standardized collection form.

The other category included cases of plastic or ophthalmologic surgeries of the head and neck regions.

2.5 | Statistical analysis

Study variables were summarized according to HA-VTE case or control status using medians and interquartile ranges (IQRs) for continuous variables and counts and percentages for categorical variables. Unadjusted and adjusted logistic regression models with Firth penalized likelihood were used to assess associations with VTE development due to small numbers in some groups. Variables with a p value of less than 0.10 from unadjusted analyses were further assessed in an adjusted model, and then a backward selection procedure with a significance level of 0.05 to retain variables was performed to arrive at the final parsimonious model. Statistical analysis was conducted using SAS Software version 9.4 (SAS Institute).

3 | RESULTS

A total of 2171 participants were identified in the CHAT Registry on March 25, 2020, and 798 (36.8%) had surgery during their hospitalization. After exclusion of 309 participants with cardiac surgery, and 118 participants who had multiple surgeries, 371 were included for analysis, representing 163 HA-VTE cases and 208 controls (Figure 1).

Table 1 presents results from descriptive analyses and unadjusted logistic regression analyses involving participants who underwent a single noncardiac surgery ($n = 371$). The median age of cases was 5.7 years (IQR, 0.3–14.2), and the median age of controls was 7.5 years (IQR, 3.65–12.85; $p = 0.07$). Males represented 54.6% of cases ($n = 89$) and 45.4% of controls ($n = 103$). The most common anatomic sites of surgery were abdominal/genitourinary ($n = 69$; 42.3%) and neurosurgeries ($n = 41$; 25.2%) among cases, and abdominal/genitourinary ($n = 62$; 29.8%) and ENT surgeries ($n = 61$; 29.3%) among controls.

Unadjusted logistic regression analyses identified several putative risk factors for the multivariable model including prior hospitalization, ICU admission/transfer, immobility; CVC placement; length of stay; and surgery type. Due to a high frequency of missing data, race, thrombophilia, and Braden Q mobility score were only descriptively analyzed.

Variables with a p value of less than 0.10 from unadjusted analyses were included in multivariable analysis shown in Table 2. In the adjusted model, ICU admission/transfer, prior hospitalization within 1 month of admission, and CVC placement were each statistically significant, independent risk factors for HA-VTE. These factors remained independently statistically significant in an additional parsimonious model using backward elimination.

4 | DISCUSSION

HA-VTE remains a cause of morbidity and mortality in hospitalized pediatric surgical patients.[15,16] After multivariable adjustment, this multicenter case–control study of hospitalized pediatric participants undergoing noncardiac surgery identified CVC, ICU stay, and hospitalization within the prior month as independent risk factors for HA-VTE.

One of the early findings from the CHAT Registry was that 57% of HA-VTE participants were admitted/transferred to an ICU during their hospital stay.[9] Our study demonstrated that in those participants undergoing noncardiac surgery, the odds of developing a HA-VTE was increased in those admitted/transferred to the ICU with an odds ratio (OR) of 4.88. Almost 72% of the participants who developed a HA-VTE developed the thrombus while admitted in the ICU, and the remainder were after discharge from the ICU. There is a lack of previous studies of pediatric surgery-associated VTE specifically evaluating ICU admission as a risk factor. However, previous studies did evaluate clinical acuity and markers of illness severity in other ways including ASA score, preoperative blood transfusions, preoperative ventilation, intubation, septic shock, and sepsis and found an association with increased risk of VTE.[11,12,28-30] Ahn et al.[12] and Sherrod et al.[29] both found preoperative ventilator requirement was associated with the development of a VTE. Also Cairo et al.[28] in 2018 and Sherrod et al.[29] showed preoperative sepsis to be associated with the development of a postoperative VTE. Additionally, Hanson et al.[31] looked at critically ill patients undergoing surgery and found that in those on mechanical ventilation with a CVC and major surgery/trauma to the brain or abdomen, the adjusted risk of VTE was greater than 2%. Robinson et al.[30] evaluated patients admitted to the NICU and found that those who had undergone an invasive surgery had an OR of 3.24 for developing a VTE. It is clear that the critically ill nature of the patients admitted to the ICU is associated with an increased risk of development of a thrombus. Our study suggests that the noncardiac surgical population admitted/transferred to the ICU has higher odds of developing a HA-VTE than if these participants were admitted to non-ICU areas of the hospital; however, our study was neither designed nor powered to detect differential risk factors with separate subpopulations of critically ill versus non–critically ill children.
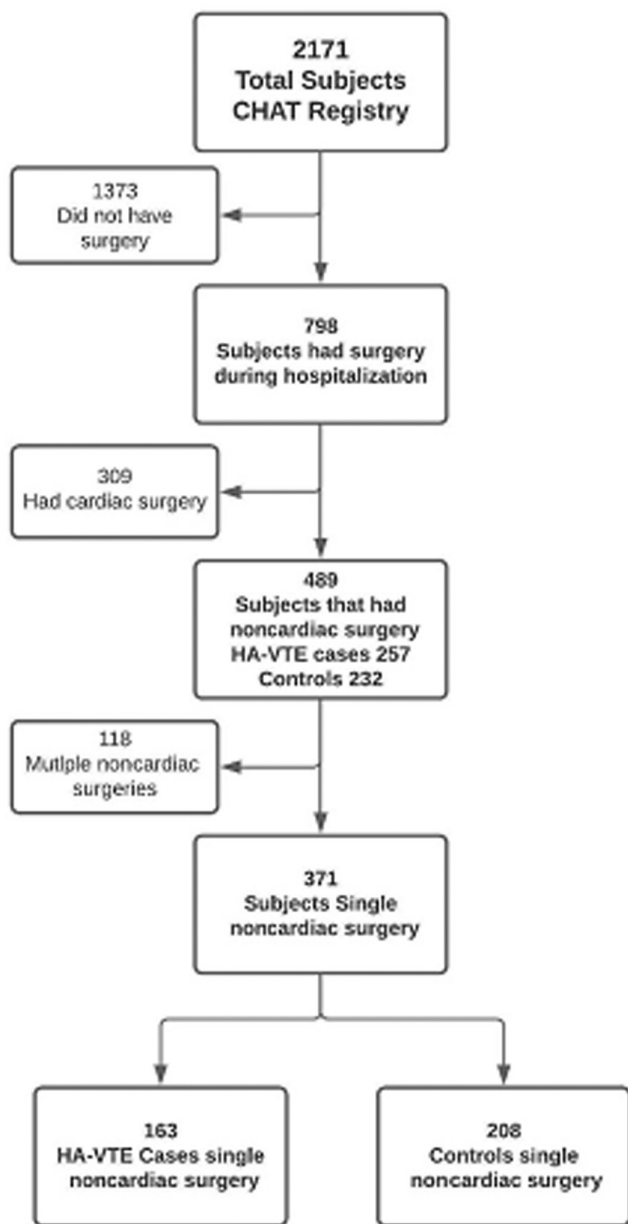

FIGURE 1 Participant inclusion and exclusion from the CHAT Registry

TABLE 1 Descriptive characteristics and results of univariate logistic regression analysis for HA-VTE cases and non–HA-VTE controls

Variables	Control (N = 208)	HA-VTE case (N = 163)	Unadjusted OR (95% CI)	p value
Age at admission, years, median (IQR)	7.5 (3.65–12.85)	5.7 (0.3–14.2)	0.97 (0.94–1.00)	0.07
Sex, n (%)				
Male	103 (49.52)	89 (54.6)	1.23 (0.81–1.85)	0.33
Female	105 (50.48)	74 (45.4)	Reference	
Race, n (%)				
White	49 (23.56)	65 (39.88)	e	
Black	9 (4.33)	9 (5.52)	e	
Asian/Pacific Islander/Native Americans	6 (2.88)	6 (3.68)	e	
Missing	144 (69.23)	83 (50.92)	e	
Ethnicity, n (%)				
Hispanic/Latino	66 (31.73)	54 (33.13)	1.18 (0.75–1.85)	0.48
Non-Hispanic	125 (60.1)	87 (53.37)	Reference	
Missing	17 (8.17)	22 (13.5)	e	
BMI, median (IQR)	17.06 (15.09–21.15)	16.68 (14.45–19.94)	0.98 (0.94–1.01)	0.22
History or current diagnosis of cancer, n (%)	13 (6.25)	19 (11.66)	1.98 (0.95–4.14)	0.07
History of autoimmune/inflammatory disorders,[a] n (%)	4 (1.92)	9 (5.52)	2.98 (0.90–9.86)	0.07
History of VTE and other related conditions,[b] n (%)	6 (2.88)	11 (6.75)	2.44 (0.88–6.73)	0.09
Asparaginase, rFVIIa, or estrogen administration, n (%)	2 (0.96)	4 (2.45)	2.59 (0.47–14.33)	0.28
Hospitalized within 1 month prior to admission, n (%)	20 (9.62)	60 (36.81)	5.48 (3.13–9.59)	<0.001
Immobile at admission, n (%)	12 (5.8)	17 (10.43)	1.89 (0.88–4.08)	0.10
Trauma 1 week prior to admission, n (%)	12 (5.77)	12 (7.36)	1.30 (0.57–2.97)	0.54
Thrombophilia, n (%)				
Yes	2 (0.96)	16 (9.82)	e	
No	2 (0.96)	19 (11.66)	e	
Unknown	204 (98.08)	128 (78.53)	e	
Intensive care unit admission/transfer	29 (13.94)	120 (73.62)	17.22 (10.19–29.11)	<0.001
CVC during admission, n (%)				
No	189 (90.87)	38 (23.31)	Reference	
Yes	19 (9.13)	125 (76.69)	32.72 (18.04–59.34)	<0.001
Recent Braden Score, n (%)				
Completely immobile	1 (0.48)	1 (0.61)	e	
Very limited	3 (1.44)	16 (9.82)	e	
Slightly limited	11 (5.29)	24 (14.72)	e	
No limitations	5 (2.40)	6 (3.68)	e	
Unknown	188 (90.38)	116 (71.17)	e	
Length of hospital admission,[c] median days (IQR)	2 (1–4)	8 (4–18)	1.12 (1.08–1.17)	<0.001
Anatomic sites of surgery, n (%)				
Abdominal/genitourinary	62 (29.81)	69 (42.33)	Reference	
ENT	61 (29.33)	7 (4.29)	0.10 (0.04–0.24)	<0.001
Neurosurgery	20 (9.62)	41 (25.15)	1.84 (0.98–3.48)	0.06
Orthopedic	54 (25.96)	21 (12.88)	0.35 (0.19–0.64)	<0.001
Thoracic	5 (2.4)	18 (11.04)	3.23 (1.13–9.23)	0.03
Other	6 (2.88)	7 (4.29)	1.05 (0.33–3.29)	0.94
Surgery length,[d] hours (IQR)	1.18 (0.53–2.78)	1.94 (1.02–4.3)	1.08 (0.99–1.17)	0.08

Abbreviations: BMI, body mass index; CI, confidence interval; CVC, central venous catheter; ENT, ear, nose, and throat; HA-VTE, hospital-acquired venous thromboembolism; IQR, interquartile range; OR, odds ratio; rFVIIa, recombinant factor VIIa; VTE, venous thromboembolism.

[a]Includes autoimmune/inflammatory disorder not specified, systemic lupus erythematosus, celiac disease, inflammatory bowel disease, and juvenile rheumatoid arthritis.

[b]Includes protein-losing enteropathy, unstable hemoglobin, thrombophilia, and parenteral nutrition dependence.

[c]Per day from admission to VTE diagnosis for cases or discharge for controls. ORs were calculated using length of hospital admission as a continuous variable.

[d]Among N = 146 cases and N = 194 controls due to missing data.

[e]Not estimated due to low affected subject numbers or high numbers of unknown/missing values.

TABLE 2 Results of multivariable logistic regression analysis for HA-VTE cases and non–HA-VTE controls

Variables	Model 1[a] OR (95% CI)	p value	Model 2[b] OR (95% CI)	p value
Age at admission	1.01 (0.95–1.07)	0.708		
History or current diagnosis of cancer	0.68 (0.21–2.21)	0.517		
History of autoimmune/inflammatory disorders[c]	2.77 (0.51–15.05)	0.237		
History of VTE and other conditions[d]	0.60 (0.12–2.91)	0.526		
Hospitalized within 1 month prior to admission	**2.77 (1.23–6.25)**	**0.014**	**2.75 (1.24–6.13)**	**0.013**
Immobile at admission	1.13 (0.32–3.97)	0.853		
Intensive care unit admission/transfer	**6.32 (2.78–14.35)**	**<0.001**	**5.31 (2.53–11.16)**	**<0.001**
CVC	**12.11 (5.66–25.95)**	**<0.001**	**14.69 (7.06–30.55)**	**<0.001**
Length of hospital admission, days[e]	1.01 (0.99–1.02)	0.420		
Anatomic sites of surgery				
Abdominal/genitourinary	Reference		Reference	
ENT	0.52 (0.17–1.60)	0.254	0.43 (0.14–1.30)	0.14
Neurosurgery	1.01 (0.36–2.81)	0.983	1.22 (0.46–3.25)	0.70
Orthopedic	1.31 (0.50–3.40)	0.582	1.34 (0.53–3.36)	0.54
Thoracic	2.54 (0.51–12.52)	0.254	2.88 (0.62–13.40)	0.18
Other	0.49 (0.07–3.63)	0.483	0.69 (0.10–4.94)	0.71
Surgery length, h	1.07 (0.94–1.21)	0.323	1.06 (0.94–1.20)	0.34

Abbreviations: CI, confidence interval; CVC, central venous catheter; ENT, ear, nose, and throat; HA-VTE, hospital-acquired venous thromboembolism; OR, odds ratio; VTE, venous thromboembolism.

[a]Includes variables with unadjusted p-value <0.10; model used $n = 338$ observations due to missing covariate values.

[b]Final parsimonious model with surgery type, surgery length, and variables identified from backward selection of model 1; model used $n = 340$ observations due to missing surgery length values for $n = 31$ participants.

[c]Includes autoimmune/inflammatory disorder not specified, systemic lupus erythematosus, celiac disease, inflammatory bowel disease, and juvenile rheumatoid arthritis.

[d]Includes protein losing enteropathy, unstable hemoglobin, thrombophilia, and parenteral nutrition dependence.

[e]From admission to VTE diagnosis for cases or discharge for controls.

Bolded are the statistically significant values.

Given what is known regarding thrombotic risks of CVCs, it is not surprising that our study found that the odds of developing a HA-VTE in children undergoing noncardiac surgery are significantly increased in the presence of a CVC, with an OR of 14.69.[9,13,14,17,20,32-42] Amankwah et al.[43] found that critically ill neonates in the NICU with a CVC in place have an OR of 29.04 of developing a HA-VTE. In this same study, major surgery increased the odds of developing HA-VTE in a univariate analysis; however, this did not remain statistically significant in the multivariate model.

Hospitalization in the month prior to admission was an independent risk factor for developing a HA-VTE with an OR of 2.9. In the pediatric population, there is a trend of increased readmission rates with up to 12% of children being readmitted within 30 days of discharge.[3] This trend is most prominent in the those with chronic medical conditions, a population known to be at risk for HA-VTE.[3] Raffini et al.[1] specifically looked at the increased incidence trends of VTE and found that 63% of the patients who developed VTE had one or more chronic medical conditions. The risk factor associated with an increase in pediatric patients with chronic medical conditions seems to be influencing readmission rate and association with the development of a HA-VTE.[1,3,15,19] This is supported by our results showing the odds of developing a HA-VTE was 2.93 in those

participants undergoing noncardiac surgery with inflammatory/autoimmune disorders.

Our study demonstrated that the odds of developing a HA-VTE did not differ among the different anatomic sites of noncardiac surgery. Based on previous studies, this was not expected. From the American College of Surgeons' National Surgical Quality Improvement Project (NSQIP) Pediatric Registry, Mets et al.[11] found cardiothoracic surgery, compared to general surgery, had increased odds of VTE with an OR of 3.2, but did not find an increased risk of VTE with six other surgical specialties. Sherrod et al.[29] also used data from the NSQIP Pediatric Registry to demonstrate that cardiothoracic surgery had the highest HA-VTE rate, followed by general surgery, ENT, and neurosurgery. The difference in our results compared to these is likely explained by the adjustment for other HA-VTE risk factors, mainly ICU admission/transfer and CVC placement.

In contrast to previous studies, our study did not find age, obesity, contraceptive use, use of asparaginase, immobility, hospital length of stay, and trauma to be independent risk factors for HA-VTE in children undergoing noncardiac surgery.[10,14,18,21,37] This is likely due to our sample size and missing data elements around these risk factors. It could also be related to the operational definitions employed for these risk factors and the methods/quality of their data capture. For

instance, immobility is captured at the time of admission, and it is unclear if a subject's immobility scores changed during or after the surgery. Additional studies will be necessary to understand the impact of these factors on risk of pediatric surgery-related HA-VTE.

One of the limitations of this study is that several HA-VTE participants had missing data points, including thrombophilia testing results, Braden Q mobility scores, and race/ ethnicity. These missing data may influence the ability to find an association with these risk factors and their associated odds of HA-VTE. Additionally, the use of a registry did not allow us to probe further into categorizing surgeries as urgent, scheduled, or emergent, which may have provided additional insight into risk. Another limitation is that our study inclusion criteria included only pediatric participants that had a single non-cardiac surgery, so the matching schema of our cases and controls developed by the CHAT Registry to match 1:1 by institution and year may not have been strictly maintained. This may have given rise to institution- or surgery-specific variables that could not be fully accounted for in our analysis. Additionally, the sample sizes for each type of surgery in our cases and controls differed, which may have skewed our results to those cases and controls with more extensive or invasive surgeries. Another limitation is that we were not able to evaluate some intraoperative risk factors that have been previously identified to be risk factor for HA-VTE. While the CHAT Registry was not designed to evaluate intraoperative risk factors for VTE, the risk factors found from these previous studies are an important component of assessing HA-VTE risk in this population and may impact the risk factors for HA-VTE in our study.

The next step will be to develop a risk assessment model for this patient population that can be applied and validated prospectively to aid clinicians in determining a priori HA-VTE risk among pediatric patients undergoing noncardiac surgery to assist in clinical decision-making regarding HA-VTE prevention measures.

In conclusion, among children undergoing noncardiac surgery, the presence of a CVC, ICU stay, and previous hospitalization within 1 month are each statistically significant, independent risk factors for HA-VTE.

AUTHOR CONTRIBUTIONS

The CHAT Consortium Registry was conceived by J. Jaffray, B. Branchford, G. Young, and N. A. Goldenberg. This subanalysis was conceived by E. T. Stephens and J. H. Fargo and analyzed by A. H. Nguyen and E. Amankwah. J. H. Fargo provided mentorship and guidance for the study. All other authors entered patient data. E.T. Stephens was the lead investigator and wrote the first draft of the manuscript, which was subsequently edited by all co-authors.

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