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ORIGINAL ARTICLE

Proportion and risk factors for hospital-acquired venous thromboembolism in children: a systematic review and meta-analysis of data from 20 million individuals in 22 countries

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Abstract

Background: Hospital-acquired venous thromboembolism (HA-VTE) in children has been widely regarded.

Objectives: We aimed to analyze the proportion and risk factors for HA-VTE in hospitalized children.

Methods: We conducted a comprehensive systematic search across 4 databases from 1990 to 2023. Cochran Q test was used to evaluate the heterogeneity of the effect sizes of study, and I^2 statistic was used to quantify the heterogeneity. Pooled estimates were calculated by the inverse-variance weighted method in a fixed-effect model or a random-effect model when heterogeneity was low ($I^2 < 25\%$) or high ($I^2 > 25\%$), respectively.

Results: In total, 105 original papers and 20,718,294 patients were included in the study, and the proportion of HA-VTE in children was 4.1% (95% CI, 2.9%-5.2%). Although the proportion of venous thromboembolism increased over the various research periods, the differences were not statistically significant. In the subgroup analysis based on country, the proportion of pediatric HA-VTE was lowest in the United Kingdom and highest in Spain, whereas when based on region, the proportion was lowest in Asia and highest in North America. Multiple HA-VTE risk factors were identified, including central venous catheter use, age of >10 years, surgery, injury, infection, obesity, mechanical ventilation, blood transfusion, malignancy, coagulation and hemorrhagic disorders, and length of hospital stay.

Conclusion: In this study, we systematically analyzed the proportion and risk factors of HA-VTE in hospitalized children. Our findings provide valuable insights for the prevention and treatment of HA-VTE in pediatric patients.

KEYWORDS
meta-analysis, pediatric, proportion, risk factors, venous thromboembolism

Jintuo Zhou, Yanting Zhu, and Ying Liu contributed equally to this study.

Essentials

- Review on hospital-acquired venous thromboembolism (HA-VTE) in children has not been updated.
- We conducted an updated systematic review of pediatric HA-VTE based on 20 million individuals.
- The proportion of HA-VTE in children was 4.1% (95% CI, 2.9%-5.2%).
- Risk factors for HA-VTE were identified, including central venous catheter and surgery.

1 | INTRODUCTION

Hospital-acquired venous thromboembolism (HA-VTE) has been regarded as a common comorbidity in hospitalized adults, which is often underdiagnosed and considered rare among pediatric patients [1–3]. In recent years, with the improvement of medical diagnostic equipment and levels, more HA-VTE events in children have been reported [4,5]. This is also attributed to the increased utilization of central venous catheters (CVC) as well as improved survival of pediatric patients. Pediatric HA-VTE mostly occurs in intensive care unit, and neonatal HA-VTE has the highest incidence [6,7]. The increased incidence of HA-VTE in children raises concerns about increased disease comorbidities, such as postthrombotic syndrome, and mortality.

Recent studies have revealed that children with HA-VTE often have at least 1 risk factor. Reported risk factors for pediatric HA-VTE include genetic predispositions such as congenital prethrombotic diseases, medical conditions such as CVC use, and external environmental factors such as trauma [4,8–11]. However, our current understanding of the risk factors for pediatric HA-VTE is limited by variations in study quality, with most data derived from a single-institution or multicenter national registries within a single country. The reported results indicate that the risk factors contributing to pediatric HA-VTE remain controversial, and a comprehensive analysis is needed for further understanding of these potential risk factors [12,13].

Studies have comprehensively analyzed the risk factors for HA-VTE in children hospitalized in intensive care unit recently [14]. However, there is a lack of updated analysis on HA-VTE risk factors in all hospitalized children, and the risk factors for pediatric HA-VTE have not been conclusively determined. In this study, our aim was to systematically analyze the proportion and risk factors for HA-VTE in hospitalized children, providing more valuable insights for the prevention and treatment of HA-VTE in pediatric patients.

2 | METHODS

This systematic review was registered in the PROSPERO database under the registration number CRD42024497429 and strictly followed the guidelines outlined in the Preferred Reporting Project for Systematic Review and Meta-Analysis.

2.1 | Search strategies

We searched for relevant English literature published between 1990 and 2023 in 4 databases: Web of Science, Embase, PubMed, and the Cochrane Library. The search strategies were constructed using the terms "venous thromboembolism," "risk," and "children," incorporating various subject headings and text words for each concept. The complete search strategy is available in the Supplementary Table.

2.2 | Study selection

The inclusion criteria comprised (a) articles in English focusing on human subjects, (b) electronic publications reporting cases of HA-VTE, (c) cross-sectional studies and both retrospective and prospective cohort studies, (d) cases of HA-VTE in individuals below 21 years old, as per the National Institute of Child Health and Human Development's definition of pediatric age, and (e) articles presenting information on the proportion of pediatric HA-VTE or its associated risk factors.

The exclusion criteria encompassed (a) individuals aged >21 years; (b) cases involving arterial events; (c) articles not in English, case reports, case-control studies, protocols, literature reviews, and conference papers; and (d) articles lacking information on the proportion of HA-VTE in children or its related risk factors.

2.3 | Data extraction

The retrieval results were managed using Endnote software. Following the removal of duplicates, data extraction was carried out independently by 2 authors (J.T.Z. and Y.T.Z.). Initial data extraction included year of publication, country, first author, study design, study period, sample size, proportion of HA-VTE, risk factors, and risk estimate for HA-VTE (odds ratios [ORs] and corresponding 95% CIs). Risk factors for HA-VTE included CVC, age (>10 years), surgery (general surgery, cardiothoracic surgery, and orthopedic surgery), injury (head, chest, and spinal cord injury), infection (meningitis, abscess, necrotizing enterocolitis, pneumonia, osteomyelitis, bacteremia, fungemia, tracheitis, and pyelonephritis), obesity (body mass index > 30 kg/m^2 or >95th percentile), mechanical ventilation, blood transfusion, malignancy, coagulation and hemorrhagic disorders, and length of hospital stay (LOS; per each additional day). Variables were categorized when definitions differed between papers. Disagreements

were resolved through negotiation, and if necessary, the third author (H.J.C.) would be invited to arbitrate.

2.4 | Quality assessment

Quality assessment of all included articles was conducted independently by J.T.Z. and Y.T.Z. The choice of a suitable assessment tool for evaluating literature quality depended on the article type. Cross-sectional studies were appraised using the Joanna Briggs Institute scale, whereas cohort studies underwent evaluation with the Newcastle-Ottawa Scale.

2.5 | Statistical analysis

Statistical analyses were conducted using R version 4.3.2 (R Foundation for Statistical Computing). Heterogeneity among study effect sizes was assessed by Cochran Q test, and quantified heterogeneity was assessed by I^2 statistic. Meta-analyses were conducted for risk factors that were investigated in a minimum of 3 studies. Statistical significance was defined at an alpha level of 5% ($\alpha = .05$). A Bonferroni correction was used because many subanalyses were performed, and statistical significance was set at an adjusted alpha (α_a) level of 0.45% ($\alpha_a = .05/n$; n, the number of subanalyses). Pooled estimates were calculated by the inverse-variance weighted method in a fixed-effect model or a random-effect model when heterogeneity was low ($I^2 < 25\%$) or high ($I^2 > 25\%$), respectively.

3 | RESULTS

3.1 | Literature search

The initial literature search included 1487 citations. Initially, 330 duplicate papers were removed. Subsequently, a comprehensive review of titles and abstracts resulted in the exclusion of 884 articles. After a meticulous examination of the remaining 209 articles, 104 articles were subsequently excluded. These included 6 duplicates, 11 review studies, and 87 articles lacking information on children's HA-VTE proportion and risk factors. In the final analysis, 105 original papers that met the stipulated inclusion and exclusion criteria were incorporated into this study (Figure 1).

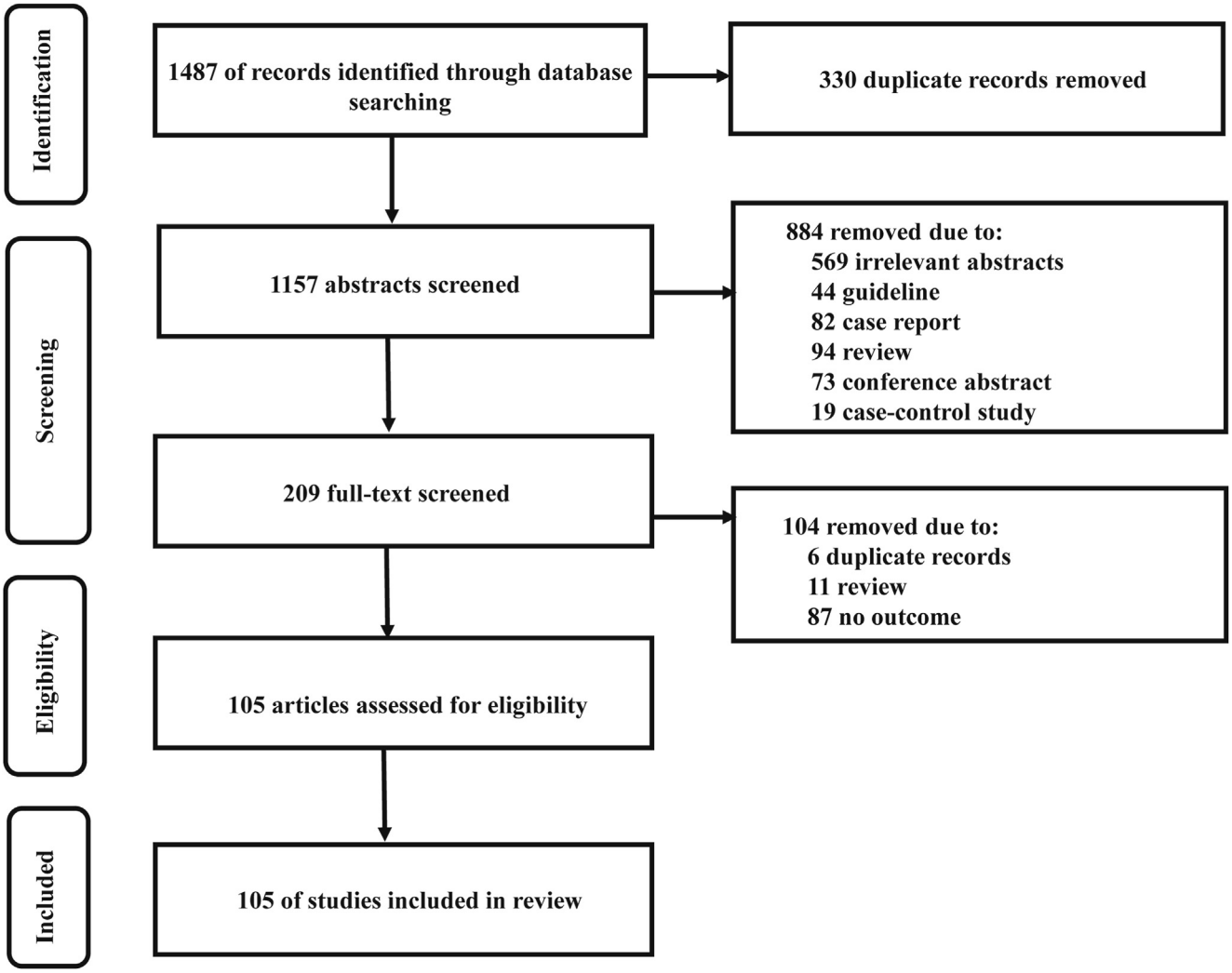

FIGURE 1 The Preferred Reporting Project for Systematic Review and Meta-Analysis flowchart.

TABLE 1 Basic information of the included literature.

Study	Publish year	Study type	Country	Research period	Event	Total	Outcome	Quality score
Radecki et al. [15]	1994	RC	USA	1983-1987	25	532	①	7
McBride et al. [16]	1994	RC	USA	1987-1993	6	28,692	①	7
Uderzo et al. [17]	1995	RC	Italy	1985-1993	12	452	①	7
Peťäjä et al. [18]	1996	RC	Finland	1985-1994	18	1604	①	7
DeAngelis et al. [19]	1996	RC	USA	1993-1994	3	76	①	7
Rohrer et al. [20]	1996	CS	USA	1994	1	59	①	16
Beck et al. [21]	1998	RC	France	1996-1997	20	107	①	7
Boo et al. [22]	1999	CS	Malaysia	1997	2	49	①	15
Tabori et al. [23]	2004	RC	Israel	1990-2003	3	462	①	7
Jones et al. [24]	2005	RC	USA	1991-1993	70	1585	①⑤	7
Azu et al. [25]	2005	RC	USA	1994-2003	2	3345	①	5
Soyer et al. [26]	2006	RC	Turkey	1994-2004	4	68	①	6
Cyr et al. [27]	2006	RC	Canada	1999-2002	11	3291	①②⑤	7
Dubois et al. [28]	2007	RC	France	2004-2005	20	214	①	7
Sandoval et al. [5]	2008	RC	USA	1992-2005	99	102,502	①	7
Connolly et al. [29]	2008	RC	USA	1998-2004	60	194	①	7
Schiavetti et al. [30]	2008	CS	Italy	2008	5	42	①	16
Candrilli et al. [31]	2009	CS	USA	2003	648	240,387	①	16
Hanson et al. [32]	2009	PC	USA	2006-2008	41	1070	①	7
Barclay et al. [33]	2010	RC	UK	2003-2008	4	154	①	7
O'Brien et al. [34]	2011	RC	USA	2001-2005	826	135,032	①②⑤	7
Lipay et al. [35]	2011	RC	BLR	2000-2009	44	2061	①	7
Al-Aridi et al. [36]	2011	RC	Lebanon	2002-2009	8	111	①	7
Higgerson et al. [37]	2011	RC	USA	2006-2007	66	6653	①②⑧	7
Wright et al. [38]	2011	RC	USA	2006-2008	92	41,906	①	7
Setty et al. [39]	2012	CS	USA	2006	4708	2,410,351	①	15
Gray et al. [40]	2012	RC	USA	2005-2009	60	333	①	7
Nylund et al. [41]	2013	CS	USA	19997, 2000, 2003, 2006, and 2009	806	68,394	①②⑩	15
Zitomersky et al. [42]	2013	RC	USA	2006-2011	10	532	①	7
Van Arendonk et al. [43]	2013	RC	USA	2008-2010	1655	402,329	①②③④⑤⑦⑨	7
Neto et al. [44]	2014	RC	Brazil	1995-2013	37	486	①	7
Harris et al. [45]	2014	CS	USA	2009	267	58,529	①②③④⑤⑧	16
de Oliveira et al. [46]	2015	RC	Brazil	2000-2012	2	1063	①	7
Humes et al. [47]	2015	RC	UK	2001-2011	6	15,637	①	7
Smitherman et al. [48]	2015	RC	USA	2009-2012	36	1135	①	6
Shah et al. [49]	2015	RC	USA	2010-2012	62	3733	①	7
Allen et al. [50]	2016	RC	USA	2000-2012	22	1934	①②③④⑤⑦⑨	7
Carpenter et al. [51]	2016	RC	USA	2005-2008	21	229	①②	7

(Continues)

TABLE 1 (Continued)

Study	Publish year	Study type	Country	Research period	Event	Total	Outcome	Quality score
Choi et al. [52]	2016	RC	Korea	2003-2016	25	76,402	①	7
Menéndez et al. [53]	2016	RC	Spain	2012-2015	88	265	①	7
Klaassen et al. [54]	2017	RC	Netherlands	1989-2013	78	2183	①③⑩	7
Ghanem et al. [55]	2017	RC	Canada	2002-2015	13	209	①③	7
Knight-Perry et al. [56]	2017	RC	USA	2003-2016	19	458	①	7
Leeper et al. [57]	2017	RC	USA	2005-2014	21	753	①	7
Schönning et al. [58]	2017	RC	Sweden	2005-2015	12	163	①	7
Shin et al. [59]	2017	RC	USA	2010-2013	292	1110	①②③⑤⑥	7
Atchison et al. [60]	2018	RC	USA	2006-2013	65	2718	①②④⑥⑧⑬⑭	7
Gnannt et al. [61]	2018	RC	Germany	2010-2015	57	2180	①	7
Hennessey et al. [62]	2018	RC	USA	2006-2016	1663	5,803,546	①	7
Tran et al. [63]	2018	RC	USA	2009-2014	1602	158,299	①②③④⑧⑩⑭⑯	7
Ligon et al. [64]	2018	RC	USA	2008-2016	224	901,851	①	7
Rangarajan et al. [65]	2018	RC	USA	2010-2014	290	4158	①	7
Guzman et al. [66]	2018	CS	USA	2012	387	57,183	①②⑤⑦⑪⑬	17
Kumar et al. [67]	2018	RC	USA	2009-2015	181	10,454	①⑬⑮	7
Prasca et al. [68]	2018	RC	USA	2008-2016	27	294	①	7
Woods et al. [69]	2018	RC	USA	2009-2015	12	414	①	7
Ahn et al. [70]	2018	RC	USA	2012-2015	320	267,299	①③⑦⑧⑨⑩	7
Onyeama et al. [71]	2018	RC	USA	2012-2016	22	198	①②③⑦⑫	7
Faustino et al. [72]	2018	PC	USA	2014-2017	9	88	①②	7
Klaassen et al. [73]	2019	RC	Netherlands	1997-2012	18	205	①③	7
Klaassen et al. [74]	2019	RC	Netherlands	2004-2013	59	778	①⑩	7
McKie et al. [75]	2019	RC	Georgia	2006-2012	661	72,686	①④⑦⑨⑪	6
Carrillo et al. [76]	2019	RC	USA	2005-2016	20	6191	①②③	7
Carpenter et al. [77]	2019	RC	USA	2010-2012	11	370	①	7
Murphy et al. [78]	2019	RC	USA	2010-2014	7	2783	①	7
Alturki et al. [79]	2019	RC	Saudi Arabia	2011-2016	3	95	①	7
Lau et al. [80]	2019	RC	USA	2011-2016	5	746	①	7
Sherrod et al. [81]	2019	RC	USA	2012-2015	305	153,220	①⑧⑨⑪⑫	7
Östlund et al. [82]	2019	RC	Sweden	2015-2016	64	211	①②	7
Steen et al. [83]	2019	CS	USA	2017	66	851	①⑥⑫	17
Brown et al. [84]	2020	RC	USA	1990-2014	18	6374	①	7
Shore et al. [85]	2020	RC	USA	2005-2009	40	4583	①	7
Barzilai-Birenboim et al. [86]	2020	RC	Israel	2003-2018	89	1191	①③	7
Ren et al. [87]	2020	RC	China	2007-2018	29	2423	①	7
Mets et al. [88]	2020	RC	USA	2012-2016	378	361,384	①③④⑭	7
Cunningham et al. [89]	2020	RC	USA	2013-2016	729	481,485	①	7

(Continues)

TABLE 1 (Continued)

Study	Publish year	Study type	Country	Research period	Event	Total	Outcome	Quality score
Garg et al. [90]	2020	RC	India	2013-2017	6	92	①	7
El-Naggar et al. [91]	2020	RC	Canada	2014-2016	587	39,971	①	7
Kerris et al. [92]	2020	RC	USA	2013-2017	56	2204	①②④⑯	7
Liu et al. [93]	2020	RC	USA	2015-2016	106	3934	①	7
Robinson et al. [94]	2021	RC	USA	1997-2015	2367	1,158,755	①②④⑧⑫	7
Howie et al. [95]	2021	RC	Canada	2000-2017	2	1262	①	7
Samineni et al. [96]	2021	RC	USA	2009-2016	373	810,097	①	7
Graham et al. [97]	2021	RC	USA	2010-2018	8	338	①②④⑦	7
Allahabadi et al. [98]	2021	RC	USA	2015-2020	9	1480	①	7
Hauser et al. [99]	2022	RC	USA	2011-2014	192	22,572	①⑤⑮	7
O'Brien et al. [124]	2022	RC	USA	2008-2019	52,401	6,357,452	①	7
Badawy et al. [100]	2022	RC	Germany	2010-2017	10	115	①	7
Mets et al. [101]	2022	RC	USA	2012-2017	60	81,490	①③④⑤⑨⑪⑭	7
Harrar et al. [102]	2022	RC	USA	2013-2019	8	184	①	7
Ullman et al. [103]	2022	PC	USA	2013-2019	540	42,562	①	7
Bhatia et al. [104]	2022	RC	Canada	2014-2018	186	4860	①②⑫	7
Easterlin et al. [105]	2022	RC	USA	2016-2019	2720	201,033	①②④⑥⑯	7
Wright et al. [106]	2023	RC	USA	2004-2015	19	2400	①	7
Purtell et al. [107]	2023	RC	USA	2009-2018	7	335	①⑥⑮	7
Rudic et al. [108]	2023	RC	USA	2010-2020	38	11,775	①③⑦⑪	7
Bala et al. [109]	2023	RC	USA	2010-2021	8	492	①	7
Hoffmann et al. [110]	2023	RC	Germany	2013-2019	257	44,128	①②⑥	7
Tongta et al. [111]	2023	RC	Thailand	2015-2019	5	419	①	7
Yin et al. [112]	2023	RC	China	2015-2019	159	7640	①	7
Keefe et al. [113]	2023	RC	USA	2014-2021	74	263	①⑥	7
Ren et al. [114]	2023	RC	China	2016-2021	7	567	①	7
Barlas et al. [115]	2023	RC	Turkey	2019-2021	21	215	①	7
Tobias et al. [116]	2023	PC	USA	2019-2021	11	355	①	7
Havlicek et al. [117]	2023	RC	USA	2020-2022	18	170	①	7

BLR, Republic of Belarus; CS, cross-sectional; PC, prospective cohort; RC, retrospective cohort.

① Proportion; ② CVC; ③ Age > 10 years; ④ Surgery; ⑤ Injury; ⑥ Infection; ⑦ Obesity; ⑧ Mechanical ventilation; ⑨ Blood transfusion; ⑩ Malignancy; ⑪ Coagulation and hemorrhagic disorders; ⑫ Sepsis; ⑬ LOS; ⑭ Age < 1 year; ⑮ ICU stay; ⑯ ECMO.

3.2 | Study characteristics

The baseline characteristics of the included studies are available in Table 1 [15–117]. In total, 20,718,294 patients were included in the study, of whom 77,946 were diagnosed with HA-VTE. Among the 105 included studies, 72 were conducted in North America, 18 in Europe, 7 in Asia, 6 in the Middle East, and 2 in Latin America and the Caribbean. Nine of the 105 included studies were cross-sectional, and each of them utilized the Joanna Briggs Institute scale to evaluate the risk of bias. Four studies were prospective cohort studies, and 92 were retrospective cohort studies, all of which were evaluated using Newcastle-Ottawa Scale.

3.3 | Meta-analysis of the proportion of HA-VTE

The proportion of HA-VTE was reported in 105 studies. The meta-analysis showed 99.84% heterogeneity between studies ($P < .001$), so the random-effect model was employed for pooled estimates. The pooled proportion of HA-VTE in children was 4.1% (95% CI, 2.9%-5.2%; Figure 2).

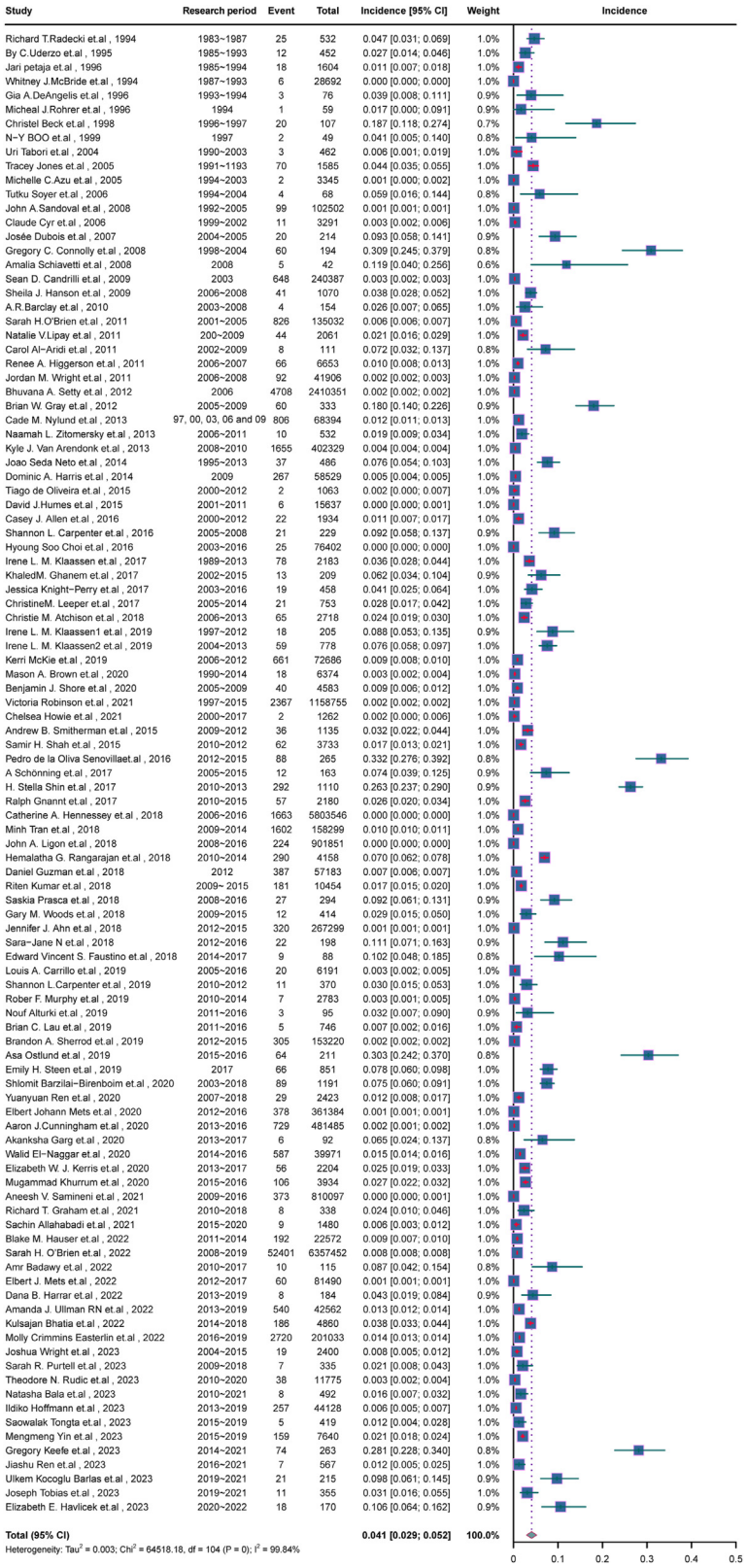

FIGURE 2 Forest plot of pooled proportion of venous thromboembolism in children.

3.4 | Subgroup analysis

Given the notable heterogeneity among the included studies, subgroup analyses were performed. The proportion of children diagnosed with HA-VTE during the periods of 1985-1989, 1990-1999, 2000-2009, 2010-2019, and 2020-2023 was 2.7%, 3.0%, 3.6%, 4.4%, and 7.5%, respectively. Although the proportion of VTE increased over the various research periods, the difference was not statistically significant (Figure 3,

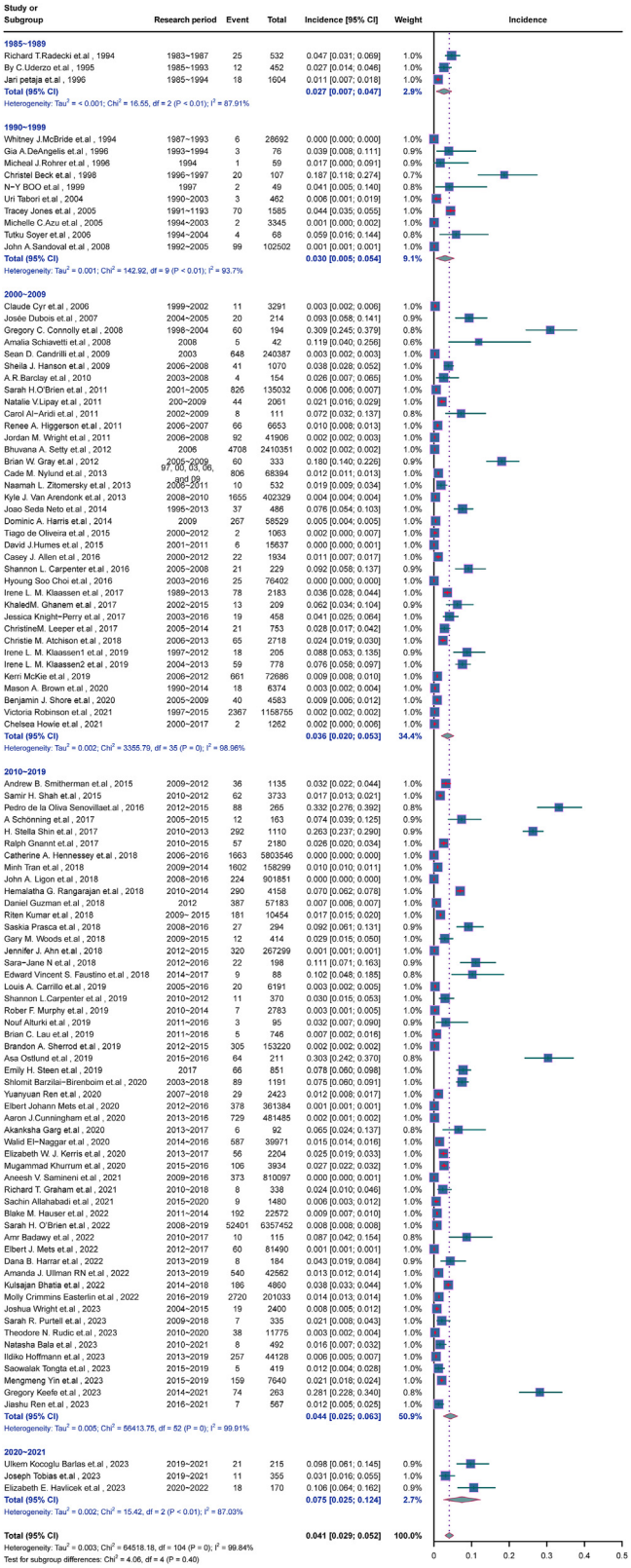

FIGURE 3 Forest plot for studies reporting the proportion of venous thromboembolism, subgroup by the median year of data collection.

Supplementary Figure S3, and Table 2). In the subgroup analysis based on country, the lowest proportion of HA-VTE in children was 1.0% (95% CI, 0%-3.4%) in 2 UK studies involving 15,801 participants, whereas the highest was 33.2% (95% CI, 27.6%-39.2%) in a Spanish study with 353 participants (Supplementary Figure S1 and Table 2). The regional proportion of HA-VTE varied, with rates of 3.3% (95% CI, 2.0%-4.5%) in North America, 8.1% (95%

TABLE 2 Proportion and subgroup analysis of venous thromboembolism in children.

Subgroup	Study (*n*)	Effect size (%)	95% CI (%)	*P* value	Heterogeneity I^2 (%)
Overall					
Proportion	105	4.1	2.9-5.2	<.001	99.84
Research period					
1985-1989	3	2.7	0.7-4.7	<.001	87.91
1990-1999	10	3.0	0.5-5.4	<.001	93.7
2000-2009	36	3.6	2.0-5.3	<.001	98.96
2010-2019	53	4.4	2.5-6.3	<.001	99.91
2020-2021	3	7.5	2.5-5.2	<.001	87.03
Country					
USA	67	3.4	2.0-4.7	<.001	99.89
Italy	2	6.0	0-14.6	<.001	70.15
Finland	1	1.1	0.7-1.8	<.001	-
France	2	13.5	4.4-.22.6	<.001	79.21
Malaysia	1	4.1	0.5-14.0	<.001	-
Israel	2	4.0	0-10.7	<.001	98.45
Turkey	2	8.3	4.7-12.0	<.001	18.90
Canada	5	2.1	0.1-4.0	<.001	98.54
UK	2	1.0	0-3.4	<.001	97.34
Republic of Belarus	1	2.1	1.6-2.9	<.001	-
Lebanon	1	7.2	3.2-13.7	<.001	-
Brazil	2	3.8	0-11.1	<.001	97.34
Korea	1	0	0	<.001	-
Netherlands	3	6.3	3.1-9.5	<.001	90.22
Georgia	1	0.9	0.8-1.0	<.001	-
Spain	1	33.2	27.6-39.2	<.001	-
Sweden	2	18.7	0-41.2	<.001	97.31
Germany	2	3.3	0-7.3	<.001	95.50
Saudi Arabia	1	3.2	0.7-7.3	<.001	-
China	3	1.6	0.9-2.2	<.001	82.74
India	1	6.5	2.4-13.7	<.001	-
Thailand	1	1.2	0.4-2.8	<.001	-
Region					
North America	72	3.3	2.0-4.5	<.001	99.89
Europe	18	8.1	3.7-12.4	<.001	98.54
Asia	6	1.3	0.5-2.0	<.001	97.07
Middle East	6	5.4	2.5-8.4	<.001	94.12
Latin America and the Caribbean	2	3.8	0-11.1	<.001	97.34

CI, 3.7%-12.4%) in Europe, 3.8% (95% CI, 0%-11.1%) in Latin America and the Caribbean, 1.3% (95% CI, 0.5%-2.0%) in Asia, and 5.4% (95% CI, 2.5%-8.4%) in the Middle East (Supplementary Figure S2 and Table 2). The sensitivity analysis confirmed the robustness of the results (Figure 4).

3.5 | Analysis of risk factors for HA-VTE in children

Thirty-nine studies identified multiple factors associated with HA-VTE in children. These factors encompassed CVC use (OR, 4.41; 95% CI, 2.83-6.88; I^2 = 99.72%; $P < .001$), age > 10 years (OR, 1.80; 95% CI, 1.43-2.25; I^2 = 80.67%; $P < .001$), surgery (OR, 2.77; 95% CI, 1.84-4.17; I^2 = 94.47%; $P < .001$), injury (OR, 2.41; 95% CI, 1.59-3.65; I^2 = 83.17%; $P < .001$), infection (OR, 3.70; 95% CI, 1.79-7.64; I^2 = 80.43%; $P < .001$), obesity (OR, 1.90; 95% CI, 1.30-2.77; I^2 = 79.35%; $P < .001$), mechanical ventilation (OR, 2.49; 95% CI, 2.11-2.93; I^2 = 42.71%; $P < .001$), blood transfusion (OR, 2.38; 95% CI, 1.56-3.62; I^2 = 77.66%; $P < .001$), malignancy (OR, 1.99; 95% CI, 1.56-2.54; I^2 = 80.67%; $P < .001$), coagulation and hemorrhagic disorders (OR, 3.85; 95% CI, 1.70-8.72; I^2 = 95.64%; $P < .001$), and LOS (per each additional day, OR, 1.04; 95% CI, 1.02-1.05; I^2 = 83.69%; $P < .001$; Figure 5, Table 3).

4 | DISCUSSION

With continuous improvement of examination methods and treatment techniques, the diagnosis rate of HA-VTE in children has been steadily increasing. Current research on the epidemiology and risk factors for HA-VTE in children is limited by sample size and geographic scope. The existing systematic analyses are outdated, and the quality of the studies is poor, in which the case-control studies were included [118,119]. So, there is a lack of relevant, up-to-date systematic reviews of good quality. In this study, we systematically analyzed the proportion, temporal trends, and risk factors for HA-VTE in hospitalized children. Our results indicated that the proportion of HA-VTE among pediatric patients ranged from 0% to 33.2%, with an average of about 4.1%. The proportion of pediatric HA-VTE was much higher than that reported in a systematic review published in 2023 [118]. In terms of temporal trends, our analysis of the proportion of pediatric HA-VTE per decade experienced an increasing trend, however, with no statistically significant difference.

The proportion of HA-VTE varies among hospitalized children across different countries and geographic regions. In a subgroup analysis based on country, our results indicated that the proportion of pediatric HA-VTE was lowest in the United Kingdom and highest in Spain, whereas in a subgroup analysis based on region, the proportion of pediatric HA-VTE was lowest in Asia and highest in North America. There is no agreement on whether the proportion of HA-VTE is related to the region. A retrospective regional study of HA-VTE in children aged 0 to 18 years showed that the incidence

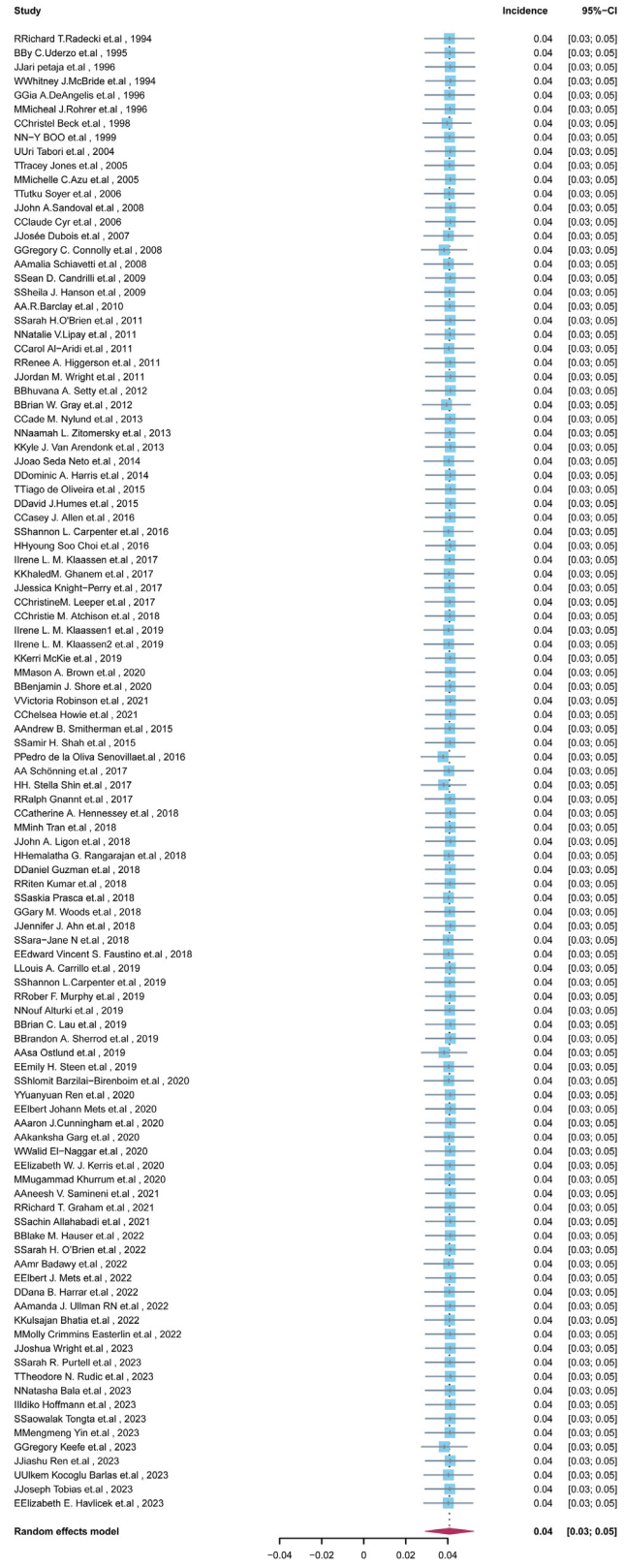

FIGURE 4 Results of sensitivity analysis by removing one study at a time.

of pediatric HA-VTE in Sweden was 0.8 per 10,000 children [120]. In contrast, a higher number of HA-VTE events in pediatric patients during hospitalization was observed in a low-middle-income country, with a rate of 5.9 per 10,000 hospitalizations [121]. It seems that the high proportion of HA-VTE is related to poor medical conditions. However, a study conducted to identify the spectrum of pediatric HA-VTE–associated disease in Canada indicated that most HA-VTE events occurred in the Midwest and the least occurred in the South [122], which was consistent with our finding. This paradoxical phenomenon can be explained by both the advancing interventions and increasing recognition of HA-VTE in developed countries and also the limited sample size of the studies. We believe that with the improvement of medical technology, the incidence of pediatric HA-VTE in a low-middle-income country will follow an upward trend in the following years.

We found that the patient-related risk factors for HA-VTE in children included age and obesity. Our findings showed that age of ≥10 years was a risk factor for HA-VTE in pediatric patients, consistent with the results of a single-center retrospective cohort study conducted at Children's Hospital of Philadelphia. This study confirmed that age ≥ 12 years was significantly associated with HA-VTE recurrence [123]. A prior study also demonstrated an elevated rate of incident HA-VTE in adolescents [124]. Studies have shown that the incidence of HA-VTE in children is bimodal, with the first peak in infancy and the second peak in adolescence [125]. Obesity was another physiological factor for HA-VTE in pediatric patients. Approximately one-third of thromboembolic events have been reported to be associated with obesity, and people who are overweight in childhood and young adulthood have a significantly increased risk for HA-VTE in adulthood compared with a normal-weight reference group [126].

Our study showed that CVC, surgery, injury, infection, mechanical ventilation, blood transfusion, malignancy, coagulation and hemorrhagic disorders, and LOS were hospital-related risk factors for pediatric HA-VTE. CVC was the leading risk factor for pediatric HA-VTE, which was consistent with previous studies [14,118]. An Italian study reported that CVC was the most important risk factor, accounting for more than half of HA-VTE events [127]. Similarly, an electronic survey assessing risk and prevention practices for pediatric HA-VTE conducted by the Children's Hospital-Acquired Thrombosis Consortium found that acute systemic inflammation and CVC were risk factors for VTE [128]. The use of CVCs can lead to endothelial damage and blood vessel obstruction, which ultimately promotes thrombosis [63]. In addition, children with underlying medical or surgical diseases, such as trauma, cardiovascular disease, cancer, and infection, can trigger VTE events. A UK study reported that decreased mobility, thrombogenicity, malignancy, surgery, use of combined oral contraceptives, and congenital venous malformations are major risk factors for VTE in adolescents [129]. Parallel to our study, a Canadian report

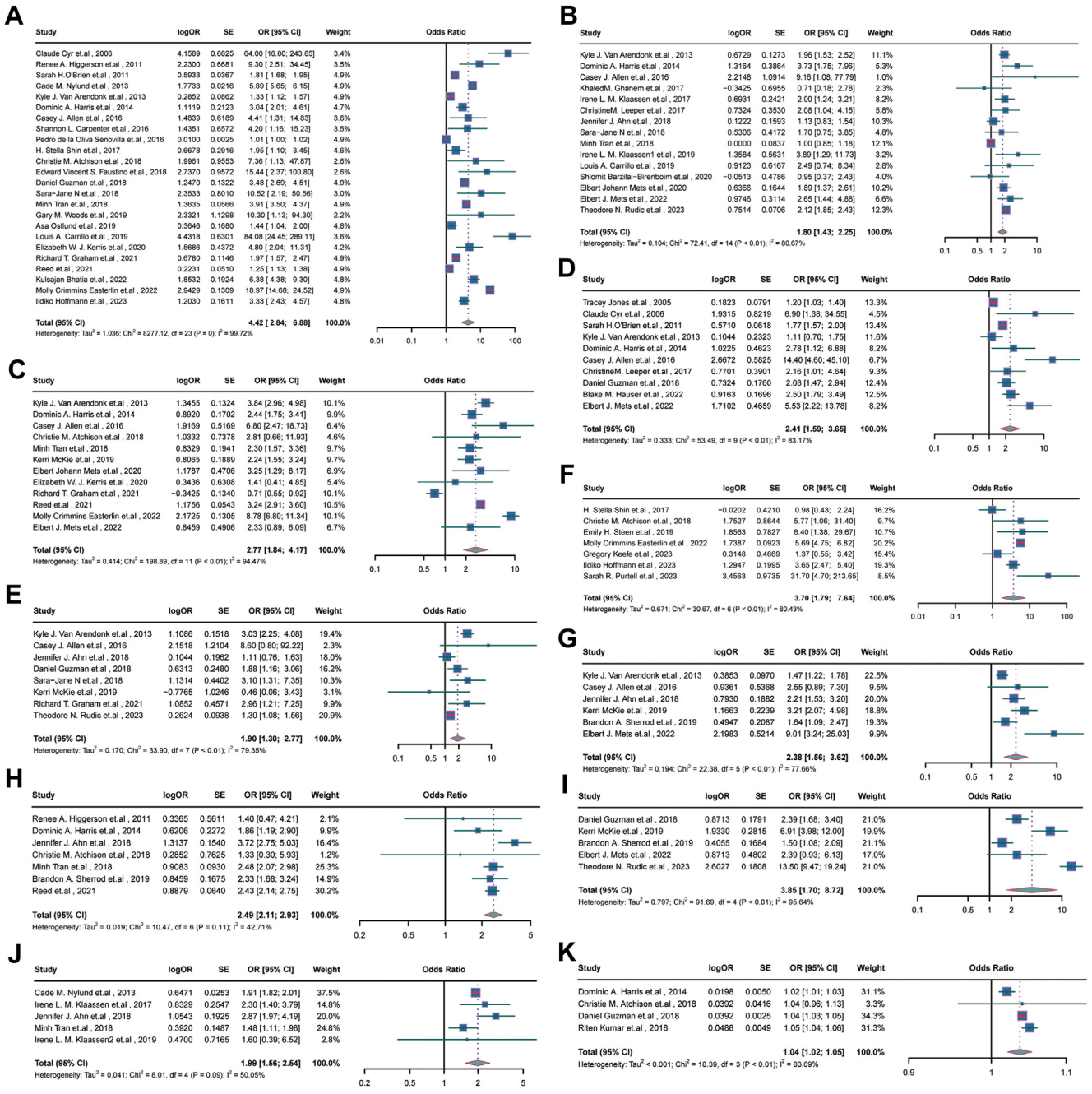

FIGURE 5 Forest plot for risk factors of venous thromboembolism in children. (A) Central venous catheter, (B) age > 10 years, (C) surgery, (D) injury, (E) obesity, (F) infection, (G) blood transfusion, (H) mechanical ventilation, (I) coagulation and hemorrhagic disorders, (J) malignancy, and (K) length of hospital stay. OR, odds ratio.

observed that 18% of postoperative thrombotic complications in neonates were due to cyanosis, surgery, anticoagulant/antiplatelet therapy, and blood transfusion [130]. Infections such as tuberculosis, viral hepatitis, and sepsis are striking risk factors for VTE. A Danish study showed that community-acquired bacteremia was an independent risk factor for thrombosis in hospitalized adults [131]. Similarly, hospital-acquired infections have also been identified as one of the most common risk factors for HA-VTE in pediatric patients [121]. The mechanism may be related to endothelial lesions, molecular dysfunction, and the release of inflammatory cytokines, which eventually leads to the generation of intravascular microthrombus [132]. Invasive mechanical ventilation (IMV) has been regarded as a life-saving procedure. However, patients with prolonged IMV have a significantly increased risk of thrombosis. Consistent with our study, data from the Pediatric Health Information Systems registry have confirmed that IMV was a potential risk factor for HA-VTE in critically ill children [133], and a multicenter, matched case-control study showed that HA-VTE was associated with prolonged IMV duration in

TABLE 3 Risk factors for venous thromboembolism in children.

Risk factor	Study (*n*)	OR (95% CI)	*P* value	I^2 (%)
Central venous catheter	24	4.41 (2.83-6.88)	<.001	99.72
Age > 10 y	15	1.79 (1.43-2.25)	<.001	80.67
Surgery	13	2.76 (1.83-4.16)	<.001	94.47
Injury	10	2.41 (1.58-3.64)	<.001	83.71
Obesity	8	1.89 (1.29-2.77)	<.001	79.35
Infection	7	3.69 (1.78-7.64)	<.001	80.43
Mechanical ventilation	7	2.49 (2.27-2.72)	<.001	42.71
Blood transfusion	6	2.38 (1.56-3.62)	<.001	77.66
Malignancy	5	1.99 (1.56-2.54)	<.001	50.05
Coagulation and hemorrhagic disorders	5	3.85 (1.69-8.72)	<.001	95.64
LOS	4	1.04 (1.02-1.05)	<.001	83.69

LOS, length of hospital stay; OR, odds ratio.

critically ill children undergoing IMV [134]. IMV-induced VTE in pediatric patients may be related to ventilator-induced lung injury accompanied by local or systemic inflammatory response and eventually lead to an acquired hypercoagulable state [135].

The increasing incidence of pediatric HA-VTE has raised worldwide awareness of HA-VTE prevention and risk assessment. Most physicians are willing to provide thromboprophylaxis to patients with risk factors. A single-center retrospective study indicated that children with CVC-VTE had an increased risk of VTE recurrence, and secondary prophylaxis with full-dose anticoagulation was associated with a 65% reduction in thrombotic events [136]. One study has shown that anticoagulant prophylaxis can help reduce thrombotic events in children with multisystem inflammatory syndrome caused by COVID-19 [137]. However, the role of anticoagulants in the prevention of HA-VTE in pediatric patients requires further investigation.

Several limitations need to be acknowledged in our study. Firstly, persistent unexplained heterogeneity was observed even after subgroup analysis. Secondly, the subgroup analysis of HA-VTE rates relied on the median year of data collection, potentially hindering the accurate capture of specific perinatal and follow-up periods. Thirdly, the inclusion of observational studies introduces the possibility of selection, recall, or attrition bias, thereby potentially biasing the confidence of effect estimates and limiting the validity of the findings. Lastly, the exclusion of non-English literature in our study may impact the accurate assessment of prevalence of HA-VTE in children.

5 | CONCLUSION

In conclusion, this updated systematic review and meta-analysis, based on 20 million individuals in 22 countries, systematically analyzed the proportion and risk factors of HA-VTE in hospitalized children. Our findings provide valuable insights for the prevention and treatment of HA-VTE in pediatric patients.

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AUTHOR CONTRIBUTIONS

Conception and design of study: J.T.Z. and J.H.Z.; acquisition of data: Y.T.Z., Y.L., and P.G.N.; analysis and interpretation of data: J.T.Z. and Y.T.Z.; drafting the manuscript: J.T.Z., Y.T.Z., and P.G.N.; revising the manuscript critically for important intellectual content: H.J.C. and J.H.Z. All authors approved the version of the manuscript to be published.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

DATA AVAILABILITY

Data will be available on request from the authors.

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SUPPLEMENTARY MATERIAL

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