Hospital-associated venous thromboembolism in pediatrics: a systematic review and meta-analysis of risk factors and risk-assessment models

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ABSTRACT

Hospital-associated venous thromboembolism, including deep vein thrombosis and pulmonary embolism, is increasing in pediatric centers. The objective of this work was to systematically review literature on pediatric hospital-acquired venous thromboembolism risk factors and risk-assessment models, to inform future prevention research. We conducted a literature search on pediatric venous thromboembolism risk via PubMed (1946-2014) and Embase (1980-2014). Data on risk factors and risk-assessment models were extracted from case-control studies, while prevalence data on clinical characteristics were obtained from registries, large (n>40) retrospective case series, and cohort studies. Meta-analyses were conducted for risk factors or clinical characteristics reported in at least three studies. Heterogeneity among studies was assessed with the Cochran Q test and quantified by the I^2 statistic. From 394 initial articles, 60 met the final inclusion criteria (20 case-control studies and 40 registries/large case series/cohort studies). Significant risk factors among case-control studies were: intensive care unit stay (OR: 2.14, 95% CI: 1.97-2.32); central venous catheter (OR: 2.12, 95% CI: 2.00-2.25); mechanical ventilation (OR: 1.56, 95%CI: 1.42-1.72); and length of stay in hospital (per each additional day, OR: 1.03, 95% CI: 1.03-1.03). Three studies developed/applied risk-assessment models from a combination of these risk factors. Fourteen significant clinical characteristics were identified through non-case-control studies. This meta-analysis confirms central venous catheter, intensive care unit stay, mechanical ventilation, and length of stay as risk factors. A few pediatric hospital-acquired venous thromboembolism risk scores have emerged employing these factors. Prospective validation is necessary to inform risk-stratified prevention trials.

Introduction

The incidence of hospital-associated venous thromboembolism (HA-VTE), which includes deep vein thrombosis and pulmonary embolism, is increasing in pediatrics.[1,2] This is attributed to improved survival of pediatric subspecialty patients as well as increased utilization of life-saving measures, e.g. central venous catheters (CVC). This increasing incidence of pediatric VTE prompts concern about increased acute and chronic co-morbidities (e.g. post-thrombotic syndrome) and mortality. Indeed, the Children's Hospitals' Solutions for Patient Safety has determined that VTE is the second most common cause of preventable harm in the 80 pediatric hospitals currently associated with this network.[3]

In 2008, the Surgeon General issued a Call to Action to emphasize the need for increased awareness about VTE, evidence-based practices for VTE management, and more research on the causes, prevention, and treatment of VTE.[4] The financial burden of HA-VTE also underscores the need for effective and evidence-based risk assessment and prevention strategies. Recent research evaluating total health care costs over a 6-month period for medically ill adults found that those who developed HA-VTE had more than double overall costs: $52,127 (± $24,389) *versus* $24,164 (± $11,148).[5] It can be presumed that a significant increase in hospitalization costs is likewise associated with HA-VTE in children. As an added financial impact of HA-VTE to hospitals themselves, HA-VTE occurring post-operatively leads to reimbursement penalties *via* Medicaid and Medicare.[6]

For all the aforementioned reasons, The Joint Commission, Institute for Safe Medication Practices and Surgical Care Improvement Project each recommend hospital-wide strategies for the prevention of HA-VTE and related harm. These recommendations apply to adult populations in which VTE is identified as the most common cause of preventable mortality in hospitalized patients,[7] and for which there is high-quality evidence from randomized controlled clinical trials on the efficacy and safety of VTE prophylaxis strategies.[8]

A similar need for guidelines on safe and effective, evidence-based VTE prevention exists in pediatric VTE, but the lack of high-quality evidence has impeded the development of such guidelines for this population. Other mitigating fac-

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tors include the relatively low incidence compared with that in adults, slow acceptance by some pediatricians of the increasing incidence of HA-VTE, lack of evidence on preventability, and – in particular – the paucity of studies applying appropriate methodologies for establishing independent risk factors and validating risk models derived from them. Challenges regarding how to best/consistently define a risk factor – e.g. immobility—also exist, as they do in adults.

Lending further credence to the importance of developing evidence-based HA-VTE prevention guidelines for children, the International Society of Thrombosis and Haemostasis (ISTH) convened a Working Group, *via* the Pediatric/Neonatal Hemostasis and Thrombosis Subcommittee Scientific and Standardization Committee (SSC), to develop recommendations for standardization and future research regarding pediatric HA-VTE risk factors and risk assessment models. As a prerequisite to the development of guidelines, current evidence must be rigorously analyzed. Accordingly, the purpose of this report is to present findings of a systematic review and meta-analysis of the literature on pediatric HA-VTE risk factors and risk-assessment models.

Methods

Search strategy

We identified English articles using PubMed (1946-May, 2014) and Embase (1980-May, 2014). The search strategies comprised "venous thromboembolism," "risk" and "children" with multiple subject headings and text-words per concept. Given the large body of VTE literature, we began with a sensitive query and progressively specified subsequent queries using *major focus* syntax and text-word title field restrictions. Selectively exploding subject headings, with relevant subcategories, permitted ever-increasing specificity. The full search strategy for Pubmed is available as *Online Supplementary Table S1*.

Study selection

We excluded studies of patients older than 21 years based on the definition of pediatric age from the National Institute of Child Health and Human Development.[9] For studies that included pediatric and adult patients, we excluded those without clear sub-analyses for patients under 21 years. Similarly, we excluded studies on arterial thromboembolism unless cases of VTE were included and clearly delineated in sub-analyses. Studies were categorized as narrative reviews, commentaries, single case reports, retrospective case series, cross-sectional studies, case-control studies, cohort studies (retrospective and prospective), registry studies, or clinical trials, the first three of which were excluded. Cases series were retained if they included at least 40 cases. Conflicting opinions regarding study design, where insufficiently or inconsistently described, were resolved through group consensus.

Data extraction

The following data were initially extracted by a pair of reviewers (BB, AM) and independently confirmed by a second pair (LR, CHvO): study design; number of patients/hospital unit; summary statistics on patients' age, gender; VTE location; time from VTE sign/symptom onset to diagnosis; duration of hospital stay; risk-assessment strategies; nature and duration of prophylactic interventions; frequency of, and risk estimates for [odds ratios (OR) and corresponding 95% confidence intervals (95% CI)], putative HA-VTE risk factors [antecedent surgery or trauma, altered mobility, CVC, infection, mechanical ventilation, venous anomalies (Paget-Schroetter and May-Thurner syndromes, atresia of the inferior vena cava)], dehydration, autoimmune disease, nephrotic syndrome, cancer, pregnancy and post-partum state, complex congenital heart disease, personal or family history of VTE, inherited thrombophilia states, and prothrombotic medications (estrogen-containing oral contraceptive pill, asparaginase, recombinant factor VIIa).

Variables were sub-categorized on the basis of available information. CVC was divided into "short-term" (<6 weeks) and "long-term."[10] Infection was sub-categorized as systemic (i.e., bacteremia, sepsis, meningitis, urosepsis) *versus* local (e.g., mastoiditis, osteomyelitis). When available, we identified surgery type: major abdominal, cardiac, orthopedic, neurosurgery, trauma (general and acute spinal cord injury), and spinal surgery.

Data analysis

For purposes of analysis, studies were grouped into case-control studies and non-case-control studies. This division was based upon the case-control studies having evaluated risk factors for incident VTE whereas the cross-sectional studies described VTE patients' characteristics and the cohort studies evaluated outcomes of incident VTE. Given this work's focus on risk factors and risk-assessment models for incident VTE, the case-control studies provided the best evidence.

Statistical analyses were conducted using Stata statistical software version 13 for case-control studies and R for non-case-control studies. We tested heterogeneity among study effect sizes with the Cochran Q test (α set at 0.1) and quantified heterogeneity by the I^2 statistic. We performed meta-analyses for each risk factor investigated in at least three studies. Pooled estimates were generated using the inverse-variance weighted method in a fixed-effect model when heterogeneity was low (I^2 <25%); otherwise random-effect models were used. Publication bias was assessed graphically using funnel plots and qualitatively using Egger regression, with asymmetry tests if the number of studies allowed (n ≥10).[11]

Results

Search results

The overall search results and step-wise elimination schema are provided in Figure 1. From 394 initial article titles and abstracts identified from the search methods detailed above, we excluded 223 after abstract review and an additional 111 after manuscript review, yielding 60 articles that met final eligibility criteria. Of these, 20 were case-control studies and 40 were non-case-control studies, the designs of which are detailed in Figure 1. Of note, there were no randomized clinical trials.

Risk factors – case-control studies

In the 20 case-control studies, there were cumulative totals of 4,312 cases and 608,774 controls reported. Among six separate risk factors from these studies, four were evaluated with Forest plots and pooled OR (Figure 2). These risk factors consisted of: intensive care unit (ICU) stay (OR: 2.14; 95% CI: 1.97-2.32);[2,12-17] CVC (OR: 2.12; 95% CI: 2.00-2.25);[2,14,15] mechanical ventilation (OR: 1.56; 95% CI: 1.42-1.72);[12,13,15,18] and length of stay (LOS) in hospital (OR, per each additional day: 1.03; 95% CI: 1.03-1.03)[12,13,18] (Table 1). For each risk factor, the number of VTE cases ranged from 271 to 3,702 and that of control patients ranged from 700 to 606,424. Heterogeneity between studies was observed for all risk factors (i.e. I^2 ≥25%).

Eight studies including a total of 3,702 VTE cases and 606,424 controls reported the association between any CVC placement and VTE risk. In all eight studies, CVC was reported as present or absent without further detail regarding duration of CVC presence. One study was a review of the National Trauma Data Bank and included 135,032 patients with trauma with 826 patients experiencing lower extremity deep vein thrombosis or pulmonary embolism but excluding upper extremity deep vein thrombosis.[15] Based on the concern that many CVC are placed in upper extremities and the exclusion of upper extremity DVT may under-estimate the OR of CVC, we conducted a sensitivity analysis excluding this study. This revealed a higher pooled risk estimate [OR 3.12 (95% CI=2.78-3.49)] for CVC.

ICU stay had the second highest OR and of the three studies, two specified initial patients' admission to the ICU while the third used ≥4 days in the ICU as the criterion for evaluation without specifying whether this included both patients with initial ICU admission and those transferred to the ICU from a lower-acuity unit. Presence of mechanical ventilation was defined irrespective of duration in three of the four studies and in the fourth was defined as ≥4 days on the ventilator. Regarding LOS, three studies with a total of 2,000 cases and 459,096 controls were available for evaluation, and revealed that for each additional day of hospitalization, VTE risk increased by 3%. A fourth study was excluded from these analyses as it only reported LOS as a dichotomous variable (specifically, <7 *versus* ≥7 days).[2]

Obesity, thrombophilic conditions and systemic infection as putative risk factors were not evaluable by meta-analysis, due to a lack of at least three studies with OR for each individual thrombophilic condition. One retrospective case-control study evaluated obesity.[19] This study involved 48 cases and 274 age- and gender-matched controls. Of note, this study explicitly reported their use of Center for Disease Control gender-specific charts relating body mass index and age and identified overweight children (85th-95th percentile) and obese children (>95th percentile).[20] They found an unadjusted OR of 2.1 (95% CI, 1.1-4.0) for VTE development in obese children but an OR of 0.7 (95% CI, 0.2-1.8) for overweight children. In addition, age was not found to be a risk factor in a meta-analysis. However, age, particularly adolescents and neonates, had been shown to be a risk factor in some individual case-control studies,[2,18] and as noted below, adolescents and neonates were the most common age groups represented in non-case-control studies. Lastly, we could not conduct any quantitative analyses for publication bias in risk factors among case-control studies because of the paucity of studies available for each risk factor.

Risk-assessment models

There were three risk-assessment models published during this study's timeframe that utilized various combinations of the aforementioned risk factors. In a single institution case-control study, Branchford *et al.*[18] demonstrated statistically significant independent risk for mechanical ventilation, systemic infection, and hospital stay ≥5 days and that this combination in a risk-model yielded a post-test probability of 3.6% for HA-VTE development. By contrast, Sharathkumar *et al.*[2] found six statistically independent risk factors, with associated "points" determined from the β coefficient from a logistic regression model: immobilization (3 points), LOS ≥7 days (2 points), oral contraceptive pills (2 points), CVC (1 point), bacteremia (1 point), and direct admission to critical care (0.5 points).

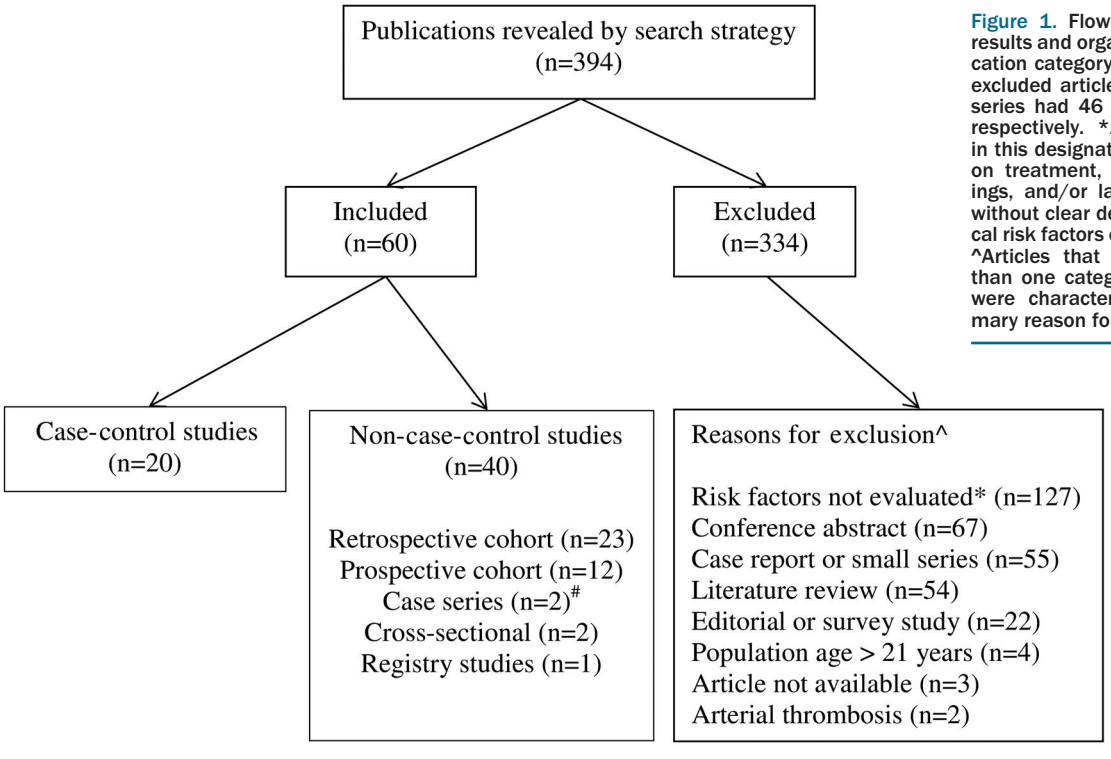

Figure 1. Flow chart of search results and organization by publication category for included and excluded articles. #The two case series had 46 and 72 patients, respectively. *Articles included in this designation were focused on treatment, radiological findings, and/or laboratory science without clear delineation of clinical risk factors or characteristics. ^Articles that fitted into more than one category for exclusion were characterized by the primary reason for exclusion.

They determined that a cumulative score of ≥3 yielded a positive predictive value of 2.45% for HA-VTE prevalence of 0.71%. A third risk assessment model by Prentiss[21] describes a risk scoring system and levels of risk, Risk Score 1-3, but does not detail which specific risk factors comprise the scoring system and what their individual point values are.

Clinical characteristics – non-case-control studies

Among the 40 non-case-control studies, a total of 8,726 HA-VTE patients were evaluated, and 17 unique clinical characteristics described. Due to significant heterogeneity among studies, we used random effect models to estimate pooled prevalences (Table 1). Apart from male sex, the most prevalent clinical characteristics among HA-VTE patients in these studies were CVC [pooled prevalence, 0.36 (95% CI: 0.23-0.48)] and oral contraceptive pill use [pooled prevalence 0.34 (95% CI: 0.11-0.56)]. Infection was evaluated in the greatest number of studies (n=21), with a pooled prevalence of 0.21 (95% CI: 0.14-0.29). One clinical characteristic, pregnancy and/or post-partum state, was not analyzed because only two studies were available for evaluation.

In evaluating mobility, nine studies listed patients as having decreased mobility. Of those nine, eight studies used the terms "immobilization" or "immobility" and one study defined it as "non-ambulatory status at diagnosis of VTE." None of the studies provided further detail regarding degree, chronicity, or cause of immobility.

Discussion

In this study, we assessed risk factors and clinical characteristics from case-control and non-case-control studies, respectively, associated with HA-VTE in children from a wide range of studies. After evaluating 19 studies, we found five significant risk factors: systemic infection, ICU admission, CVC, mechanical ventilation, and prolonged hospitalization with pooled OR ranging from 1.03-2.42. We found 14 significant clinical characteristics from 41 non-case-control studies with a range of summary prevalences from 0.13-0.55 with male sex being the most prevalent characteristic associated with HA-VTE. We observed moderate to high heterogeneity between studies for all risk factors and clinical characteristics.

Our findings are important in determining clinical risk factors that confer an increased risk of HA-VTE in children. As expected for a meta-analysis, the pooled analyses substantiate a number of previously reported risk factors and provide a more reliable measure of the magnitude of HA-VTE risk for each. At the same time, our systematic review and meta-analysis identifies the need for standardized definitions and assessment methodologies for factors such as immobility and thrombophilia. Given the rising incidence and/or recognition of pediatric HA-VTE and the emergence of institution-based HA-VTE prevention clinical care guidelines/pathways at children's hospitals, it is imperative that clinicians utilize best evidence on HA-VTE risk factors in order to inform these risk-assessment and

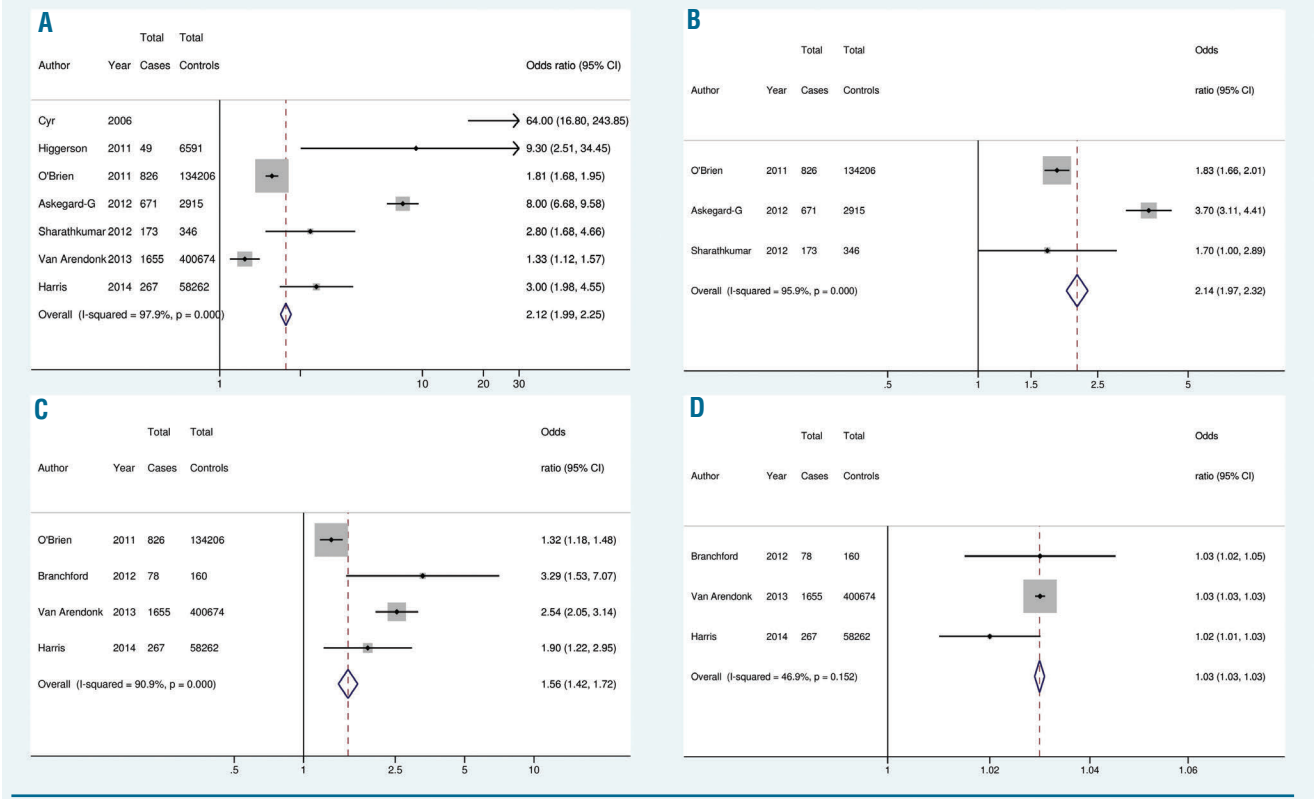

Figure 2. Forest plots for the significant risk factors from case-control studies. (A) CVC. (B) ICU admission. (C) Mechanical ventilation. (D) Prolonged hospitalization.

prevention efforts. There are safety risks associated with mechanical and, in particular, pharmacological HA-VTE prophylaxis and data on efficacy benefits are sparse as yet in pediatrics.[22] A recent meta-analysis in pediatric oncology patients, comprising a small number of studies evaluating a heterogeneous group of pharmacological prophylaxis (e.g., low molecular weight heparin, warfarin, antithrombin replacement), demonstrated a lack of clear benefit in this setting.[23]

Our meta-analysis helps to confirm previous single-institution work to define risk of individual pediatric patients with risk-assessment models.[2,18,21] A recent study by Atchison *et al.*,[24] published after the date range for this review, demonstrated independent risk through multivariate analyses for CVC (5 points), infection (2 points), and LOS ≥4 days (1 point) specifically in non-critically ill children. The risk score demonstrated that with 8, 7, or ≤6 points, the risk of HA-VTE was 12.5%, 1.1%, and 0.1%, respectively. These studies show commonality in what factors are considered to be high risk but all have the same limitations; namely: low prevalence of VTE and lack of sub-analyses (e.g. extremity VTE *versus* non-extremity VTE), retrospective review of patients, heterogeneous populations of patients although Atchison *et al.* excluded critically ill children, and, with the exception of the study by Sharathkumar *et al.*, lack of a separate validation cohort. While these studies represent important initial work, they clearly demonstrate the need for collaborative, multi-institutional, prospective studies.

Some of the individual risk factors and clinical characteristics warrant further discussion. Thrombophilia evaluation from case-control studies was not conducted because a minimum number of studies needed for pooled analysis was not met. Regarding, thrombophilia in the non-case-control studies, meta-analysis was thwarted by the lack of standardized definitions. Two of the 17 studies in the prevalence data simply listed "hypercoagulable state" without further definition. Of the 15 studies that did define conditions, some detailed the numbers of heterozygotes and homozygotes for factor V Leiden and prothrombin gene mutations whereas others did not. Some studies listed thresholds for defining protein C, protein S, and/or antithrombin deficiency and others did not. For the studies that did have thresholds, they varied from study to study. Similar issues applied to homocysteine, lipoprotein(a), and antiphospholipid antibody measurements. We included these data from the non-case-control studies to demonstrate pooled prevalences but these issues further highlight the need for standardized definitions of thrombophilia states in order to assess their potential impact in HA-VTE risk and, hence, to inform future studies on whether there is a role for selected thrombophilia tests in a VTE risk-assessment model. A prior meta-analysis by Young and international co-authors identified anticoagulant deficiencies as risk factors for incident pediatric VTE (not restricted to HA-VTE).[26] Until such time as additional high-quality primary studies are published on the association between thrombophilia states and incident pediatric VTE, we support the thrombophilia findings of the aforementioned meta-analysis as being complementary to the non-thrombophilia findings reported here.

With regard to gender, males were more prevalent (0.55) than females in non-case-control studies. This prevalence is concordant with the percentage of males with HA-VTE found by Raffini and colleagues *via* the Pediatric Health Information System database.[1] The potential role of age in HA-VTE risk warrants further study. Previous work[1] has shown that neonates and adolescents are most commonly affected by HA-VTE; however, in some of the more recent case-control studies[2,18] age is used as a matching criterion and hence could not be assessed as a potential risk factor. Furthermore, HA-VTE case validation *via* radiological record review was not employed in a number of studies which suggested age is a risk factor in children.

Furthermore, some risk factors that have been well-studied in adults, e.g. obesity, have been less well-studied in children. This may be due in part to a lack of use of standard definitions, and to challenges in having complete data from height assessment during hospital admissions. Only one case-control study explicitly stated what threshold was used for identifying a child as obese and of the four non-case-control studies addressing obesity, none reported their definition of obesity. Future studies in children should use the Centers for Disease Control and Prevention standardized growth charts for identifying children as overweight or obese.

The strengths of our systematic review and meta-analysis include its broad search strategy, use of an independent dual-reviewer approach to study eligibility determination, and large, final numbers of pediatric HA-VTE cases and controls. The limitations of our work are largely related to the limitations of the individual studies included in the meta-analysis. Studies often lacked rigorous HA-VTE case

Table 1. Risk factors and clinical characteristics from the case-control and non-case-control studies, respectively.

Risk Factor	Number of studies	Case control studies Pooled OR (95% CI)	I^2 (%)
Admission to ICU	3	2.14 (1.97-2.32)	95.9
Any CVC	8	2.12 (2.00-2.25)	97.9
Mechanical ventilation	4	1.56 (1.42-1.72)	90.9
Length of stay in hospital	3	1.03 (1.03-1.03)	46.9
Clinical characteristic		**Non-case-control studies Summary prevalence (95% CI)**	
Male sex	17	0.55 (0.48-0.61)	82.6
CVC	16	0.36 (0.23-0.48)	95.4
Oral contraceptive pill	5	0.34 (0.11-0.56)	92.9
Thrombophilia	17	0.28 (0.18-0.38)	95.1
Obesity	4	0.26 (0.08-0.45)	88.1
Trauma	8	0.22 (0.05-0.39)	94.6
Orthoped non-spinal surgery	5	0.22 (0.00-0.43)	98.2
Infection	21	0.21 (0.14-0.29)	93.1
a. Systemic infection	8	0.13 (0.08-0.18)	65.5
b. Other infection	13	0.27 (0.15-0.38)	94.7
Any surgery	10	0.20 (0.07-0.32)	92.7
Asparaginase	6	0.18 (0.03-0.33)	92.5
Complex congenital heart disease	9	0.15 (0.07-0.23)	92.3
Decreased mobility	9	0.15 (0.06-0.21)	81.9
Cancer	13	0.13 (0.08-0.18)	88.0
Family history	7	0.13 (0.08-0.18)	65.3
Inflammatory/autoimmune disease	7	0.05 (0.03-0.07)	0.0
Nephrotic syndrome	4	0.02 (0.00-0.04)	26.0

definition and validation, with regard to the uniform application of both VTE-defining criteria (e.g., involving review of radiological records, for objective confirmation of thrombus in the venous circulation, pulmonary arterial tree, or right atrium) and criteria for the definition of "hospital-acquired" (e.g., *via* review of history and examination findings at the time of hospital admission, for absence of signs and symptoms of VTE, unless previously hospitalized in the past several weeks). Furthermore, studies included in the meta-analysis were generally heterogeneous with regards to design, sample size, and definitions used for risk factors and clinical characteristics. Publication bias could not be evaluated for the case-control studies due to small numbers of studies per risk factor. However, for the non-case-control studies, funnel plots and Egger tests suggest publication bias may have played a role in the clinical characteristics.

Notwithstanding these limitations, the present work is among the few meta-analyses to date to establish clinical risk factors for pediatric HA-VTE across a broad spectrum of patient populations and hospital settings. In identifying key risk factors, as well as published risk-assessment models that utilize them, the present work provides an important foundation for much-needed future prospective multicenter validation studies on pediatric HA-VTE risk scores. Such studies, in turn, will better inform clinical decision-making and the design of risk-stratified clinical trials of pediatric HA-VTE prevention.

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Authorship and Disclosures

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References

1. Raffini L, Huang Y-S, Witmer C, Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. Pediatrics. 2009;124(4):1001-1008.
2. Sharathkumar A, Mahajerin A, Heidt L, et al. Risk-prediction tool for identifying hospitalized children with a predisposition for development of venous thromboembolism: Peds-clot clinical decision rule. J Thromb Haemost. 2012;10(7):1326-1334.
3. Hilbert K, Bailey J, editors. Children's Hospitals' Solutions for Patient Safety Recommended Bundles. Cincinnati (OH): Solutions for Patient Safety; 2013 [cited 2014 Apr 29]. Available from: http://www.solutionsforpatientsafety.org/wp-content/ uploads/SPS-Recommended-Bundles.pdf.
4. Goldhaber SZ, Ortel TI, editors. Office of the Surgeon General (US); National Heart, Lung, and Blood Institute (US). The Surgeon General's Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism [Internet]. Rockville (MD): Office of the Surgeon General (US); 2008 [cited 2014 Apr 16]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK44178/pdf/TOC.pdf.
5. Wang L, Sengupta N, Baser O. Risk of venous thromboembolism and benefits of prophylaxis use in hospitalized medically ill U.S. patients up to 180 days post-hospital discharge. Thromb J. 2011;9(1):15.
6. CMS final rule to improve quality of care during hospital inpatient stays [Internet]. Baltimore (MD): Centers for Medicaid and Medicare Services; 2013 [cited 2014 Nov 12]. Available from: http://www.cms.gov/newsroom/mediareleasedatabase/fact-sheets/2013-fact-sheets-items/2013-08-02-3.html.
7. Shojania KG, Duncan BW, McDonald KM, Wachter RM, Markowitz AJ. Making health care safer: a critical analysis of patient safety practices. Evid Rep Technol Assess (Summ). 2001;(43):i-x,1–668.
8. Guyatt GH, Eikelboom JW, Gould MK, et al. Approach to outcome measurement in the prevention of thrombosis in surgical and medical patients. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-based clinical practice guidelines. Chest. 2012;141(2 Suppl):e185S-194S.
9. National Institute of Child Health and Human Development [Internet]. Pediatric Terminology: Current Efforts. [updated 2013 Aug 20; cited 2013 May 13].Available from: http://www.nichd.nih.gov/health/ clinical-research/clinical-researchers/terminology/Pages/current.aspx.
10. Galloway S, Bodenham A. Long-term central venous access. Br J Anaesth. 2004;92(5):722-734.
11. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]. The Cochrane Collaboration, 2009. Available from: www.cochrane-handbook.org.
12. Harris DA, Lam S. Venous thromboembolism in the setting of pediatric traumatic brain injury. J Neurosurg Pediatr. 2014;13(4):448-455.
13. Van Arendonk KJ, Schneider EB, Halder AH, Colombani PM, Stewart FD, Haut ER. Venous thromboembolism after trauma: when do children become adults? JAMA Surg. 2013;148(12):1123-1130.
14. Askegard-Giesmann JR, O'Brien SH, Wang W, Kenney BD. Increased used of enoxaparin in pediatric trauma patients. J Pediatr Surg. 2012;47(5):980-983.
15. O'Brien S, Candrilli S. In the absence of a central venous catheter, risk of venous thromboembolism is low in critically injured children, adolescents, and young adults: evidence from the National Trauma Data Bank. Pediatr Crit Care Med. 2011;12(3):251-256.
16. Higgerson RA, Lawson KA, Christie LM, et al. Incidence and risk factors associated with venous thrombotic events in pediatric intensive care units. Pediatr Crit Care Med. 2011;12(6):628-634.
17. Cyr C, Michon B, Pettersen G, David M, Brossard J. Venous thromboembolism after severe injury in children. Acta Haematol. 2006;115(3-4):198-200.
18. Branchford BR, Mourani P, Bajaj L, Manco-Johnson M, Wang M, Goldenberg NA. Risk factors for in-hospital venous thromboembolism in children: a case-control study employing diagnostic validation. Haematologica. 2012;97(4):509-515.
19. Stokes S, Breheny P, Radulescu A, Radulescu VC. Pediatr Hematol Oncol. 2014;31(5):475-480.
20. Center for Disease, Control, and Prevention. About BMI for children and teens. Available from: http://www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html. [updated 2011 Sep 13; cited 2015 Apr 11].
21. Prentiss AS. Early recognition of pediatric venous thromboembolism: a risk-assessment tool. Am J Crit Care. 2012;21(3):178-184.
22. Stem J, Christensen A, Davis D, Raffini L. Safety of prophylactic anticoagulation at a pediatric hospital. J Pediatr Hematol Oncol. 2013;35(7):e287-291.
23. Schoot RA, Kremer LCM, van de Wetering MD, van Ommen CH. Systemic treatments for the prevention of venous thromboembolic events in paediatric cancer patients with tunnelled central venous catheters. Cochrane Database of Systematic Reviews. 2013, Issue 9. Art. No.: CD009160. DOI: 10.1002/14651858.CD009160.pub2.
24. Atchison CM, Arlikar S, Amankwah E, et al. Development of a new risk score for hospital-associated venous thromboembolism in noncritically ill children: findings from a large single-institutional case-control study. J Pediatr. 2014;165(4):793-798.
25. Young G, Albisetti M, Bonduel M, et al. Impact of inherited thrombophilia on venous thromboembolism in children: a systematic review and meta-analysis of observational studies. Circulation. 2008;118(13):1373-1382.