

Pediatric Orthopaedic Venous Thromboembolism

A Systematic Review Investigating Incidence, Risk Factors, and Outcome

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Investigation performed at Boston Children's Hospital, Boston, Massachusetts

Background: There is growing evidence of increased venous thromboembolism (VTE) incidence in children with trauma or infection. The purpose of this study was to conduct a systematic review of existing literature related to VTE in the pediatric orthopaedic population, to estimate the overall incidence of VTE and identify risk factors associated with this condition.

Methods: A systematic review of the available literature was performed to identify articles that described VTE in pediatric orthopaedic surgery or admission. Literature queries were performed to identify articles published from 1980 to 2021 that included patients \leq 21 years of age. A stepwise search strategy of 5 electronic databases yielded 1,426 articles, which were filtered by 2 reviewers to identify 30 articles for full-text review. The primary aim was to determine the rate of VTE, and the secondary aim was to identify risk factors for VTE. The pooled incidence of VTE was estimated and reported in cases per 10,000. Studies were stratified by study size, by trauma versus elective surgery, and by orthopaedic subspecialty.

Results: The 30 articles reported 3,113 VTE events in 2,467,764 pediatric patients (including those with nonorthopaedic conditions), for a pooled VTE incidence of 20 events (95% confidence interval [CI] = 10.8 to 37.2) per 10,000. Four of the studies were excluded for incomplete data or high heterogeneity. The remaining 26 studies had 850,268 orthopaedic patients with 1,108 cases of VTE, for a pooled VTE incidence of 16.6 events (95% CI = 9.1 to 30.5) per 10,000. Studies with <10,000 patients and those involving a diagnosis of trauma had the highest VTE incidence when stratification was performed. The most frequently analyzed risk factors in 15 available studies included age, sex, obesity/ body mass index, type of surgery, and use of a central venous catheter.

Conclusions: This systematic review indicated that the risk of VTE associated with pediatric orthopaedic surgery or admission remains low, at <17 events per 10,000 cases. However, orthopaedic surgeons should be aware of the most common risk factors associated with pediatric orthopaedic VTE and should pay special attention to traumatic etiologies, as these yielded the highest incidence.

Levels of Evidence: Prognostic Level III. See Instructions for Authors for a complete description of levels of evidence.

enous thromboembolism (VTE) affects an estimated 1 million Americans per year^{1,2}. Although VTE is relatively rare in the pediatric population, with an average incidence over the last 2 decades of only 0.07 to 0.49 per 10,000 children, it is much higher in hospitalized children (30 to 58 VTEs per 10,000 hospitalizations of children) and is the second leading cause of hospital-acquired morbidity among children in the U.S.³⁻⁷. Understanding preventable risk factors that provoke VTE in pediatrics is a leading national initiative⁸.

The epidemiology and pathophysiology of pediatric VTE are very different from those of adult VTE^{9,10}. Only 5% of all

observed VTE events in children are considered idiopathic in etiology, compared with approximately 40% in adults^{4,11-15}. The pediatric VTE incidence is bimodal, with the highest rates seen in infants aged 1 to 23 months and in teenagers, particularly teenage girls^{5,11}. Catheter-related thrombosis has been reported as the most frequent cause of pediatric VTE in children under 24 months of age¹⁶. The VTE incidence peaks in adolescents due to contraception use, smoking, and obesity as well as the fact that the composition of the hemostatic system in adolescents is transitioning to that of the comparable adult system^{17,18}. Despite the substantial differences in epidemiology and pathophysiology

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between pediatric and adult VTE, most management guidelines for children have been extrapolated from the adult literature, without evidence for efficacy in children^{18,19}.

Previous research regarding pediatric orthopaedic VTE has been limited to small case series and scattered retrospective studies, making analysis, comparison, and consensus involving these data challenging. The estimated incidence of VTE in pediatric orthopaedics has been calculated at 10 VTEs per 10,000 hospitalizations of children¹³. However, several studies have suggested that the overall incidence in pediatric VTE is increasing, although this trend has not been substantiated within pediatric orthopaedics, to our knowledge3,12,20-22. Further review and synthesis of the pediatric orthopaedic literature regarding VTE is needed to help guide decision-making and protocol development and to optimize national care delivery. Therefore, the purpose of this study was to conduct a systematic review of the existing literature related to VTE in the pediatric orthopaedic population, to grade the quality of the evidence, and to summarize findings in a systematic fashion. Our primary aim was to determine the overall incidence of VTE in pediatric orthopaedics, and our secondary aim was to identify risk factors associated with VTE.

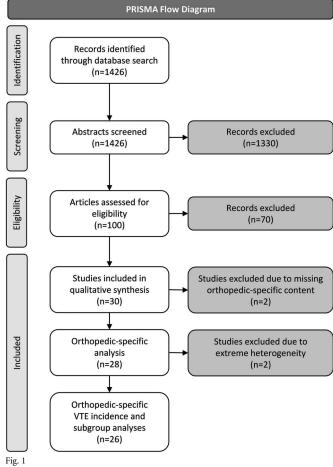
Materials and Methods

Data Sources

systematic review of the available literature was performed using multiple separate search strategies. The PubMed, CINAHL, Web of Science, Embase, and Cochrane Library databases were searched from January 1, 1980, to December 31, 2021. Search strings involved keywords and medical subject headings related to "venous thromboembolism" or "VTE," "child," "adolescent," "orthopaedic surgery," "risk factors," "deep vein thrombosis" or "DVT," "pulmonary embolism" or "PE," and "fracture." The literature search strategy is summarized in Fig 1. Forward and backward citation tracing was conducted through Scopus and the included studies, respectively.

Study Selection

The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines were followed for this systematic review²³. A total of 1,426 article titles from the initial search query were independently reviewed by 2 authors, and 100 were found to be related to VTE in pediatric patients. The references of these 100 articles were reviewed for additional relevant articles, but none were found. The abstracts of the 100 articles were reviewed, and 70 were eliminated on the basis of the inclusion or exclusion criteria. The full text of the remaining 30 articles was reviewed. Inclusion criteria were (1) publication from January 1, 1980, to December 31, 2021, (2) English language, (3) inclusion of at least 10 patients, (4) a retrospective or prospective design, and (5) description of the diagnosis of VTE in pediatric orthopaedic surgical and nonsurgical patients ≤ 21 years of age. Exclusion criteria were (1) patient age of \geq 22 years of age; (2) no mention of trauma, orthopaedic-related conditions, or surgery (e.g., infection, musculoskeletal cancer); (3) diagnosis of VTE before surgical intervention or nonsurgical treatment; (4) no clinical outcomes; (5) neonatal cases only; and



PRISMA diagram of the systematic review.

(6) exclusively non-musculoskeletal-related cancer cohorts. Articles that included adult patients were only used if the pediatric data could be separated, extracted, and interpreted separately. Discrepancies were settled by discussion among the reviewers, and further disagreement was resolved by the senior author.

Data Extraction

The article title, first author, type of study, year of publication, dates of data collection, and age-related inclusion criteria were recorded (Table I). Summary statistics for the patient population, the number of orthopaedic-specific VTEs reported, and the total number of patients reviewed were extracted from each article and summarized. The diagnosis of VTE was commonly made from review of ICD-9 or 10 (International Classification of Diseases, Ninth or Tenth Revision) codes and review of radiology reports. Potential risk factors for VTE that were evaluated were recorded, as well as whether the study found them to be significantly associated with VTE incidence.

Statistical Analysis

Meta-analysis of the VTE incidence for all reviewed data and for orthopaedic-specific events was conducted using random-

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Study	Type of Study	VTE Type	Subgroup	Mean or Median Age <i>(yr)</i>	% Male	Ν	VTE Events	VTE Incidence per 10,000†
Samineni (2021) ⁴⁴	Retro.	VTE	Comb.	10.3	NR	810,097	373	4.6 (4-5)
Connelly (2016) ⁴	Retro.	VTE	Trauma	9	66%	536,423	1,141	21.3 (20-23)
Cunningham (2020) ⁴⁵	Retro.	VTE	Trauma	9	64%	481,485	729	15.1 (14-16)
Murphy (2015) ⁴⁹	Retro.	DVT, PE	Trauma	12.9	NR	285,611	167	5.8 (5-7)
Georgopoulos (2016) ¹⁵	Retro.	VTE	Orth. elect.	11.1	53%	117,676	74	6.3 (5-8)
/avilala (2002) ²⁴	Retro.	DVT, PE	Trauma	NR	67%	58,716	45	7.7 (6-10)
Guzman (2018) ¹⁴	Retro.	VTE	Trauma	NR	67%	57,183	387	67.7 (61-75)
De la Garza Ramos (2016) ⁴³	Retro.	VTE	Spine	14	25%	36,335	22	6.1 (4-9)
ain (2014) ²⁵	Retro.	VTE	Spine	13.7	37%	21,955	46	21 (15-28)
Nogaro (2020) ²⁶	Retro.	PE	Orth. elect.	16.9	73%	16,125	6	3.7 (1-8)
Baker (2016) ¹³	Retro.	DVT, PE	Comb.	11.3	48%	14,776	15	10.2 (6-17)
Cunningham (2020) ⁴⁶	Retro.	VTE	Trauma	10	66%	8,271	30	36.3 (25-52)
Shore (2020) ²⁷	Retro.	VTE	Orth. elect.	NR	56%	4,583	4	8.7 (2-22)
ruitt (2005) ²⁸	Retro.	VTE	Trauma	NR	NR	3,637	3	8.2 (2-24)
zu (2005) ²⁹	Retro.	VTE	Trauma	NR	64%	3,345	2	6 (0-22)
Murphy (2019) ³⁰	Retro.	DVT	Orth. elect.	15	46%	2,783	7	25.2 (10-52)
Allen (2016) ³¹	Retro.	VTE	Trauma	11	70%	1,943	22	113.2 (71-171)
Greenwald (2012) ³²	Retro.	DVT	Trauma	8.41	NR	1,782	3	16.8 (3-49)
Allahabadi (2021) ⁴⁷	Retro.	VTE	Orth. elect.	14.4	37%	1,480	9	60.8 (28-115)
Erkilinc (2021) ⁴⁸	Retro.	DVT	Spine	12.1	30%	1,471	2	13.6 (2-49)
au (2019) ³³ .	Retro.	DVT, PE	Orth. elect.	15.2	48%	746	2	26.8 (3-967)
Ellis (2019) ³⁴	Prosp.	PE	Orth. elect.	14.8	50%	657	1	15.2 (0-85)
lollmig (2007) ³⁵	Retro.	DVT	MSKI	NR	62%	212	11	518.9 (262-909)
Zwingmann (2015) ³⁶	Retro.	VTE	Trauma	9.3	58%	208	0	0 (0-176)
Kochai (2019) ³⁷	Retro.	DVT, PE	Spine	14.6	43%	73	0	0 (0-493)
eslie (1981) ³⁸	Prosp.	DVT	Spine	13.5	30%	54	2	370.4 (45-1,275)
Kaabachi (2010) ³⁹	Prosp.	DVT	Spine	14.8	43%	40	0	0 (0-881)
Crary (2006) ⁴⁰	Retro.	DVT	MSKI	8.8	63%	35	10	2,857.1 (1,463-4,630
atalski (2012) ⁴¹	Prosp. and retro.	VTE	Comb.	15.4	37%	35	0	0 (0-1,000)
Watanabe (2014) ⁴²	Prosp.	VTE	Orth. elect.	15	11%	27	0	0 (0-1,277)

*VTE = venous thromboembolism, retro. = retrospective study, comb. = combination of subgroups, NR = not reported, DVT = deep vein thrombosis, PE = pulmonary embolism, orth. elect. = orthopaedic elective procedures, prosp. = prospective study, MSKI = musculoskeletal infection. †The values are given as the estimate, with the 95% confidence interval in parentheses.

effects generalized linear mixed models with a logit link. The pooled incidence of VTE was estimated along with an exact Clopper-Pearson 95% confidence interval (CI) for all events and for orthopaedic-specific events. Because of the heterogeneity, subgroup stratification was conducted for orthopaedic events by study size (>10,000 versus <10,000 patients), by trauma versus elective surgery (or a combination or other), and by orthopaedic subspecialty (spine, sports, trauma, or a combination or other). Forest plots were created for each subgroup, and included the raw VTE incidence in each study in the subgroup and the pooled incidence. All VTE incidence was

reported as cases per 10,000. A funnel plot to investigate publication bias was created for VTE incidence. The Egger test was conducted and revealed no significant evidence of asymmetry (p = 0.68; Fig. 2).

Source of Funding

No funding was received for this investigation.

Results

total of 2,467,764 pediatric patients were included in the A total of 2,467,764 pediatric patients were included in the $30 \text{ studies}^{4,13-15,24,49}$, and 3,113 were diagnosed with VTE

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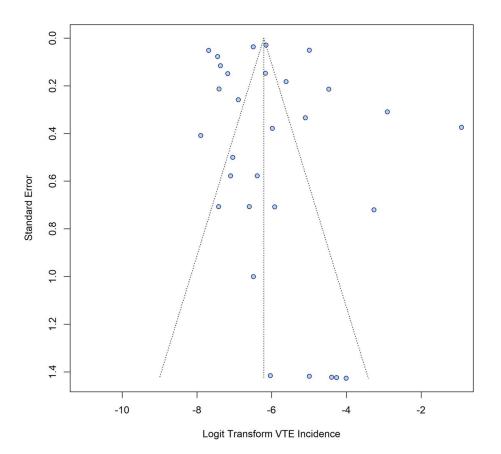


Fig. 2

Funnel plot for bias in reported VTE incidence across all studies. There was no significant evidence of asymmetry (p = 0.68).

(Table I). After applying our study exclusions, the remaining 26 studies had 850,268 orthopaedic patients with 1,108 cases of VTE.

The aggregate median across all studies that reported a central measure of age was 13 years, and the aggregate median proportion of male patients across all studies that reported sex was 52%.

Study Design and Characteristics

The existing literature related to VTE in pediatric trauma or orthopaedic patients primarily consists of a variety of retrospective and prospective studies, systematic reviews, and case reports. The 30 selected articles included 25 retrospective studies, which represent a very low quality of evidence according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) guidelines⁵⁰. Of the remaining articles, 4 were prospective studies and 1 had a combination of retrospective and prospective cohorts (Table I).

VTE Incidence in All Studies

The VTE incidence in the individual studies ranged from 0 to 2,857 events per 10,000 children (Table I). Meta-analysis revealed a pooled VTE incidence of 20 events (95% CI = 10.8 to 37.2) per 10,000. Heterogeneity was very high across all studies, with a τ^2 of 2.44 and an I² of 99%.

VTE Incidence in the Orthopaedic Subpopulation

A total of 1,129 VTEs occurred in 850,515 pediatric orthopedic patients across 28 studies; 2 studies did not report complete patient and VTE numbers and were excluded^{4,28}. Meta-analysis revealed a pooled VTE incidence of 22.7 events (95% CI = 10.7 to 48.2) per 10,000. Heterogeneity was very high across all studies, with a τ^2 of 3.32 and an I² of 98%. Two of the studies reported VTE incidences of 519 and 2,857 per 10,000 in patients with osteomyelitis^{35,40}. When this population was removed from the analysis, the τ^2 value dropped from 3.32 to 1.86 and the pooled VTE incidence in orthopaedic patients dropped to 16.6 events (95% CI = 9.1 to 30.5) per 10,000. All further subgroup analyses were conducted in the orthopaedic patients in the remaining 26 non-osteomyelitis studies.

Subgroup Analysis by Study Size

The pooled VTE incidence was found to be 9.4 events (95% CI = 4.5 to 19.6) per 10,000 in the studies with >10,000 patients compared with 27.2 events (95% CI = 12.2 to 60.3) per 10,000 in the studies with <10,000 patients (p = 0.06). When stratified by study size, the heterogeneity was not reduced in the large studies with >10,000 patients; however, it was reduced to 88% in the small studies with <10,000 patients (Fig. 3).

Subgroup Analysis by Trauma Versus Elective Studies

The pooled VTE incidence was highest for studies involving trauma, with an estimated 29.3 events (95% CI = 10.2 to 83.8)

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			Events per 10000	VTE	
Study	VTEs	Total	observations	incidence	[95% CI]
N = >10,000		1			
Samineni 2021	28	188669		1.5 [1.0; 2.1]
Cunningham 2020+	294	89829 🗖		32.7 [2	29.1; 36.7]
Murphy 2015	167	285611		5.8 [5.0; 6.8]
Georgopoulos 2016	74	117676		6.3 [4.9; 7.9]
Guzman 2018	387	57183 🔲		67.7 [6	61.1; 74.7]
Ramos 2016	22	36335 🗖		6.1 [3.8; 9.2]
Jain 2014	46	21955 🗖		21.0 [1	15.3; 27.9]
Nogaro 2020	6	16125		3.7 [1.4; 8.1]
Baker 2016	15	14776 🗖		10.2 [5.7; 16.7]
Random effects model		828159		9.4 [4.5; 19.6]
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 1$.2257, <i>p</i> < 0.01				
N = <10,000					
Vavilala 2002	10	6043		16.5 [7.9; 30.4]
Cunningham 2020	15	1336			3.0; 184.5]
Shore 2020	4	4583			2.4; 22.3]
Azu 2005	0	540			0.0; 68.1]
Murphy 2019	7	2783			10.1; 51.8]
Allen 2016	14	251			8.3; 918.1]
Greenwald 2012	3	1782			3.5; 49.1]
Allahabadi 2021	9	1480 🖽			7.8; 115.1]
Erkilinc 2021	2	1471		-	1.6; 49.0]
Lau 2019	2	746 🕀		-	3.2; 96.5]
Ellis 2019	1	657 🗗		-	0.4; 84.5]
Zwingmann 2015	0	208			0.0; 175.8]
Kochai 2019	0	73			0.0; 492.8]
Leslie 1981	2	54	— <u> </u>		5.2; 1274.7]
Kaabachi 2010	0	40			0.0; 881.0]
Latalski 2012	0	35			0.0; 1000.3]
Watanabe 2014	0	27		-	0.0; 1277.0]
Random effects model	C C	22109 +			2.2; 60.3]
Heterogeneity: $I^2 = 88\%$, $\tau^2 = 1$	$6727 \ p < 0.01$			L .	,
Heterogeneity: $I^2 = 98\%$, $\tau^2 = 1$					
Test for subgroup differences:	$q_{1}^{2} = 3.67$, df = 1 (p =	0.06) 0 20	0 400 600 8001000 14	00	
Fig 3	vi, «, , , , , , , , , , , , , , , ,				

Fig. 3

Orthopaedic-specific VTE incidence stratified by study size. "Cunningham 2020+" indicates reference 45 (with "Cunningham 2020" indicating reference 46), and df = degrees of freedom.

per 10,000, lower for studies involving elective procedures, with 14.1 events (95% CI = 7.6 to 26.0) per 10,000, and lowest for studies involving a combination or other procedures, with 3.7 events (95% CI = 1.0 to 13.7) per 10,000 (p < 0.001) (Fig. 4). When stratified into these groups, heterogeneity remained high for trauma (I² = 99%), was reduced to 94% for a combination or other procedures, and was lowest (I² = 89%) for elective procedures (Fig. 4).

Subgroup Analysis by Orthopaedic Subspecialty

The pooled VTE incidence was highest for studies involving trauma, with an estimated 29.3 events (95% CI = 10.2 to 83.8) per 10,000, followed by spine studies, with 17.5 events (95% CI = 5.6

to 54.9) per 10,000, and sports studies, with 11.5 events (95% CI = 4.4 to 30.2) per 10,000, and was lowest for studies involving a combination or other procedures, with 8.0 events (95% CI = 2.9 to 22.5) per 10,000 (Fig. 5). However, the difference across the orthopaedic subspecialty subgroups was not significant (p = 0.35). When stratified by orthopaedic subspecialty, heterogeneity was unchanged for trauma studies (I² = 99%), was reduced to 86% for spine articles and 78% for sports articles, and remained high at 95% for combination or other articles (Fig. 5).

Risk Factors

Risk factors were reported in 15 of 28 studies. The factors that were most commonly reported as analyzed included age, sex,

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Study	VTEs	Total	Events per 10000 observations	VTE incidence	[95% CI]
Subgroup = Trauma Cunningham 2020+ Murphy 2015 Vavilala 2002 Guzman 2018 Cunningham 2020 Azu 2005 Allen 2016 Greenwald 2012 Zwingmann 2015 Random effects model Heterogeneity: $l^2 = 99\%$, $\tau^2 = 2.7$	294 167 10 387 15 0 14 3 0	89829 285611 6043 57183 1336 540 251 1782 208 442783 ◆		5.8 16.5 67.7 112.3 0.0 557.8 [16.8 0.0	[29.1; 36.7] [5.0; 6.8] [7.9; 30.4] [61.1; 74.7] [63.0; 184.5] [0.0; 68.1] [308.3; 918.1] [3.5; 49.1] [0.0; 175.8] [10.2; 83.8]
Subgroup = Elective Georgopoulos 2016 Ramos 2016 Jain 2014 Nogaro 2020 Shore 2020 Murphy 2019 Allahabadi 2021 Erkilinc 2021 Lau 2019 Ellis 2019 Kochai 2019 Leslie 1981 Kaabachi 2010 Watanabe 2014 Random effects model Heterogeneity: $I^2 = 89\%$, $\tau^2 = 0.7$	74 22 46 6 4 7 9 2 2 1 0 2 0 0	117676 36335 21955 16125 4583 2783 1480 1471 746 657 73 54 40 27 204005		60.8 13.6 26.8 15.2 0.0 370.4 [0.0 0.0	[4.9; 7.9] [3.8; 9.2] [15.3; 27.9] [1.4; 8.1] [2.4; 22.3] [10.1; 51.8] [27.8; 115.1] [1.6; 49.0] [3.2; 96.5] [0.4; 84.5] [0.0; 492.8] [45.2; 1274.7] [0.0; 881.0] [0.0; 1277.0] [7.6; 26.0]
Subgroup = Combination Samineni 2021 Baker 2016 Latalski 2012 Random effects model Heterogeneity: $l^2 = 94\%$, $\tau^2 = 0.8$ Heterogeneity: $l^2 = 98\%$, $\tau^2 = 1.8$ Test for subgroup differences: χ_{2}^{2} Fig. 4	3569, p < 0.01	188669 14776 35 203480 : 0.05) 0 20	 	3.7	[1.0; 2.1] [5.7; 16.7] [0.0; 1000.3] [1.0; 13.7]

Fig. 4

Orthopaedic-specific VTE incidence stratified by trauma, elective, or combination populations. "Cunningham 2020+" indicates reference 45 (with "Cunningham 2020" indicating reference 46), and df = degrees of freedom.

obesity/body mass index (BMI), type or location of surgery, and use of a central venous catheter (CVC) (Table II). Those most commonly reported as predictive of VTE risk included age, type or location of surgery, diagnosis, CVC use, and obesity/BMI.

Discussion

The VTE incidence in patients <15 years old is 100 times lower than that in a typical 80-year-old patient, but adolescents are known to be at significantly higher risk for VTE after trauma compared with their younger counterparts^{51,52}. Furthermore, despite the apparent low incidence, reviews have suggested that the incidence of VTE in the pediatric population and the resulting morbidity has substantially increased over the past 2 decades¹². The present meta-analysis found an overall VTE incidence of 16.6 per 10,000 pediatric orthopaedic patients. This is higher than in some previous studies of pediatric orthopaedic patients, but less than in studies of adults^{13,15,51}. Interestingly,

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Study	VTEs	Total	Events per 10000 observations	VTE incidence	[95% CI]
Subgroup = Trauma Cunningham 2020+ Murphy 2015 Vavilala 2002 Guzman 2018 Cunningham 2020 Azu 2005 Allen 2016 Greenwald 2012 Zwingmann 2015 Random effects model Heterogeneity: I^2 = 99%, τ^2 = 2.144	294 167 10 387 15 0 14 3 0	89829 285611 6043 57183 1336 540 251 1782 208 442783	-	5.8 16.5 67.7 112.3 0.0 557.8 16.8 0.0	[29.1; 36.7] [5.0; 6.8] [7.9; 30.4] [61.1; 74.7] [63.0; 184.5] [0.0; 68.1] [308.3; 918.1] [3.5; 49.1] [0.0; 175.8] [10.2; 83.8]
Subgroup = Spine Ramos 2016 Jain 2014 Erkilinc 2021 Kochai 2019 Leslie 1981 Kaabachi 2010 Watanabe 2014 Random effects model Heterogeneity: l^2 = 86%, τ^2 = 1.085	22 46 2 0 2 0 0 83, <i>p</i> < 0.01	36335 21955 1471 73 54 40 27 59955	-	13.6 0.0 370.4 0.0 0.0	[3.8; 9.2] [15.3; 27.9] [1.6; 49.0] [0.0; 492.8] [45.2; 1274.7] [0.0; 881.0] [0.0; 1277.0] [5.6; 54.9]
Subgroup = Sports Nogaro 2020 Murphy 2019 Lau 2019 Ellis 2019 Random effects model Heterogeneity: I^2 = 78%, τ^2 = 0.564	6 7 2 1 48, <i>p</i> < 0.01	16125 2783 746 657 20311		3.7 25.2 26.8 15.2 11.5	[1.4; 8.1] [10.1; 51.8] [3.2; 96.5] [0.4; 84.5] [4.4; 30.2]
Subgroup = Combination Samineni 2021 Georgopoulos 2016 Baker 2016 Shore 2020 Allahabadi 2021 Latalski 2012 Random effects model Heterogeneity: $l^2 = 95\%$, $\tau^2 = 1.299$ Heterogeneity: $l^2 = 98\%$, $\tau^2 = 1.850$ Test for subgroup differences: $\chi^2_3 = 100$	69, <i>p</i> < 0.01	188669 117676 14776 4583 1480 35 327219 = 0.35) 0 1	- - 000 2000 3000 4000 500	8.7 60.8 0.0 8.0	[1.0; 2.1] [4.9; 7.9] [5.7; 16.7] [2.4; 22.3] [27.8; 115.1] [0.0; 1000.3] [2.9; 22.5]

Fig. 5

Orthopaedic-specific VTE incidence stratified by trauma, spine, sports, or combination populations. "Cunningham 2020+" indicates reference 45 (with "Cunningham 2020" indicating reference 46), and df = degrees of freedom.

when stratified by study size (>10,000 or <10,000 patients), the incidence of VTE in pediatric orthopaedic patients was almost 3 times as high in the smaller studies.

The reported incidence of VTE has varied across previous pediatric orthopaedic studies due to differences in inclusion

criteria and in how the events were captured. For example, 1 study that included only pediatric patients with osteomyelitis found a VTE rate of 28.6% in that cohort of 35 patients⁴⁰. Studies including only pediatric orthopaedic trauma patients found a VTE incidence that ranged from 0 to 387 per 10,000

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TABLE II Summary of Reported Risk Factors*					
Risk Factor	Studies Evaluating the Factor	No. (%) That Found the Factor Was Predictive			
Age	15 (54%)	11 (73%)			
Sex	12 (43%)	1 (8%)			
Obesity/BMI	10 (36%)	4 (40%)			
Type of surgery/location of injury	10 (36%)	9 (90%)			
CVC	7 (25%)	5 (71%)			
Ethnicity	7 (25%)	2 (29%)			
Diagnosis	7 (25%)	6 (86%)			
Spinal cord injury	6 (21%)	2 (33%)			
Infection	5 (18%)	2 (40%)			
Hematologic, renal, endocrine, and gastrointestinal disorders	5 (18%)	3 (60%)			
Neuromuscular and neurologic conditions	5 (18%)	4 (80%)			
Blood clot condition or family history	5 (18%)	2 (40%)			
Malignancy	4 (14%)	1 (25%)			
Emergency vs. urgent	4 (14%)	4 (100%)			
LOS	4 (14%)	3 (75%)			
Inpatient vs. outpatient	3 (11%)	3 (100%)			
OCP	3 (11%)	1 (33%)			
Complication	2 (7%)	1 (50%)			
ICU	2 (7%)	2 (100%)			
Transfusion	2 (7%)	O (O%)			
Heart disease	1 (4%)	O (O%)			
Surgical approach	1 (4%)	O (O%)			
Smoking	1 (4%)	1 (100%)			
Duration of surgery	1 (4%)	1 (100%)			
Burns	1 (4%)	0 (0%)			
*Based on 28 studies. BMI = body mass index, CVC = central					

venous catheter, LOS = length of stay, OCP = oral contraception, ICU = intensive care unit.

children^{14,36}. Our meta-analysis found that VTE incidence was much higher in orthopaedic trauma surgery (29 per 10,000 children) compared with elective orthopaedic surgery (14 per 10,000 children)^{14,15,24-27,29-34,36-39,42,43,45-49}. In our study, the median age of pediatric orthopaedic VTE patients was 13 years, which is older than in previous studies investigating pediatric VTE for all hospitalized patients. There are specific VTE risk factors during the newborn and adolescent periods. VTE incidence is postulated to be elevated during the newborn period due to narrow blood vessels, an immature hematologic system, and more frequent use of CVCs⁵³. Later, the incidence peaks in adolescents due to contraception, smoking, and obesity as well as the fact that the composition of the hemostatic system in adolescents is comparable with that in adults^{17,18}.

Unlike the clinical situation in adults, VTE in children is rarely considered idiopathic; studies have shown that 95% of children with VTE had at least 1 associated condition^{4,11,15}. A meta-analysis of hospital-associated VTE in pediatrics found that CVC placement, intensive care unit stay, mechanical ventilation, and length of hospital stay were significant risk factors for the development of VTE⁵⁴. Among pediatric orthopaedic patients, the authors of 1 study have identified a gastrointestinal comorbidity, renal comorbidity, hematologic disorder, elevated aspartate aminotransferase (AST) level, abnormal partial thromboplastin time (PTT), and hyponatremia as patient risk factors associated with VTE in this population, but obesity and age were not found to be risk factors in that study¹³. Another study found that CVC placement, coagulopathy, spinal cord injury, blood loss anemia, osteomyelitis, external fixation, obesity, and diabetes were risk factors for VTE development in pediatric orthopedic patients¹⁴. Our systematic review also identified other parameters that have been previously reported as risk factors for VTE.

A survey of Pediatric Orthopaedic Society of North America (POSNA) members found that although VTE was uncommon, with only 46 cases among the patients of the surveyed members, there was a risk of fatal VTE among pediatric patients with musculoskeletal conditions, as 2 of the 46 patients died. One also had cerebral palsy and the other was suspected to also have anti-thrombin 3 deficiency, but in both cases the mortality was believed to be attributable to the VTE event⁵⁵. Three of the studies included in the systematic review and the survey of POSNA members reported VTE cases in pediatric orthopaedics in which the patient died^{14,15,31,55}. One of those studies found a fatality rate of 5.4% among the pediatric orthopaedic patients who developed VTE¹⁵. Two of the 4 deaths in that study were associated with septic shock, and 1 patient had cerebral palsy, but the mortality was believed to be attributable to the VTE event¹⁵.

Even though thromboprophylaxis is considered essential to decreasing morbidity and mortality in adult patients undergoing orthopaedic surgery, there are no established national standards for VTE screening or thromboprophylaxis in children. The Wells Deep Venous Thrombosis Risk Score can be used for risk stratification of pediatric patients, although it should not be used as a standalone method^{3,56}. One study of pediatric orthopaedic patients with pelvic or femoral fractures found that >91% of the patients did not receive any thromboprophylaxis, and none of the patients who did not receive prophylaxis developed VTE³². The authors concluded that widespread use of thromboprophylaxis was not necessary in children treated for femoral or pelvic fractures³². Another of the included studies suggested that pediatric orthopaedic patients who have a complicated postoperative course should be monitored closely for VTE or receive prophylaxis, but the authors agreed that routine thromboprophylaxis for patients without risk factors probably carries more risks than benefits¹³. To date, there has only been 1 cohort study that examined the incidence of VTE in pediatric patients who received low-molecular-weight heparin (LMWH) after an orthopaedic procedure, to our knowledge, and none of the 35 patients

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developed VTE⁴¹. The increase in incidence of pediatric VTE combined with the unique risk factors in children indicate that there is a population at risk who require screening and prophylaxis protocols.

The results of this study must be interpreted in light of several limitations. Although the literature review was thorough, there is a possibility that additional studies regarding pediatric orthopaedic VTE were missed in our review, which could have an effect on our results. Furthermore, the strength of a systematic review is only as great as the strength of the available literature. We found that the majority of studies on this subject represented a low quality of evidence according to the GRADE guidelines, and this limits the strength of our conclusions; however, the large pooled sample size of our cohort is noteworthy. Another limitation is the wide variety among the included studies in terms of both size and patient population, which resulted in the high heterogeneity in the model used to determine VTE incidence in the entire pediatric orthopaedic cohort. To address this heterogeneity, studies were stratified on the basis of size (greater or less than 10,000 patients), type of orthopaedic subspecialty, and trauma versus elective orthopaedic cases. Finally, the diagnosis of VTE in children can often be elusive. Since many of the included studies were retrospective in nature, it is quite plausible that this systematic review, which demonstrates a higher overall incidence in pediatric orthopaedic patients than previously, still provides an underestimation of the true incidence of the problem in pediatric orthopaedic patients.

In conclusion, this systematic review involving a pooled analysis of almost 1 million children found that the risk of VTE associated with orthopaedic surgery or admission was 17 events per 10,000 children. Orthopaedic surgeons should be aware of risk factors associated with pediatric orthopaedic VTE, which include age, sex, BMI, CVC use, and the type of surgery. A traumatic etiology is especially important to consider, given that this study found the VTE incidence among pediatric orthopaedic patients to be 3 times as high in that subgroup. In addition, adolescents may have a greater risk of VTE than younger patients after orthopaedic surgery or admission, and prophylaxis should be considered in that population.

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