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Risk Factors For Venous Thromboembolism In Children After Surgery In General & Specific To Orthopaedics

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Abstract

RISK FACTORS FOR VENOUS THROMBOEMBOLISM IN CHILDREN AFTER SURGERY IN GENERAL & SPECIFIC TO ORTHOPAEDICS.

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Venous thromboembolism (VTE, including deep venous thrombosis and pulmonary embolism) was studied in children undergoing surgery in general, and those specifically undergoing orthopaedic surgery. Due to the low overall incidence of VTE in this population, VTE chemoprophylaxis is not routinely recommended. However, understanding and quantifying risk factors can help define the risk/benefit considerations of these practices.

The study populations were identified from 2012-2016 National Surgical Quality Improvement Project Pediatric (NSQIP-P) database. Patient demographics, comorbidity factors, and 30-day postoperative outcomes were defined. The populations were then dichotomized into those that did and not have VTE diagnosed in the first 30 postoperative days. In multivariate analysis, patient and surgical factors were controlled for to identify independent risk factors for VTE.

For the overall pediatric surgical population, 361,384 patients were identified, of which VTE was diagnosed in 378 (0.10%). Predictors of VTE in the pediatric surgical population were found to be: American Society of Anesthesiologists (ASA) class of II or greater, age 16-18 years old, non-elective surgery, general surgery (compared to several

other surgical specialties), cardiothoracic surgery, and longer operative time ($p<0.001$ for each comparison). Further, most adverse events investigated were associated with increased risk of subsequent VTE ($p<0.001$).

For the orthopaedic-specific study, (2) Of 81,490 pediatric orthopaedic surgical patients, 60 (0.07%) were identified as experiencing postoperative VTE. Predictors of VTE in pediatric orthopaedic surgical population were found to be: age 16-18 years ($p = 0.002$; compared to ages 11-15), ASA class III-V ($p = 0.003$; compared to ASA class I-II), preoperative blood transfusion ($p < 0.001$), arthrotomy ($p < 0.001$), and femur fracture ($p < 0.001$). Further, any adverse event, major adverse events, minor adverse events, reoperation, and readmission were found to be associated with increased risk of subsequent VTE ($p < 0.001$ for each category of adverse outcome).

The overall incidence of VTE in the postoperative pediatric population and orthopaedic population was found to be 0.10% and 0.07%, respectively. For both cohorts, defined patient, surgical, and postoperative factors were found to be associated with such VTE events. The identification of risk factors for VTE in both patient populations raises the question of VTE prophylaxis in select high-risk subpopulations.

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Introduction to Chapters

Venous thromboembolism (VTE, which includes deep vein thrombosis and pulmonary embolism) is a rare but highly morbid adverse outcome among children undergoing surgery that is possibly preventable with appropriate prophylaxis.[1-4] Predisposing factors for VTE following surgery have been extensively characterized in adults.[5-7] Nonetheless, similar studies have been limited in the pediatric populations due to low incidence and limited power for related studied.

Given the paucity of evidence around VTE in pediatric surgical candidates and its severity, this thesis aims to expand the literature for this serious complication in both the general surgical population, and pediatric orthopaedic patients, who have historically thought to be at greater risk. To this end, in Chapter 1, we characterize the incidence ofrisk factors for VTE in children undergoing surgery. Additionally, to identify additional dynamic risk markers for VTE in the postoperative setting, in a novel analysis, we identify adverse events whose occurrence is associated with higher risk of an ensuing VTE.

As VTE is a rare but serious adverse event in children, large datasets are required to draw conclusions about patient and perioperative factors that predispose patients to this complication. Therefore, in the analyses presented here, I leverage the American College of Surgeons (ACS) National Surgical Quality Improvement Project (NSQIP) Pediatric database, which captures patient and perioperative variables for children undergoing a range of surgical procedures. All patients in the database are followed by specifically trained nurses for 30 days after surgery, and the data is subject to regular quality audits, ensuring its integrity and accuracy. Given the robustness of the dataset and the fact that data is drawn from large hospital systems across the United States, I felt that this dataset was well suited to this analysis.

Starting broadly, Chapter 1 focuses on VTE in children undergoing surgery for any indication. As a range of frequencies have been reported in the literature, the analysis begins by characterizing the incidence of VTE in pediatric surgical patients. Risk factors for the complication are then identified, considering patient and perioperative factors, including patient demographics, surgeon's specialty (a proxy for type of surgery) and operative time. Further, postoperative adverse outcomes and hospital length of stay were evaluated as possible risk factors for subsequent development of a VTE. Chapter 2 focuses specifically on the pediatric orthopaedical surgical population and employs a similar methodology.

Chapter 1

Venous Thromboembolism in Children Undergoing Surgery: Incidence, Risk Factors, and Related Adverse Events

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Background

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[1,2,5-11]), and in children after trauma (estimated incidence between 0.02% and 0.33%[12,13]), there has been little investigation of VTE in children undergoing surgery.[14-16]

Several risk factors for VTE in children have been identified, including hematologic malignancy (2.5-fold increased risk),[10] orthopaedic surgery (2.2-fold increased risk),[10] severe or critical injury (2.5 to 43.5-fold increased risk),[13,17-20] prolonged ventilator use (1.3-fold increased risk),[21] and longer hospital length of stay (1.03-fold increased risk)[20]. Among children, VTE is most common in neonates and adolescents, with adolescents at highest risk.[2,8-10,17,19-22] Additionally, VTE occurs more commonly in tertiary care centers than in community hospitals.[2,7]

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.[16] Georgopoulos *et al*. investigated VTE in children after elective pediatric orthopaedic surgery and found the incidence to be 0.063% and risk factors to be older age, obesity, and surgical complications.[5]

Additionally, Ahn *et al*. and Cairo *et al*. have recently identified risk factors for VTE among pediatric surgical patients, both using the NSQIP-Pediatric database.[14,15] 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),[3,4] and increased risk of mortality (relative risk of 6.27 compared to patients without VTE,[2,3] with mortality related to VTE estimated at 2.2%).[1] Further, among pediatric patients treated after trauma, VTE has been linked to higher costs and longer hospital lengths of stay.[12,18]

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.[20,23,24]

In the United Kingdom, the Association of Pediatric Anesthetists of Great Britain and Ireland (APAGBI) published guidelines for prevention of perioperative VTE in pediatric patients.[24] The guidelines suggest that all pediatric surgical candidates 13 and older should be evaluated for their risk of VTE. In addition to nonpharmacologic prophylactic measures (early mobilization, reduction of risk factors), in ‘higher risk’ adolescents (those with more than 2 risk factors) expected to have significantly reduced mobility for more than 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].”[25] 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.[23,26] 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 sub-populations.

Methods

Student Contributions

The thesis author (EJM) was responsible for study design, data collection, data analysis and interpretation, manuscript preparation, and critical revision of the manuscript. Co-author RPM contributed to study design and data analysis, while faculty sponsor JNG contributed to study design, interpretation of analysis, and critical revision of the manuscript.

Ethics Statement

This research was conducted to the highest ethical standards, with respect to patient confidentiality and data privacy. In accordance with American College of Surgeons' policies, no attempts were made to identify patients based on the information provided in the National Surgical Quality Improvement Project database. Data were used strictly for the analyses presented herein.

Human Subjects Research

Given that this study utilized data from a de-identified, publicly available database provided through the American College of Surgeons, this project was found to be exempt from Institutional Review Board approval.

The dataset used for this analysis closely represents the national pediatric surgical population, and it includes patients of all races and sexes.

Study design and patient population

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

All patients in the database from 2012-2016 with complete data were included in the analysis. The current study was found to be exempt from Institutional Review Board review.

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 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). Neurologic 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, hematologic 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 they were classified into medical and surgical adverse events. Surgical adverse events were nerve injury, wound dehiscence (further subclassified as superficial or deep), surgical site infection (SSI; superficial, deep, or organ/space), bleeding requiring transfusion, and flap failure. Medical adverse events were reintubation, pneumonia, sepsis, septic shock, seizure, cardiac arrest, urinary tract infection (UTI), stroke, renal failure and insufficiency, central line associated bloodstream infection (CLABSI), *Clostridium difficile* colitis, 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 venous thromboembolism (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 (i.e., 'any adverse event') and then number of medical adverse events. NSQIP-P includes variables which note the postoperative day on which all 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), 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 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 (i.e., these variables were included as predictor variables in each model), a second set of twenty-six Firth logistic regressions was performed to determine the odds ratios 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.[27]

Bonferroni corrections for multiple comparisons were performed for each group of univariate analyses. Statistical analysis was performed using Stata version 16.0 (StataCorp, LLC, College Station, TX, 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±standard deviation (SD) age was 7.39±5.69 years (range 0-18 years), with 56.88% being male, and 43.19% being female (Table 1).

Regarding comorbidities, 24.54% of patients had an ASA class of three or greater (table 1, 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 to 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 neurologic 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 orthopaedic surgery (69,605, 19.26%) and otolaryngologic surgery (45,226, 12.51%; Table 3). About a quarter of surgeries (26.67%) 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 (e.g., general surgery vs. orthopaedic 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 minutes, 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 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%). Further, 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 odds ratios of VTE for demographic and operative variables. Demographic variables significantly associated with VTE included: age of 16-18 years relative to 11-15 years old (odds ratio [OR] 1.892, 95% confidence interval [CI] 1.374-2.606, $p<0.001$), age 6-10 years (OR 0.625, 95% CI 0.414-0.940, $p = 0.024$), and ASA class of II or higher ($p< 0.001$ for each ASA class greater than I). In the same model, operative variables significantly associated with higher risk of VTE were: non-elective surgery (OR 1.678, 95% CI 1.332-2.114, $p<0.001$) and longer operative time in minutes (OR 1.004, 95% CI 1.003-1.004, $p<0.001$). Compared to general surgery, cardiothoracic surgery was associated with a higher likelihood of VTE (OR 3.248, 95% CI 2.317-8.745, $p < 0.001$). Further, compared to general surgery, several surgical specialties were associated with lower odds of VTE. These were: neurosurgery (OR 0.622, 95% CI 0.463-0.837, $p=0.002$), orthopaedic surgery (OR 0.496, 95% CI 0.341-0.704, $p<0.001$), otolaryngology (OR 0.465, 95% CI 0.288-0.749, $p=0.002$), urology (OR 0.310, 95% CI 0.162-0.594, $p<0.001$), and plastic surgery (OR 0.141, 95% 0.045-0.443, p=0.001). ORs and 95% CIs for this model are given in Table 6.

After controlling for patient age, sex, and ASA class, twenty-six 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 10.490-16.060, p<0.001), surgical adverse events (OR 12.275, 95% CI 10.490-16.060, p<0.001), medical adverse events (OR 11.750, 95% CI 8.957-14.543, p<0.001), reoperation (OR 11.479, 95% CI 8.668-14.290, p<0.001), and readmission (OR 11.471, 95% CI 8.931-14.551, 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, eight of thirteen medical adverse events were associated with increased risk of an ensuing VTE (p<0.001 for each significant comparison). Reoperation (OR 11.474, 95% CI 8.668-14.290, p<0.001) and readmission (OR 11.741, 95% CI 8.931-14.551, p<0.001) were associated with subsequent VTE. 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 pharmacologic 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 reports of VTE in children, which find incidences of VTE of between 0.0629%[5] and 0.10%[28] in orthopaedic surgery, 0.038% in general surgery,[16] and 0.12%[29] to 8.9%[30] in trauma[9,20,31,32].

Regarding risk factors for VTE, controlling for demographic and surgical variables, compared to patients aged 11-15 years old, the present study identifies significantly increased risk of VTE among patients aged 16 to 18 years (OR=1.892, $p<0.001$), with children 6-10 years old 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.[12,19,20,31,33] As an example, a study of hospitalized pediatric patients finds that compared to patients aged 1 to 4 years, those 15 to 17 years old are at more than twice the risk of VTE.[10] Similarly, the APAGBI guidelines identify patients older than 13 years as being at higher risk for VTE.[24]

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 which differs from previous studies, which have suggested that neonates are at increased risk for VTE.[21] The results of the present study could differ from those of prior analyses because of differences in the procedures and populations studied, as well because of the nature of drawing from a national database.

Regarding comorbidities, controlling for other factors, worse health status—as indicated by an ASA class greater than I—was significantly associated with VTE (compared to ASA I, ASA II OR=4.502, ASA III OR=19.715, ASA IV OR=71.170, ASA V OR=154.953; $p < 0.001$ for all). Consistent with this finding, compared to 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 pediatrics 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.[8] This is also consistent with the finding that, amongst adult patients, those with a higher comorbidity burden are at higher risk for VTE.[34-36]

Surgical specialty was another factor independently associated with patients' risk of VTE. Controlling for demographic and other operative factors, compared to general surgery (the specialty that treated the greatest number of patients in the study population), the present study finds several surgical specialties to be independently associated with lower risk of VTE, including orthopaedic surgery and plastic surgery (OR=0.372, $p<0.001$ and OR=0.163, $p=0.002$, respectively). The result of plastic surgery is consistent with adult literature.[37] However, the result with orthopaedic 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 to 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 to patients receiving general surgery. This is consistent with pervious literature in pediatric surgery, which finds higher rates of VTE after cardiothoracic procedures.[38]

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 has been reported previously,[10,19,29] as with operative time.[14,15,38] These findings are further corroborated in the literature around VTE in adults, where studies have found that longer operative times[39] and longer hospital stays[39] 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 orthopaedic surgery.[28] These findings are consistent with the adult literature, which identifies non-elective surgery as a risk factor for thromboembolic events.[40]

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.[15] On multivariate analysis, the authors identify several risk factors for VTE: female sex, longer pre-hospital stay prior to surgery, current malignancy, preoperative mechanical ventilation, developmental delay, preoperative blood transfusion, preoperative infection, and anesthesia time greater than two 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, though 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 they did not account for postoperative adverse events.

Similarly, Cairo *et al* identify risk factors for VTE in children undergoing abdominopelvic surgery.[14] In multivariate analysis, the authors found associations between VTE and age greater than 15 years, longer anesthesia time, preoperative renal failure, preoperative septic shock, and ASA class greater than I. The present analysis similarly finds older age, longer operative time, and ASA class greater than II to be associated with of 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), 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.[41] Given the retrospective nature of the dataset used here, it is difficult to discern the mechanism of such an association.

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. Further, patients who develop any adverse event postoperatively, be it a surgical or medical complication, may be 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, inter-hospital 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 sub-populations undergoing surgery may be 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.

Table 1 Demographic information for patients with and without postoperative VTE

	Total		**No VTE**		**VTE**		
	n=361,384		n=361,006 (99.90%)		n=378 (0.10%)		
	n	%	n	%	n	%	P*
Age, years (mean±SD)	7.39±5.69		7.39±5.69		7.27±6.77		**<0.001**
≤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							**<0.001**
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	8,537	2.36%	8,446	2.34%	91	24.07%	
V	386	0.11%	376	0.10%	10	2.65%	

SD, standard deviation; ASA, American Society of Anesthesiologists
*Chi-square test comparing patients with and without VTE. Bolding indicates statistical significance at p<0.017 (Bonferroni correction).

Table 2 Comorbidities of patients with and without postoperative VTE

	Total n=361,384		No VTE n=361,006 (99.90%)		VTE n=378 (0.10%)		
Comorbidities	n	%	n	%	n	%	P*
ASA class ≥3	88,686	24.54%	88,390	2.45%	296	78.31%	**<0.001**
Pulmonary disease	53,486	14.80%	53,314	1.48%	172	45.50%	**<0.001**
Cardiac disease	35,282	9.76%	25,163	0.70%	119	31.48%	**<0.001**
Esophageal/gastric/intestinal disease	61,259	16.95%	61,084	1.69%	175	46.30%	**<0.001**
Neurologic disease	86,080	23.82%	85,912	2.38%	168	44.44%	**<0.001**
Hematologic disease	10,984	3.04%	10,916	0.30%	68	17.99%	**<0.001**
Preoperative steroids	8,319	2.30%	8,243	0.23%	76	20.11%	**<0.001**
Preoperative transfusion	2,948	0.82%	2,902	0.08%	46	12.17%	**<0.001**

ASA, American Society of Anesthesiologists
*Chi-square test comparing patients with and without VTE. Bolding indicates statistical significance at p<0.006 (Bonferroni correction for multiple corrections)

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

	Total		**No VTE**		**VTE**		
	n=361,384		n=361,006 (99.90%)		n=378 (0.10%)		
Operative variable	n	%	n	%	n	%	P*
Surgical specialty							**<0.001**
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%	
Orthopaedic 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%	**<0.001**

ENT, Ear, Nose, & Throat
*Chi-square test comparing patients with and without VTE. Bolding indicates statistical significance at p<0.025 (Bonferroni correction for multiple comparisons).

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

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

SD, standard deviation
*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).

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

	Total		**Before VTE**	
	n=361,384		n=221 (58.47% of 378 VTE)	
Adverse event	n	%	n	% of VTE
Any adverse event	48,935*	13.54%	221	58.47%
Surgical adverse event	29,284	8.10%	139	36.77%
Superficial SSI	3,536	0.98%	6	1.59%
Deep SSI	766	0.21%	4	1.06%
Organ/space SSI	2,766	0.77%	19	5.03%
Superficial wound dehiscence	3,514	0.97%	8	2.12%
Deep wound dehiscence	1,250	0.35%	-	0.00%
Bleeding requiring transfusion	19,454	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	1,789	0.50%	40	10.58%
Pneumonia	1,309	0.36%	20	5.29%
Sepsis	1,680	0.46%	25	6.61%
Septic shock	299	0.08%	12	3.17%
CLABSI	271	0.07%	9	2.38%
C. difficile colitis	281	0.08%	-	0.00%
UTI	1,812	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	1,195	0.33%	N/A	
Reoperation	9,812	2.72%	57	15.08%
Readmission	17,835	4.94%	48	12.70%

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

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

Table 6 Multivariable odds ratios for VTE, controlling for demographic and operative variables

Variables	OR	95% CI	P*
Age, years			
≤1	0.992	0.715-1.376	0.961
2-5	1.074	0.761-1.516	0.683
6-10	**0.625**	**0.414-0.940**	**0.024**
11-15	Referent		
16-18	**1.892**	**1.374-2.606**	**<0.001**
Sex			
Female	Referent		
Male	0.977	0.797-1.199	0.827
ASA Class			
I	Referent		
II	**4.502**	**2.317-8.745**	**<0.001**
III	**19.715**	**10.316-37.677**	**<0.001**
IV	**71.170**	**36.339-139.386**	**<0.001**
V	**154.953**	**62.838-382.097**	**<0.001**
Surgical specialty			
Cardiothoracic surgery	**3.248**	**1.293-8.156**	**0.012**
Gynecology	1.992	0.484-8.197	0.340
General surgery	Referent		
Neurosurgery	**0.622**	**0.463-0.837**	**0.002**
Orthopaedic surgery	**0.496**	**0.341-0.704**	**<0.001**
Otolaryngology (ENT)	**0.465**	**0.288-0.749**	**0.002**
Urology	**0.310**	**0.162-0.594**	**<0.001**
Plastic surgery	**0.141**	**0.045-0.443**	**0.001**
Non-elective surgery	**1.678**	**1.332-2.114**	**<0.001**
Operative time (min)	**1.004**	**1.003-1.004**	**<0.001**

OR, odds ratio; CI, confidence interval; ENT, Ear, Nose, & Throat; ASA, American Society of Anesthesiologists

*Logistic regression including all variables listed in this table. Bolding indicates statistical significance at p<0.05.

Table 7 Multivariable odds ratios for VTE, considering adverse events that occurred before a VTE

Adverse event	OR	95% CI	P*
Any adverse event	**13.275**	**10.490-16.060**	**<0.001**
Surgical adverse event	**12.358**	**9.559-15.156**	**<0.001**
Superficial SSI	**9.134**	**6.115-12.152**	**<0.001**
Deep SSI	**8.179**	**5.032-11.325**	**<0.001**
Organ/space SSI	**10.746**	**7.809-13.683**	**<0.001**
Superficial wound dehiscence	**9.132**	**6.129-12.136**	**<0.001**
Deep wound dehiscence	**		
Bleeding requiring transfusion	**12.009**	**9.207-14.810**	**<0.001**
Flap failure	**6.448**	**3.386-9.511**	**<0.001**
Nerve injury	**		
Medical adverse event	**11.750**	**8.957-14.543**	**<0.001**
Reintubation	**10.597**	**7.773-13.420**	**<0.001**
Pneumonia	**9.931**	**7.053-12.809**	**<0.001**
Sepsis	**10.244**	**7.421-13.068**	**<0.001**
Septic shock	**9.152**	**6.292-12.012**	**<0.001**
CLABSI	**9.3280**	**6.323-12.333**	**<0.001**
C. difficile colitis	**		
UTI	**9.616**	**6.709-12.524**	**<0.001**
Renal failure	**7.172**	**3.947-10.396**	**<0.001**
Renal insufficiency	**5.405**	**2.120-8.690**	**0.001**
Stroke	**		
Seizure	**		
Cardiac arrest	**		
Coma	**		
Reoperation	**11.479**	**8.668-14.290**	**<0.001**
Readmission	**11.741**	**8.931-14.551**	**<0.001**

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

*Firth logistic regressions to determine the odds ratio 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.

Chapter 2

Risk Factors for Venous Thromboembolism in Children Undergoing Orthopaedic Surgery

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Background

Venous thromboembolism (VTE)—which includes deep vein thrombosis and pulmonary embolism—is a relatively uncommon complication among pediatric patients, affecting approximately 1 in 200 patients.[42] The incidence of pediatric VTE increased by almost 70% between 2001 to 2007 among hospitalized children, a trend which calls for renewed focus on the prophylaxis and treatment of VTE in pediatric patients.[43]

In the adult orthopaedic population, VTE prophylaxis is routine. This is based on numerous studies assessing the risk-benefit considerations of such practice. To that end, guidelines have been published by American College of Chest Physicians recommending VTE prophylaxis for orthopaedic surgeries in the adult population.[44]

Conversely, VTE prophylaxis is rarely used in the pediatric orthopedic population. This is largely because of the low estimated risk of VTE and questions about associated risk-benefit balance.[45] At present, an existing published guideline for thromboprophylaxis in children cites the need for additional research to identify risk factors for VTE among pediatric patients.[25]

Previous studies of VTE in pediatric populations have identified age, immobility, and the presence of other prothrombotic conditions as risk factors for VTE.[46] Existing studies on the topic have largely focused on trauma and intensive care patients in single institutions. It remains unclear if and how pediatric orthopaedic patients, many of whom are on the older side of the pediatric age spectrum and often immobilized, should be considered for VTE prophylaxis.

Specific to pediatric patients undergoing orthopaedic surgery, few studies have examined predisposing factors for VTE.[28,47-49] A study by Baker *et al*. examined risk factors for VTE in pediatric patients undergoing orthopaedic surgery, identifying gastrointestinal, renal, and hematologic disorders as predisposing factors.[28] Despite using a large national pediatric surgical database, however, the authors' identification of risk factors was limited to univariate analysis.

The current study used a large, national, multicenter outcomes database to determine the incidence and risk factors for VTE in pediatric orthopaedic patients. The analysis compared patient demographics, comorbidities, surgical variables, and adverse events between patients who did and did not develop a postoperative VTE, and it identifies risk factors independently associated with VTE.

Methods

Student Contributions

Contributions from the thesis author (EJM), co-author RPM, and faculty sponsor (JNG) are as in *Chapter 1* above. Additional co-authors (NP, ARG, DBF) contributed to interpretation of analysis and review of the manuscript.

Ethics Statement

As in *Chapter 1* above.

Human Subjects Research

As in *Chapter 1* above.

Patient Characteristics

Patients in the 2012-2017 National Surgical Quality Improvement Program Pediatric (NSQIP-P) database undergoing orthopaedic surgery were included in the study. NSQIP-P includes patients undergoing surgery for elective and non-elective cases, but of note does not include cases of polytrauma. Patients were identified as having undergone orthopaedic surgery if their surgeon's specialty was noted as "Orthopedic Surgeon" or "Pediatric Orthopedic Surgeon."

Patient demographics were directly abstracted from the database. Demographic variables included age, sex, and American Society of Anesthesiologists (ASA) classification.

Patient comorbidities were also directly abstracted from the database. Comorbidities directly abstracted from the database included: diabetes mellitus (including insulin-dependent diabetes), esophageal/gastric/intestinal disease, hematologic disease, chronic steroid use, and receipt of blood transfusion within 48 hours prior to surgery.

Several comorbidities were grouped by type of disease. Cardiac disease was defined as having previous cardiac surgery, any cardiac risk factors, cardiopulmonary resuscitation within 7 days prior to surgery, and inotropic support at the time of surgery. Neurologic diseases included developmental delay/impaired cognitive status, structural central nervous system abnormality, neuromuscular disorder, cerebral palsy, seizure disorder, and intraventricular hemorrhage. Pulmonary diseases included bronchopulmonary dysplasia/chronic lung disease, ventilator dependence, requiring oxygen support, history of asthma, tracheostomy, and structural pulmonary/airway abnormality.

Surgical variables and 30-day outcomes

Surgery-related variables were directly abstracted from the database. Categorical surgical variables included surgeons' pediatric specialization or not and whether a surgery was elective. Continuous surgical variables directly abstracted from the database were operative time (time from skin incision to closure) in minutes, and hospital length of stay (time from admission to discharge) in days.

Thirty-day adverse events were directly abstracted form the database, and they were aggregated into any, major, and minor adverse events. Major adverse events were deep surgical site infection (SSI), organ/space SSI, unplanned reintubation, seizure, deep wound dehiscence, stroke, central-line-associated bloodstream infection (CLABSI), bleeding requiring transfusion, acute renal failure, sepsis, septic shock, cardiac arrest, coma, and death. Minor adverse events were superficial SSI, nerve injury, pneumonia, superficial wound dehiscence, *Clostridium difficile* colitis, renal insufficiency, and urinary tract infection.

Data on reoperation and readmission were abstracted from the database. Both contribute to any adverse event, but not to the number of major or minor adverse events. Any adverse event was defined as a major adverse event, minor adverse event, reoperation, or readmission.

Data on pulmonary embolism (PE) and deep vein thrombosis (DVT) were directly abstracted from the database. Patients who experienced a PE or DVT were identified as having experienced a venous thromboembolism (VTE).

The postoperative day on which each adverse event occurred was directly abstracted from the database. Among patients who experienced a VTE, adverse events occurring prior to the VTE were identified. While the frequencies of adverse events were tabulated for the entire study population, the adverse event rates for patients with a VTE include only those complications preceding a VTE.

Orthopedic-specific variables abstracted from the database included whether patients had surgery for scoliosis, had an arthrotomy or osteotomy, or had experienced a femur fracture. Patients were identified as having scoliosis if they were associated with the Current Procedural Terminology (CPT) codes 22804, 22802, or 22810. Patients were identified has having a femur fracture with CPT codes 27506 or 227511. Patients were identified as having received an arthrotomy if they had CPT codes 27030 or 27310, and an osteotomy with CPT codes 27450, 27146, 27165, or 27705.

Statistical Analysis

Categorical demographic variables (age, sex, and ASA class), comorbidities, categorical surgical variables, and adverse events were compared between patients who experienced a VTE and those who did not using Fisher's exact test. Levene's test was performed to compare the variances of age, operative time, and hospital length of stay between patients with and without VTE. These three continuous variables were then compared using two-tailed t-tests, assuming equal or unequal variances based on the result of Levene's test.

A multivariate logistic regression was created to determine the effect of comorbidities, surgical variables, and orthopaedic-specific variables on the likelihood of postoperative

VTE. This analysis controlled for demographics, surgical variables (including orthopaedic-specific variables), and comorbidities that differed significantly between groups.

Additionally, controlling for patient age, sex, ASA class, operative time, and whether surgery was non-elective, separate Firth logistic regressions were created to evaluate the effect of a postoperative adverse event on the likelihood of subsequently developing a VTE. Given the infrequency of VTE in this patient population, Firth regressions were used instead of logistic regressions, as the former is better suited to evaluating rare events.[27]

Statistical analysis was performed using Stata version 16.0 (StataCorp, LLC, College Station, TX). Statistical significance was established at $p < 0.05$. Bonferroni corrections were performed for univariate analyses to account for multiple comparisons.

Results

Patient Cohorts

In total, 81,490 pediatric patients with complete data who underwent surgery by an orthopaedist were identified from the 2012-2017 NSQIP-P datasets. Patients missing data for ASA class, operative time, and hospital length of stay were excluded (n = 206 patients excluded). Included patients were aged 9.7 ± 4.8 years, and 50.1% were male. Of the patients identified, 60 (0.07%) developed a postoperative VTE.

Patient characteristics are given in Table 1. Compared to patients who did not develop a VTE, patients who developed a VTE were older ($p < 0.001$), and more likely to have an ASA class of III or greater ($p < 0.001$) but did not differ in sex ($p = 1.00$).

Further data on patient comorbidities are given in Table 1. Patients who developed a VTE had higher rates of 4 of the 9 comorbidities considered ($p \leq 0.001$ for all significant associations). These include higher rates of pulmonary disease, esophageal/gastric/intestinal disease, hematologic disease, and preoperative transfusion.

Surgical variables are given in Tables 1 and 2. Considering these variables, patients with VTE were equally likely to be treated by a pediatric orthopaedic specialist, and to undergo non-elective surgery. Patients with VTE, however, had longer operative times ($p < 0.001$), and longer hospital lengths of stay ($p < 0.001$). Regarding orthopaedic-specific variables, patients who developed a VTE were more likely to have undergone surgery for scoliosis ($p < 0.001$), arthrotomy ($p < 0.001$), and femur fracture ($p = 0.002$), but not osteotomy.

In terms of 30-day postoperative events, 19 patients (31.7% of those with VTE) experienced an adverse event prior to VTE in comparison to 5.1% of the overall study population who experienced an adverse event (Table 3). Further, of those who developed a VTE, 9 (15.0%) experienced a major adverse event before VTE, 7 (11.7%) had a preceding minor adverse, 12 (20.0%) underwent reoperation before VTE, and 6 (10.0%) were readmitted prior to VTE.

Multivariate Analyses

In multivariate logistic regression, demographic factors and operative variables associated with a VTE were: age 16-18 years (odds ratio [OR] 2.65, 95% confidence interval [CI] 1.44-4.88, $p = 0.002$; compared to ages 11-15), ASA class III-IV (OR 2.53, 95% CI 1.37-4.45, $p = 0.003$ compared to ASA class I-II), preoperative blood transfusion (OR 9.01, 95% CI 3.24-25.01, $p < 0.001$), arthrotomy (26.10, 95% CI 10.49-64.94, $p < 0.001$), and femur fracture (OR 5.53, 95% CI 2.22-13.79, $p < 0.001$) (Table 4; Figure 1).

In multivariate logistic regression, controlling for age, sex, ASA class, operative time, and whether a surgery was elective, any adverse event (OR 10.84, 95% CI 7.96-13.71, $p < 0.001$), major adverse events (OR 9.34, 95% CI 6.46-12.22, $p < 0.001$), minor adverse events (OR 9.86, 95% CI 6.86-12.86, $p < 0.001$), reoperation (OR 10.37, 95% CI 7.49-13.25, $p < 0.001$), and readmission (OR 9.33, 95% CI 6.37-12.28, $p < 0.001$), were all significantly associated with a subsequent a VTE (Table 3; Figure 2).

Specific major adverse events associated with subsequent VTE were deep SSI, organ/space SSI, unplanned reintubation, sepsis, septic shock, CLABSI, and bleeding requiring blood transfusion. Specific minor adverse events associated with an ensuing VTE were superficial SSI, superficial wound dehiscence, and pneumonia. Odds ratios and 95% CIs for these adverse events are given in Table 3.

Discussion

Though VTE is an uncommon complication among pediatric patients, it carries a high risk of morbidity and mortality. While previous studies have examined VTE in children after trauma, as well as in hospitalized children, there has been limited consideration of VTE specifically in pediatric patients undergoing orthopaedic surgery. To better identify which pediatric orthopaedic surgical patients are at increased risk of VTE, the present study used a large national surgical dataset to characterize the incidence of and risk factors for VTE among pediatric patients undergoing orthopaedic surgery.

Using data from the 2012-2017 NSQIP-P databases, in a population of over 80,000 pediatric patients undergoing orthopaedic surgery, the present study observed an incidence of VTE of 0.07%. The incidence observed is consistent with earlier analyses of children receiving orthopaedic surgery, which have reported incidences of VTE of 0.0629%[47] and 0.10%.[28]

In the present study, patients who experienced a postoperative VTE were older than those who did not. Patients aged 16-18 years were at highest risk. This aligns with previous studies of VTE among children after surgery, which find that older children,[1,12,21,31] and neonates,[1,12] are at higher risk for VTE (note that neonates are not well represented for the orthopaedic surgical population).

ASA status was used as a marker of patients' overall health status. Controlling for patient factors, higher ASA class of III-V was associated with a nearly 3-fold higher risk of postoperative VTE. The association between higher ASA class and VTE in children after surgery is also concordant with earlier research. Specifically, children undergoing abdominopelvic general surgery with ASA classes of II or greater were found to be at higher risk of VTE.[14] Additionally, a study in adults finds that patients who developed VTE after cemented hemiarthroplasty had higher ASA classes than those who did not.[50]

On univariate analysis, patients with VTE had a significantly higher incidence of five of the ten comorbidities assessed. This aligns with previous work, which has shown that most hospitalized pediatric patients who developed VTE had at least one comorbid condition.[43] However, when controlling for other patient factors including ASA class, preoperative transfusion was the only comorbidity associated with VTE.

Using data from fewer years of the same database, a previous study of children undergoing orthopaedic surgery by Baker *et al*. identified gastrointestinal, renal, and hematological comorbidities as predictors for VTE.[28] These authors, however, identify risk factors only with univariate analysis. While the present study finds a higher incidence of pulmonary disease, esophageal/gastric/intestinal disease, and hematological disease among patients who developed VTE, these comorbidities were not independently associated with VTE when controlling for other patient factors. This suggests that these comorbidities do not themselves predispose to VTE, but they are instead associated with patient factors that are.

Preoperative blood transfusion, however, was associated with nearly nine-fold higher risk of VTE. This relationship has been described previously, with a study of risk factors for VTE in children after trauma finding that transfusion of blood products to be predictive of VTE.[31] This study extends the existing literature by rigorously demonstrating this finding in the pediatric orthopaedic surgical population.

Regarding orthopaedic-specific variables, controlling for patient and surgical factors, receipt of arthrotomy or having a femur fracture independently predicted a postoperative VTE. Previous studies in adults have identified a high prevalence of VTE among patients undergoing arthrotomy,[50-53] or among patients who had experienced lower extremity fractures.[54,55] Relatedly, a study of pediatric patients examining lower extremity trauma and VTE found that among patients with VTE who had sustained fractures, femur/femoral neck fractures were the most common site of fracture.[56]

In addition to identifying demographics, comorbidities, and surgical factors associated with postoperative VTE, the present study sought to identify adverse events predictive of a subsequent VTE. The study found that patients who experience any adverse event, a major adverse event, a minor adverse event, reoperation, or readmission prior to VTE are 9-10 times more likely to experience a subsequent VTE within 30 days of surgery. Additionally, individual major and minor adverse events strongly predicted ensuing VTE.

The present study also found a strong association between VTE and other adverse events. While the mechanism and directionality of this relationship cannot be ascertained with this dataset, it is possible that factors predispose patients to adverse events could also predispose them to VTE. Furthermore, it is possible that patients who experience adverse events required additional treatment, had longer hospitalizations, and had greater immobilization, each of which could have contributed to increased risk of VTE.[57,58]

It is proposed that the findings from the present study can help orthopaedic surgeons identify pediatric patients who might benefit from prophylactic anticoagulation. Demographically, children who have an ASA class of III are at higher risk of VTE. Further, patients who received an arthrotomy or had a femur fracture, and who have a preoperative blood transfusion, may be at higher risk of VTE. Also, though a determination of directionality cannot be made, patients with a longer length of hospital stay may be at higher risk. After surgery, patients who experience an adverse event, are readmitted, and undergo reoperation, are also at increased risk.

Using the risk factors for VTE identified in this study, further risk stratification was performed to identify the pediatric orthopaedic surgical patients at highest risk for VTE. Patients aged 16-18 years old with an ASA class of III or greater and at least one comorbidity, had a 7-fold greater risk of VTE. The incidence of VTE was 0.5% among this group of patients.

The present study has several limitations. First, this study is retrospective in nature, and thus the directionality of the relationships observed cannot be determined. Additionally, because the NSQIP dataset does not capture the polytraumatized patient population, the study was not able to characterize this sub-population of orthopaedic patients that would be expected to be at higher risk of VTE. Relatedly, as NSQIP only samples a subsample of U.S. hospitals, which might not necessarily represent institutions nationally, the generalizability of the results might be limited. Lastly, errors in diagnostic coding could lead VTE to be underreported.

Despite these limitations, in a population of over 80,000 patients, this study uses rigorous statistical analysis to identify patient factors, surgical factors, and adverse events associated with VTE after children undergoing the vast majority of orthopaedic surgeries.

In summary, the present study observed an incidence of VTE of 0.07% among pediatric orthopaedic surgical patients registered in a large national database. The study identified independent risk factors for postoperative VTE in pediatric orthopaedic patients to be age 16-18 years, ASA class of III or greater, preoperative blood transfusion, arthrotomy, and femur fracture, as well as sustaining any adverse event, reoperation, and readmission. These results can be used to identify pediatric patients undergoing orthopaedic surgery who might benefit from prophylactic anticoagulation, with the aim of reducing morbidity and optimizing postoperative outcomes.

Table 1. Patient Demographics, Comorbidities, and Categorical Surgical Variables Highlighting Patients with VTE

	Total		**VTE**		
	n = 81,490		n = 60 (0.07%)		
Variable	n	%	n	%	p*
Age, y (mean ± SD)	9.7 ± 4.8		12.3 ± 5.1		**< 0.001†**
<1	1,974	2.4%	2	3.3%	
1-5	14,912	18.3%	5	8.3%	
6-10	22,795	28.0%	10	16.7%	
11-15	29,663	36.4%	20	33.3%	
16-18	12,146	14.9%	23	38.3%	
Sex					1
Male	40,798	50.1%	30	50.0%	
Female	40,632	49.9%	30	50.0%	
ASA Class					**< 0.001**
I-II	66,178	81.2%	30	50.0%	
III-V	15,312	18.8%	30	50.0%	
Diabetes Mellitus^	180/43,295	0.4%	1/26	3.8%	0.10
Insulin-Dependent Diabetes^	120/43,295	27.7%	1/26	3.8%	0.07
Pulmonary Disease	9,178	11.3%	18	30.0%	**< 0.001**
Cardiac Disease	2,410	3.0%	1	1.7%	1.00
Esophageal/Gastric/Intestinal Disease	5,564	6.8%	12	20.0%	**0.001**
Neurological Disease	20,973	25.7%	24	40.0%	0.017
Hematologic Disease	1,094	1.3%	6	10.0%	**< 0.001**
Chronic Steroid Use	634	0.8%	3	5.0%	0.012
Preoperative Transfusion	220	0.3%	5	8.3%	**< 0.001**
Pediatric Orthopaedic Specialist	73,320	90.0%	53	88.3%	0.67
Non-Elective Surgery	20,722	25.4%	18	30.0%	0.46
Scoliosis	14,829	18.2%	23	38.3%	**< 0.001**
Arthrotomy	1,000	1.2%	10	16.7%	**< 0.001**
Osteotomy	5,626	6.9%	7	11.7%	0.19
Femur Fracture	3,099	3.8%	8	13.3%	**0.002**

*Fisher's exact test comparing patients with and without VTE, unless otherwise noted.

Levene's test.

*Fisher's exact test comparing patients with and without VTE.

Bolding indicates statistical significance at p < 0.017 (Bonferroni correction).

^Missing values

Table 2. Continuous Perioperative Variables for All Orthopedic Patients, and Those with Postoperative VTE

	Total	**VTE**	
	n = 81,490	n = 60 (0.07%)	
Operative Variable	mean ± SD	mean ± SD	p*
Operative Time, min	126.7 ± 121.0	204.0 ± 146.2	**< 0.001**
Length of Stay, days†	2.4 ± 5.9	15.7 ± 18.0	**< 0.001**

*Two-tailed t-test comaparing patients with and without VTE, assuming unequal variances based on the result of Levene's test. Bolding indicates statistical significance at $p < 0.025$ (Bonferroni correction).

Table 3. Postoperative Adverse Events Occurring Before a VTE

	Total n = 81,490		**VTE** n = 60 (0.07%)				
Adverse Event	n	%	n	% of VTE	OR	95% CI	p*
Any Adverse Event (non-VTE)	4,152	5.1%	19	31.7%	**10.84**	**7.96-13.71**	**< 0.001**
Major Adverse Event	793	1.0%	9	15.0%	**9.34**	**6.46-12.22**	**< 0.001**
Deep SSI	238	0.3%	3	5.0%	**8.49**	**5.44-11.55**	**< 0.001**
Organ/Space SSI	94	0.1%	1	1.7%	**8.18**	**4.87-11.49**	**< 0.001**
Deep Wound Dehiscence	159	0.2%	0	0.0%	**		
Unplanned Reintubation	199	0.2%	4	6.7%	**8.57**	**5.58-11.56**	**< 0.001**
Acute Renal Failure	11	0.0%	1	1.7%	4.15	-0.33-8.62	0.07
Sepsis	183	0.2%	1	1.7%	**8.16**	**4.89-11.44**	**< 0.001**
Septic Shock	33	0.0%	2	3.3%	**7.97**	**4.89-11.06**	**< 0.001**
CLABSI	9	0.0%	1	1.7%	**6.59**	**3.33-9.84**	**< 0.001**
Seizure	27	0.0%	0	0.0%	**		
Stroke	7	0.0%	0	0.0%	**		
Bleeding Requiring Transfusion	12,604	15.5%	23	38.3%	**11.71**	**8.81-14.61**	**< 0.001**
Cardiac Arrest	40	0.0%	0	0.0%	**		
Coma	4	0.0%	0	0.0%	**		
Death	31	0.0%	N/A		N/A		
Minor Adverse Event	1,933	2.4%	7	11.7%	**9.86**	**6.86-12.86**	**< 0.001**
Superficial SSI	564	0.7%	1	1.7%	**8.55**	**5.29-11.82**	**< 0.001**
Superficial Wound Dehiscence	831	1.0%	2	3.3%	**8.54**	**5.26-11.82**	**< 0.001**
Nerve Injury	121	0.1%	0	0.0%	**		
Pneumonia	298	0.4%	5	8.3%	**9.51**	**6.43-12.59**	**< 0.001**
Renal Insufficiency	15	0.0%	0	0.0%	**		
Urinary Tract Infection	253	0.3%	0	0.0%	**		
Clostridium difficile colitis	32	0.0%	0	0.0%	**		
Reoperation	1,338	1.6%	12	20.0%	**10.37**	**7.49-13.25**	**< 0.001**
Readmission	1,899	2.3%	6	10.0%	**9.33**	**6.37-12.28**	**< 0.001**

N/A = Not applicable, OR = Odds Ratio, CI = Confidence Interval, SSI = Surgical Site Infection, CLABSI = Central Line-Associated Bloodstream Infection

*Multivariate Firth logistic regressions to determine the odds ratio of VTE for a given preceding adverse event. These regression analyses control for patient age, sex, ASA class, operative time, and whether a surgery was non-elective. **Bolding** indicates statistical significance at $p < 0.05$.

**Insufficient observations for regression analysis.

Table 4. Multivariate Odds Ratios for VTE, Controlling for Select Demographics, Comorbidities, and Surgical Variables

Variables	OR	95% CI	p*
Age, years			
<1	1.35	0.29-6.38	0.70
1-5	0.59	0.20-1.71	0.33
6-10	0.77	0.34-1.74	0.54
11-15	Referent		
16-18	**2.65**	**1.44-4.88**	**0.002**
Sex			
Female	Referent		
Male	0.88	0.52-1.48	0.63
ASA Class			
I-II	Referent		
III-V	**2.53**	**1.37-4.45**	**0.003**
Pulmonary Disease	1.81	0.96-3.41	0.07
Esophageal/Gastric/Intestinal Disease	1.64	0.80-3.37	0.18
Hematologic Disease	2.39	0.93-6.11	0.07
Preoperative Transfusion	**9.01**	**3.24-25.01**	**< 0.001**
Non-Elective Surgery	2.01	0.86-4.69	0.11
Operative Time, min	1.00	1.00-1.00	0.27
Orthopaedic Variables			
Scoliosis	2.34	0.94-5.85	0.07
Arthrotomy	**26.10**	**10.49-64.94**	**< 0.001**
Osteotomy	2.33	0.89-6.09	0.09
Femur Fracture	**5.53**	**2.22-13.79**	**< 0.001**

OR = Odds Ratio, CI = Confidence Interval, ASA = American Society of Anesthesiologists

*Multivariate logistic regression including all variables listed in this table (select demographics, comorbidities, and surgical variables). Only comorbidities that differed significantly between patients with and without a VTE were included. **Bolding** indicates statistical significance at $p < 0.05$.

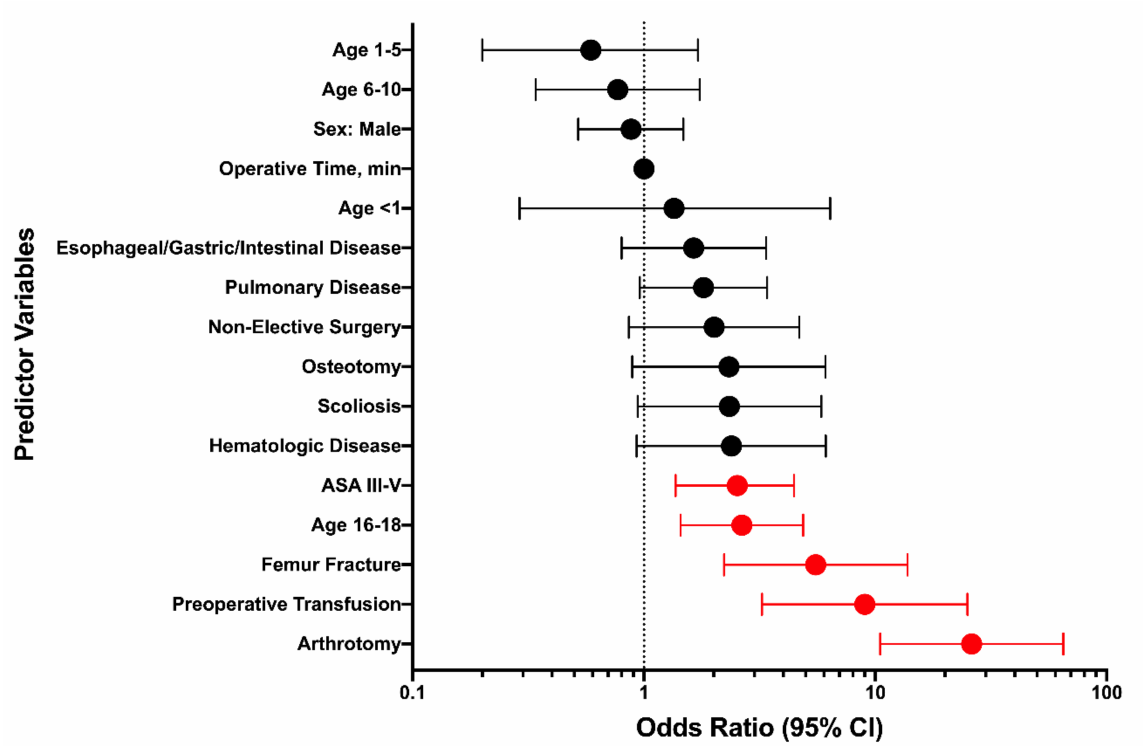

Figure 1. Forest plot depicting odds ratios (ORs; dots) and 95% confidence intervals (CIs; bars) for VTE for select patient demographics, comorbidities, and surgical variables. ORs and 95% CIs were determined using a single multivariate logistic regression including all variables in this plot (Table 7). X-axis is given in logarithmic scale. Red color indicates statistical significance at $p < 0.05$.

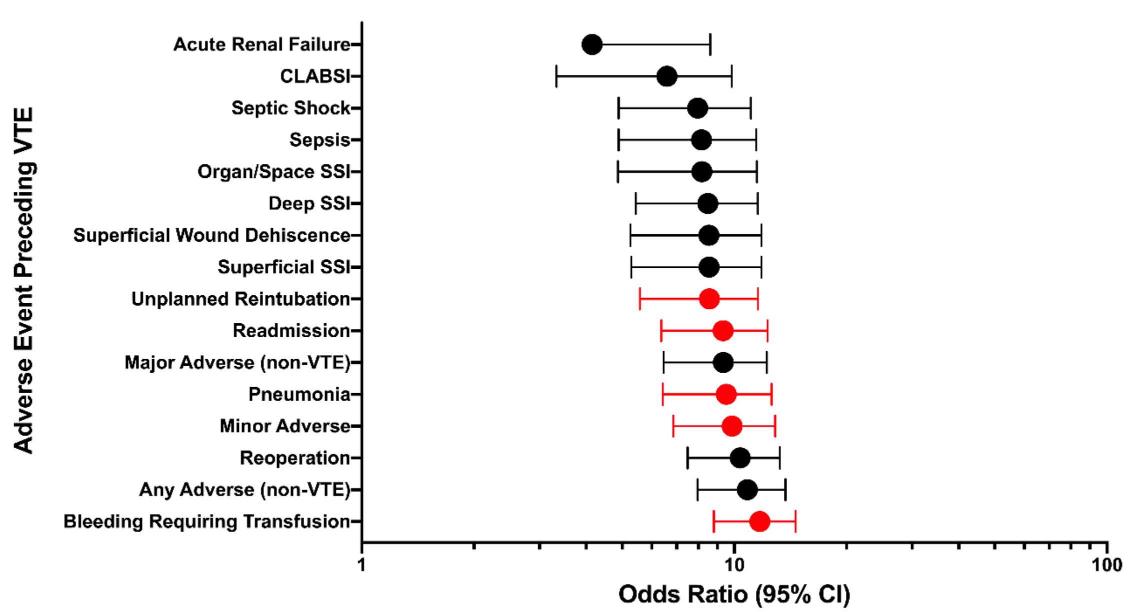

Figure 2. Forest plot depicting odds ratios (ORs; dots) and 95% confidence intervals (CIs; bars) for VTE for preceding adverse events. ORs and 95% CIs were calculated using individual Firth logistic regressions controlling for patient age, sex, ASA class, operative time, and whether surgery was elective. X-axis is given in logarithmic scale. Red color indicates statistical significance at $p < 0.05$.

Conclusion of Chapters

As venous thromboembolism (VTE) is highly morbid and not well studied to date, this thesis sought to identify the incidence of VTE and its risk factors, among children in a general surgical population (Chapter 1) and those treated by orthopaedic surgeons (Chapter 2). Both arms of the investigation applied rigorous statistical methods to large datasets derived from the ACS-NSQIP database.

In doing so, we find similar incidences of VTE across populations (0.10% and 0.07%, respectively) and identify a set of common risk factors. In both cohorts, we find VTE to be independently associated with age 16-18 years and higher ASA class (II or greater in the case of surgery generally, III or greater in the case of orthopaedics). Additionally, a range of postoperative adverse events were associated with increased risk of an ensuing VTE in both populations.

Differences arose in that non-elective surgery and longer operative time were associated with increased risk of VTE within the general surgical population but were not identified as risk factors among orthopaedic patients. These discrepancies could result from underlying differences across patient populations, or differences in the kinds of interventions performed. In addition, several orthopaedic-specific risk factors are identified in the orthopaedic cohort, which were not considered in the general surgical population, owing to the types of interventions performed.

It has been reported previously that patients undergoing orthopaedic surgery are at higher risk for VTE compared to patients receiving other kinds of surgery.[10] Therefore, it was surprising to find that in a population of over 300,000 children, children treated by orthopaedic surgeons appeared to be at lower risk of VTE compared to those undergoing general surgery. This result has not been reported previously.

Taken together, this thesis highlights pediatric patients at increased risk for postoperative VTE both within the general surgical context, and within orthopaedic surgery specifically. Augmenting existing guidelines, the findings presented here can be used to identify children at highest risk for such complications, and, after careful consideration of the risks and benefits, which patients could benefit from VTE prophylaxis. Specifically, these results could inform a pediatric risk scoring model similar to the Caprini score, which predicts VTE risk in adult surgical patients.[59]

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