

Venous Thromboembolism in Pediatric Cancer Patients with Central Venous Catheter—A Systematic Review and Meta-analysis

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Semin Thromb Hemost 2021;47:920–930.

Abstract

Pediatric cancer patients hold an increased risk of venous thromboembolism (VTE) due to their cancer. Central venous catheters (CVCs) further increase the VTE risk. This systematic literature review elucidates the VTE incidence in pediatric cancer patients with CVC. MEDLINE and EMBASE were searched in August 2020 without time limits. We included studies reporting original data on patients ≤ 18 years with any CVC type and any cancer type, who were examined for VTE with ≥ 7 days follow-up. In total, 682 unique records were identified, whereof 189 studies were assessed in full text. Altogether, 25 studies were included, containing 2,318 pediatric cancer patients with CVC, of which 17% suffered VTE. Fifteen studies ($n = 1,551$) described CVC-related VTE and reported 11% CVC-related VTE. Concerning cancer type, 991 children suffered from acute lymphoblastic leukemia (ALL) and 616 from solid tumors. Meta-analysis revealed VTE incidence (95% confidence interval) of 21% (8–37) for ALL and 7% (0.1–17) for solid tumors. Additionally, 20% of children with tunneled or nontunneled CVC and 12% of children with implantable ports suffered VTE. In conclusion, pediatric cancer patients with CVC have substantial VTE risk. Children with ALL and CVC have higher VTE incidence than children with solid tumors and CVC. Implantable port catheter should be preferred over tunneled or nontunneled CVC to reduce VTE risk. Thrombophilia investigation does not seem relevant in pediatric cancer patients with CVC and VTE. To prevent VTE, intensified catheter care is recommended, especially in children with ALL.

Keywords

- ▶ central venous catheter
- ▶ pediatric
- ▶ thromboembolism
- ▶ neoplasm

The incidence of pediatric cancer is 156 per million person-years worldwide, with leukemia being the most prevalent.¹ A relationship between cancer and venous thromboembolism (VTE) has been known since 1865.² Development of VTE is associated with lower survival, especially for children with hematological cancers.³ The VTE prevalence is around 8% in

pediatric cancer patients.⁴ Numerous risk factors for VTE in pediatric cancer patients have been identified, including cancer type,⁵ chemotherapy,⁶ and central venous catheters (CVCs).^{7,8} CVCs are frequently used in pediatric cancer patients to administer chemotherapy, transfusions, and parenteral nutrition. Although helpful, CVCs also pose a risk for

published online
September 2, 2021

Issue Theme Cardiovascular and Thromboembolic Diseases in Oncology: Novel Aspects and Revisited Issues; Antonella Tufano, MD, PhD, Antonio Coppola, MD, Maurizio Galderisi, MD, and Massimo Franchini, MD

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DOI <https://doi.org/10.1055/s-0041-1729886>.
ISSN 0094-6176.

VTE development.⁸ In adult cancer patients, the incidence of catheter-associated VTE is 6 to 15%.^{9,10} Although CVC is a confirmed VTE risk factor in pediatric cancer patients,⁸ thorough research on this is lacking, especially regarding cancer and catheter types at risk along with strategies for thromboprophylaxis.

Thus, the aim of the present systematic review was to investigate the incidence of VTE in pediatric cancer patients with CVC inserted. Additionally, the employed catheter care regimens, VTE prophylaxis regimens used, and the role of thrombophilia are elucidated.

Materials and Methods

This review was conducted according to a prespecified protocol (**Supplementary Material 1**, available in the online version only) and the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.¹¹ A systematic search of the databases MEDLINE (PubMed) and Ovid (EMBASE) was performed November 12th, 2019 with no restrictions on publication period but limited to original studies on humans published in English. The search was updated on August 4th, 2020. The search strategy included MeSH terms related to any type of cancer, CVC, and VTE, but restricted on age (child: birth-18 years).

The inclusion criteria were prospective studies reporting original data, English language, and studies on pediatric patients (≤ 18 years) with any type of CVC and any type of cancer, which reported investigation for VTE. The exclusion criteria were reviews, guidelines, letters without original data, editorials, studies with less than 10 cases, posters or conference abstracts, ongoing trials, in vitro studies, and animal studies. Moreover, studies with less than 7 days follow-up were excluded to ensure sufficient observation time for VTE development.

To validate the inclusion and exclusion criteria, a random sample of 50 abstracts was screened and discussed by A.M.H. and R.S.H. until consensus was achieved. Remaining records identified were screened by title and abstract by RSH. To validate the inclusion and exclusion criteria for studies in full text, 12 full-text studies were evaluated and discussed by A. M.H. and R.S.H. until consensus was achieved. The remaining full-text studies were evaluated by R.S.H. Data extraction was performed by R.S.H. and all extracted data were validated by A.M.H. and M.N.

Cancer Diagnosis

Cancer diagnosis was divided into the following five classifications: acute lymphoblastic leukemia (ALL), non-ALL hematological cancer, solid tumors, and any cancer if the diagnosis was not specified and any hematological cancer if the number of ALL cases was not specified.

Catheter Types

Catheters were divided into three classifications: tunneled or nontunneled CVC, implantable ports, and peripherally inserted central catheters (PICCs).

Venous Thromboembolism

VTE was defined as a clinical episode of VTE at any site, including superficial and deep vein thrombosis and pulmonary embolism. If the study reported a VTE, but no definition of VTE was provided, the incidence was also included in this review. Only studies clearly specifying VTE episodes as CVC related, were counted as CVC-related VTE. The approaches for VTE diagnosis are described for all included studies in **Table 1**.

Study Quality Assessment

For all included studies, the Study Quality Assessment Tools checklist provided by National Heart, Lung and Blood Institute was completed by R.S.H., M.N., and A.M.¹² The checklist for observational cohort and cross-sectional studies, case-control studies, and systematic reviews and meta-analysis were used, respectively. The study quality was assessed with regard to the purpose of this systematic review. Each study was rated *good*, *fair*, or *poor* according to the estimated risk of bias. After individual assessment, R.S.H., M.N., and A.M. discussed any rating disagreement until consensus was achieved.

Statistical Analyses

For VTE incidence calculation, a random-effects model was chosen since the included studies were heterogeneous and a high level of variance therefore had to be taken into consideration.¹³

The extracted incidence proportions were transformed by the double arcsine model to calculate an overall mean incidence with 95% confidence intervals (CIs) and presented in a forest plot.¹³ Statistical heterogeneity was assessed by I^2 statistics.^{14,15}

Publication bias was assessed by funnel plots.¹⁶ Statistical analyses and meta-analysis were performed using MetaXL (EpiGear International, Sunrise Beach, Queensland, Australia).

Results

The inclusion and exclusion process is depicted in **Fig. 1**. In total, 682 unique records were identified. After screening all abstracts and titles, 189 studies were assessed in full text for eligibility. Among these, 25 studies were included in the qualitative synthesis, while 17 studies reporting VTE for patients with ALL or solid tumors were also included in a quantitative synthesis (meta-analysis). Of the 25 included studies, three were randomized controlled trials,¹⁷⁻¹⁹ one was a case-control study,²⁰ and the remaining 21 studies were cohort studies.²¹⁻⁴¹ Of the 25 included studies, six were rated *good*,^{17,23,30,31,38,40} seven *fair*,^{18,22,25,26,28,36,37} and 12 *poor* quality.^{19-21,24,27,29,32-35,39,41}

In total, 2,318 pediatric cancer patients with a catheter inserted were included in the studies, of which 991 were classified as ALL, 616 solid tumors, 352 any cancer, 211 any hematological cancer, and 148 as non-ALL hematological cancer.

The total number of catheters could not be calculated due to lack of data in the included studies. In total, results on 629 tunneled or nontunneled CVCs, 444 implantable ports, 28 PICCs, and 86 nonspecified catheters were reported. Study design, characteristics of patients along with exposure and outcome are presented in **Table 1**.

Table 1 Summary of included studies investigating venous thromboembolism in pediatric cancer patients with a catheter inserted ($n = 25$)

Study Author Year Quality rating	Design Follow-up time (FT)	Characteristics Patients, n Age	Exposure Catheter type, n Catheter duration Catheter care	Outcome Venous thromboembolism, n Diagnostic approach
Previtali et al 2019 Good ⁴⁰	Cohort, single center FT: ≤ 164 days	Solid tumors, $n = 63$ Any cancer, $n = 29$ Hema cancer, $n = 11$ Age (median): 10.5 years	Type: Port, $n = 74$, PICC, $n = 28$, CVC, $n = 11$ Duration (median): 87 days Care: NR VTE-therapy: Anticoagulant therapy (not specified).	Symptomatic, $n = 0$ Asymptomatic, $n = 3$ (non-ALL hema cancer, $n = 1$, solid tumors, $n = 2$) Port related, $n = 2$ PICC related, $n = 1$ Catheter removal: NR Diagnosis: ultrasound (US) at 15, 30, and 90 days after implantation. In total, 91 of 113 catheters completed all 90 days.
Östlund et al 2019 Fair ³⁶	Cohort, single center FT: NR	Any cancer, $n = \text{NR}$ Age: NR	Type: CVC, $n = 19$ Duration: NR Care: NR.	Thrombosis, $n = 3$ Symptomatic: NR Asymptomatic: NR Catheter related: NR Catheter removal: NR Diagnosis: Followed for clinical signs and symptoms. Confirmed by US. At catheter removal US was performed.
Schoot et al 2016 Good ¹⁷	RCT, double blind FT: ≤ 6 months	Solid tumors, $n = 157$ Hema cancer, $n = 148$ Age (median): 9 years	Type: CVC, $n = 18$, Port, $n = 287$ Duration: 168 patients: 6 months 137 patients: 56 days (median) Care: Once every 1–6 week 1.5–3.0 mL lock solution (either 70% ethanol or 100 IU/mL heparin).	Symptomatic, $n = 8$ (hema cancer, $n = 7$, solid tumors, $n = 1$). Asymptomatic/total, $n = 12/185$ (hema cancer, $n = 7$, solid tumors, $n = 5$) Catheter related, $n = 14$ Catheter removal, $n = 1$ Diagnosis: Close monitoring. If clinically suspected, confirmed by imaging. In 185 patients, bilateral US was performed at study completion.
Kulkarni et al 2015 Poor ²¹	Cohort, multicenter FT: ≥ 6 months	ALL, $n = 101$ Any cancer, $n = 67$ Non-ALL hema cancer, $n = 57$ Solid tumors, $n = 30$ Age (median): 15 years	Type: CVC, $n = \text{NR}$, Port, $n = \text{NR}$, PICC, $n = \text{NR}$ Duration: NR Care: NR.	Symptomatic, $n = 75$ (ALL, $n = 29$, any cancer, $n = 23$ non-ALL hema cancer, $n = 20$, solid tumors, $n = 3$) Asymptomatic, $n = 9$ (ALL, $n = 5$, solid tumors, $n = 2$ any cancer, $n = 1$ non-ALL hema cancer, $n = 1$) Diagnosis: Symptomatic: If clinically suspected, confirmed by imaging. Asymptomatic: Incidentally detected by imaging.
Abate et al 2014 Fair ³⁷	Cohort, single center FT: NR	Solid tumors, $n = 155$ Age (median): 13.2 years	Type: CVC, $n = 153$, Port, $n = 2$ Duration (median): 281 days Care: Flushing on alternate days or at every use with 20 mL saline followed by 3 mL NaCl 0.9% with heparin 200 IU/mL VTE therapy: Following published guidelines (not specified). VTE prophylaxis: LMWH in 85 patients (only patients > 10 years old).	Symptomatic, $n = 1$ Asymptomatic: NR Port related, $n = 1$ Catheter removal, $n = 1$ Diagnosis: If symptomatic, confirmed by US, CT, or MRI.
Albisetti et al 2013 Good ³⁸	Cohort, single center FT: ≤ 7.2 years	Solid tumors, $n = 48$ ALL, $n = 38$ non-ALL hema cancer, $n = 16$ Age: NR	Type: Port, $n = \text{NR}$ Duration: NR Care: NR.	Symptomatic, $n = 5$ (ALL, $n = 3$, non-ALL hema cancer, $n = 1$, solid tumors, $n = 1$) Symptomatic, events, $n = 7$ (one ALL patient had VTE x3) Asymptomatic, $n = 31$ (solid tumors, $n = 20$, ALL, $n = 11$) Catheter related: 36 Catheter removal: NR Diagnosis: MRV.

Table 1 (Continued)

Study Author Year Quality rating	Design Follow-up time (FT)	Characteristics Patients, <i>n</i> Age	Exposure Catheter type, <i>n</i> Catheter duration Catheter care	Outcome Venous thromboembolism, <i>n</i> Diagnostic approach
Revel-Vilk et al 2010 <i>Fair</i> ²²	Cohort, multicenter FT: NR	Any cancer, <i>n</i> = 211 Age (median): 7.4 years	Type: CVC, <i>n</i> = NR, Port, <i>n</i> = NR, PICC, <i>n</i> = NR Duration: NR Care: NR.	Thrombosis, <i>n</i> = 14 events in 13 patients (One ALL with PICC had symptomatic VTE x2) Symptomatic, <i>n</i> = 12 (ALL, <i>n</i> = 6, non-ALL hema cancer, <i>n</i> = 1, solid tumors, <i>n</i> = 5) Asymptomatic, <i>n</i> = 2 (Non-ALL hema cancer, <i>n</i> = 1, solid tumors, <i>n</i> = 1) PICC related, <i>n</i> = 8 Port related, <i>n</i> = 1 CVC related, <i>n</i> = 1 Catheter removal, <i>n</i> = 3 Diagnosis: If clinically suspected, confirmed by imaging.
Mitchell et al 2010 <i>Good</i> ²³	Cohort, multicenter FT: 3.5 months	ALL, <i>n</i> = 339 Age (mean): 5.9 years	Type: CVC, <i>n</i> = NR, Port, <i>n</i> = NR Duration: 3.5 months Care: NR VTE prophylaxis: 8 of 19 patients received enoxaparin before catheter implantation during induction therapy.	Symptomatic, <i>n</i> = 19 Asymptomatic: NR Catheter related, <i>n</i> = 7 Catheter removal: NR Diagnosis: If clinically suspected, confirmed by imaging.
Revel-Vilk et al 2010 <i>Poor</i> ²⁴	Cohort, single center FT: 0.3–7.5 years	ALL, <i>n</i> = 17 Solid tumors, <i>n</i> = 16 Non-ALL hema cancer, <i>n</i> = 10 Age: NR	Type: CVC, <i>n</i> = NR, Port, <i>n</i> = NR, PICC, <i>n</i> = NR Duration: NR Care: NR.	Symptomatic, <i>n</i> = 0 Asymptomatic: NR Catheter related: NR Catheter removal: NR Diagnosis: NR.
Ociepa et al 2010 <i>Fair</i> ²⁵	Cohort, single center FT: NR	ALL, <i>n</i> = 68 Non-ALL hema cancer, <i>n</i> = 37 Solid tumors, <i>n</i> = 14 Any cancer, <i>n</i> = 5 Age (median): 8.6 years	Type: CVC, <i>n</i> = NR Duration (median): 134 days Care: Rinsed once weekly with 2 mL of unfractionated heparin (50 U/mL) VTE therapy: tPA continuously for 48 hours followed by LMWH in two patients, and LMWH as single agent in one patient.	Symptomatic, <i>n</i> = 3 (ALL, <i>n</i> = 1, non-ALL hema cancer, <i>n</i> = 1, any cancer, <i>n</i> = 1) Asymptomatic/total, <i>n</i> = 4/37 Catheter related, <i>n</i> = 7 Catheter removal, <i>n</i> = 11 Diagnosis: If clinically suspected, confirmed by US. In 37 patients, US were performed at 1–54 months after CVC removal.
Chung et al 2008 <i>Fair</i> ²⁶	Cohort, single center FT: 3.8 years	Solid tumors, <i>n</i> = 19 ALL, <i>n</i> = 11 Non-ALL hema cancer, <i>n</i> = 6 Age (median): 9.1 years	Type: CVC, <i>n</i> = 36 Duration (mean): 13 months Care: Flushed once weekly with heparin saline and simple sterile dressing was applied under aseptic technique.	Symptomatic, <i>n</i> = 1 (ALL, <i>n</i> = 1) Asymptomatic/total, <i>n</i> = 0/25 Catheter related: NR Catheter removal: NR Diagnosis: Evaluated clinically at least once per week. If clinically suspected confirmed by imaging. In 25 patients, venogram or CT were performed at 3–6 months after chemotherapy initiation.
Farinasso et al 2007 <i>Poor</i> ²⁷	Cohort, single center FT: NR	ALL, <i>n</i> = 56 Age (median): 5 years	Type: CVC, <i>n</i> = 56 Duration: NR Care: Flushed with 2.5 mL heparin (50 IU/mL) three times a week.	Symptomatic, <i>n</i> = 4 patients/5 events Asymptomatic, <i>n</i> = 39 Catheter related, <i>n</i> = 42 Catheter removal: NR Diagnosis: Evaluated clinically on a regular basis. If clinically suspected confirmed by imaging. After completion of induction treatment spiral CT or US was performed.
Ruud et al 2006 <i>Fair</i> ¹⁸	RCT, single blind, multicenter FT: 6 months	ALL, <i>n</i> = 29, Solid tumors, <i>n</i> = 22 Non-ALL hema cancer, <i>n</i> = 11 Age (median): 6.7 years Included from same hospital and same period as Ruud et al. ²⁸ Potential overlap with Ruud et al. ³¹	Type: CVC, <i>n</i> = 48, Port, <i>n</i> = 14 Duration: 6 months Care: NR VTE prophylaxis: Experimental arm: Warfarin (intended INR 1.3–1.9). Standard arm: No prophylaxis.	Symptomatic, <i>n</i> = 2 (non-ALL hema cancer, <i>n</i> = 1) Asymptomatic, <i>n</i> = 24 Catheter related: NR Catheter removal: NR Diagnosis: US of central neck veins at 1-, 3-, and 6-month after inclusion.

(Continued)

Table 1 (Continued)

Study Author Year Quality rating	Design Follow-up time (FT)	Characteristics Patients, <i>n</i> Age	Exposure Catheter type, <i>n</i> Catheter duration Catheter care	Outcome Venous thromboembolism, <i>n</i> Diagnostic approach
Ruud et al 2006 Fair ²⁸	Cohort, single center FT: NR	ALL, <i>n</i> = 30 Age (median): 6 years Included from same hospital and same period as Ruud et al. ¹⁸ Potential overlap with Ruud et al. ³¹	Type: CVC, <i>n</i> = NR Duration: NR Care: NR.	Symptomatic, <i>n</i> = 0 Asymptomatic, <i>n</i> = 15 patients Catheter related, <i>n</i> = 19 events Catheter-removal: NR Diagnosis: US of central neck veins performed just prior to asparaginase and 2 months after asparaginase initiation.
Stiakaki et al 2005 Poor ²⁹	Cohort, single center FT: NR	ALL, <i>n</i> = 19 Any cancer, <i>n</i> = 12 Age (median): 4.5 years	Type: NR Duration: NR Care: Flushing lumen with 2 mL Heplock (10 IU/mL) every third day or after use + weekly intraluminal urokinase 10,000 IU/2 mL for 4 hours before aspirated or discharged.	Symptomatic, <i>n</i> = 1 (ALL, <i>n</i> = 1) Asymptomatic: NR Catheter related, <i>n</i> = 1 Catheter removal: NR Diagnosis: NR.
Male et al 2003 Good ³⁰	Cohort, multicenter FT: 4 weeks	ALL, <i>n</i> = 85 Age: NR Substudy of Mitchell 2002 ¹⁹ with partially overlapping study population.	Type: Catheters, <i>n</i> = 86, CVC, <i>n</i> = NR, Port, <i>n</i> = NR Duration: 4 weeks Care: Small amounts of unfractionated heparin either by continuous infusion (1–3 IU/mL) or intermittent flushes (50–100 IU/mL) up to four times per day.	Symptomatic, <i>n</i> = 4 Asymptomatic, <i>n</i> = 25 Catheter related: NR Catheter removal: NR Diagnosis: Close clinical monitoring. Confirmed by US, bilateral venography, echocardiography, and MRI of head. After 4 weeks, patients who did not have symptoms of VTE were screened with each of the four radiographic tests.
Mitchell et al 2003 Poor ¹⁹	RCT FT: 1–3 months	ALL, <i>n</i> = 60 Age: NR	Type: NR Duration: 1–3 months Care: NR.	Symptomatic, <i>n</i> = 3 Asymptomatic, <i>n</i> = 19 Catheter related: NR Catheter removal: NR Diagnosis: Close monitoring. Confirmed by radiographic test. At 1–3 months: echocardiography, US of upper body, MRI of head. Bilateral venography or MRI of the upper venous system was performed at 1–3 months.
Ruud et al 2002 Good ³¹	Cohort, single center FT: 3–5 months	ALL, <i>n</i> = 27 Non-ALL hema cancer, <i>n</i> = 10 Solid tumors, <i>n</i> = 4 Age: NR Included from same hospital and by same author as Ruud et al. ^{18,28} Potential overlap.	Type: CVC, <i>n</i> = 41 Duration (mean): 266 days Care: NR VTE therapy: Aspiration problems associated with radiology proven thrombus were treated with tPA 1–2 mg or heparin (1,000 IU/mL) into the CVC.	Symptomatic, <i>n</i> = 0 Asymptomatic, <i>n</i> = 18 Catheter related: NR Catheter removal, <i>n</i> = 0 Diagnosis: 34 patients had US performed within days after CVC insertion. At 3–5 months after first examination, all patients had US performed.
Kalmanti et al 2002 Poor ²⁰	Case-control, single center FT: NR	ALL, <i>n</i> = 14 Solid tumors, <i>n</i> = 10 Non-ALL hema cancer, <i>n</i> = 6 Age (mean): 4.8 years	Type: CVC, <i>n</i> = 35 Duration (mean): 336 days Care: Study: intraluminal 2 mL urokinase (5,000 IU/mL) for 4 hours once a week, in addition to standard care. Control: HepLock (10 IU/mL) flush after use or at least every third day.	Symptomatic, <i>n</i> = 2 (Non-ALL hema cancer, <i>n</i> = 1, solid tumors, <i>n</i> = 1) Asymptomatic, <i>n</i> = 16 Catheter related, <i>n</i> = 13 Catheter removal: NR Diagnosis: Echocardiography and US regularly. If symptoms, venography, or MRI angiography was performed.
Glaser et al 2001 Poor ³²	Cohort, single center FT: ≥6 months	Solid tumors, <i>n</i> = 12 Non-ALL hema cancer, <i>n</i> = 7 ALL, <i>n</i> = 3 Age (mean): 9.8 years	Type: Port, <i>n</i> = 29 Duration (mean): 14 months Care: NR.	Symptomatic, <i>n</i> = 3 Asymptomatic, <i>n</i> = 9 Catheter related: NR Catheter removal: NR Diagnosis: Physical examination and contrast venography before removal of catheter.

Table 1 (Continued)

Study Author Year Quality rating	Design Follow-up time (FT)	Characteristics Patients, <i>n</i> Age	Exposure Catheter type, <i>n</i> Catheter duration Catheter care	Outcome Venous thromboembolism, <i>n</i> Diagnostic approach
Rubie et al 1995 <i>Poor</i> ³⁹	Cohort, Single center FT: NR	ALL, <i>n</i> = 79 Hema cancer, <i>n</i> = 33 Solid tumors, <i>n</i> = 51 Age (median): 85 months	CVC, <i>n</i> = 180 Duration: 305 days Care: In-house: Flushed with saline before infusions and with saline containing 100 IU/mL heparin either daily or after every blood sampling. Outpatients: flushed monthly with 3–5 mL diluted heparin solution (100 U/mL) VTE therapy: Urokinase 1,000 IU/mL, in CVC for 3 hours. If unsuccessful: Urokinase 1,000 U/mL, in CVC for 24 hours	Thrombosis/clots, <i>n</i> = 16/180 catheters Symptomatic, <i>n</i> = 0 Asymptomatic: NR Catheter related: NR Catheter removal: 4 Diagnosis: NR.
Cassey et al 1994 <i>Poor</i> ⁴¹	Cohort, single center FT: NR	Any cancer, <i>n</i> = 10 Age: NR	Type: CVC, <i>n</i> = 13 Duration (range): 60–240 days Care: NR.	Symptomatic, <i>n</i> = 0 Asymptomatic, <i>n</i> = 0 Catheter related, <i>n</i> = 0 Catheter removal, <i>n</i> = 0 Diagnosis: US at <6 months, 6–24 months or >24 months.
Stokes et al 1989 <i>Poor</i> ³³	Cohort, single center FT: NR	Any cancer, <i>n</i> = 18 Age (median): 4.9 years	Type: CVC, <i>n</i> = 19 Duration: NR Care: Urokinase (5,000 IU/mL) into the catheter for 60 minutes. Afterward, flushed with heparinized saline.	Thrombosis, <i>n</i> = 11 patients/12 events Symptomatic: NR Asymptomatic: NR Catheter related: 12 Catheter removal: NR Diagnosis: Catheter resistance measurement. Contrast venogram in 13 patients.
Wesenberg et al 1987 <i>Poor</i> ³⁴	Cohort FT: NR	ALL, <i>n</i> = 15 Non-ALL hema cancer, <i>n</i> = 4 Solid tumors, <i>n</i> = 3 Age: NR	Type: Port, <i>n</i> = 22 Duration: NR Care: Flushed with 20 mL saline before using and sealed with 3 mL heparinized saline (250 IU/mL) every 4–8 week.	Symptomatic, <i>n</i> = 0 Asymptomatic, <i>n</i> = 0 Catheter related, <i>n</i> = 0 Catheter removal, <i>n</i> = 0 Diagnosis: NR.
Pegejow et al 1986 <i>Poor</i> ³⁵	Cohort FT: NR	Solid tumors, <i>n</i> = 12 Hema cancer, <i>n</i> = 3 Age (mean): 8.3 years	Type: Port, <i>n</i> = 16 Duration (mean): 256 days Care: Flushed with 5 mL heparin-saline after each use and at least every 3–4 week.	Thrombosis, <i>n</i> = 2 (solid tumors, <i>n</i> = 2) Symptomatic: NR Asymptomatic: NR Catheter related, <i>n</i> = 2 Catheter removal, <i>n</i> = 1 Diagnosis: NR.

Abbreviations: ALL, acute lymphoblastic leukemia; CT, computer tomography scan; CVC, non-tunneled or tunneled central venous catheter; Hema, hematological; INR, international normalized ratio; LMWH, low-molecular-weight heparin; MRI, magnetic resonance imaging; MRV, magnetic resonance venography; NR, not reported; PICC, peripherally inserted central catheters; Port, implantable port; RCT, randomized controlled trial; tPA, tissue plasminogen activator; US, ultrasound; VTE, venous thromboembolism; VQ, ventilation–perfusion scan.

Venous Thromboembolism

Among the 2,318 pediatric cancer patients with a catheter inserted, 400 (17%) were diagnosed with VTE (► **Table 1**). Of the 400 thrombi, 210 were asymptomatic, 142 symptomatic, and in the remaining 48 cases it was not reported whether the thrombi were asymptomatic or symptomatic. Nine studies performed systematic imaging investigations for VTE,^{18–20,28,30,31,33,40,41} while 13 studies closely monitored patients and if VTE was clinically suspected imaging was performed.^{17,19–23,25–27,30,32,36,37} Six studies performed imaging at catheter removal or study completion.^{17,25–27,32,36} Five studies did not report how VTE was diagnosed.^{24,29,34,35,39}

Fifteen studies described specifically CVC-related VTE and reported 167 CVC-related VTE in 1,551 pediatric cancer patients (11%).^{17,20,22,23,25,27–29,33–35,37,38,40,41} The remaining 10 studies reported VTE in children with catheters

inserted but did not clearly state if the VTE was CVC related. Five studies described specifically CVC-related VTE in 459 children with ALL and reported 69 CVC-related VTE (15%).^{23,27–29,34} No study described specifically CVC-related VTE in children with solid tumors.

Regarding catheter type, 20% of children with tunneled or nontunneled CVC,^{20,26,27,31,33,36,37,39,41} 12% of children with implantable ports,^{32,34,35,37,40} and 4% of children with PICC⁴⁰ suffered a VTE. Twenty-one catheters were reported removed due to VTE.^{17,22,25,35,37,39}

From 12 studies reporting VTE in ALL children, the overall incidence (95% CI) for VTE, symptomatic or asymptomatic, was 21% (8–37) (► **Fig. 2A**).^{19,21,23–30,34,38}

Nine studies reported VTE in children with solid tumors with an overall incidence (95% CI) for symptomatic or asymptomatic VTE at 7% (0.1–17.0) (► **Fig. 2B**).^{17,21,24,26,34,35,37,38,40} Funnel plot

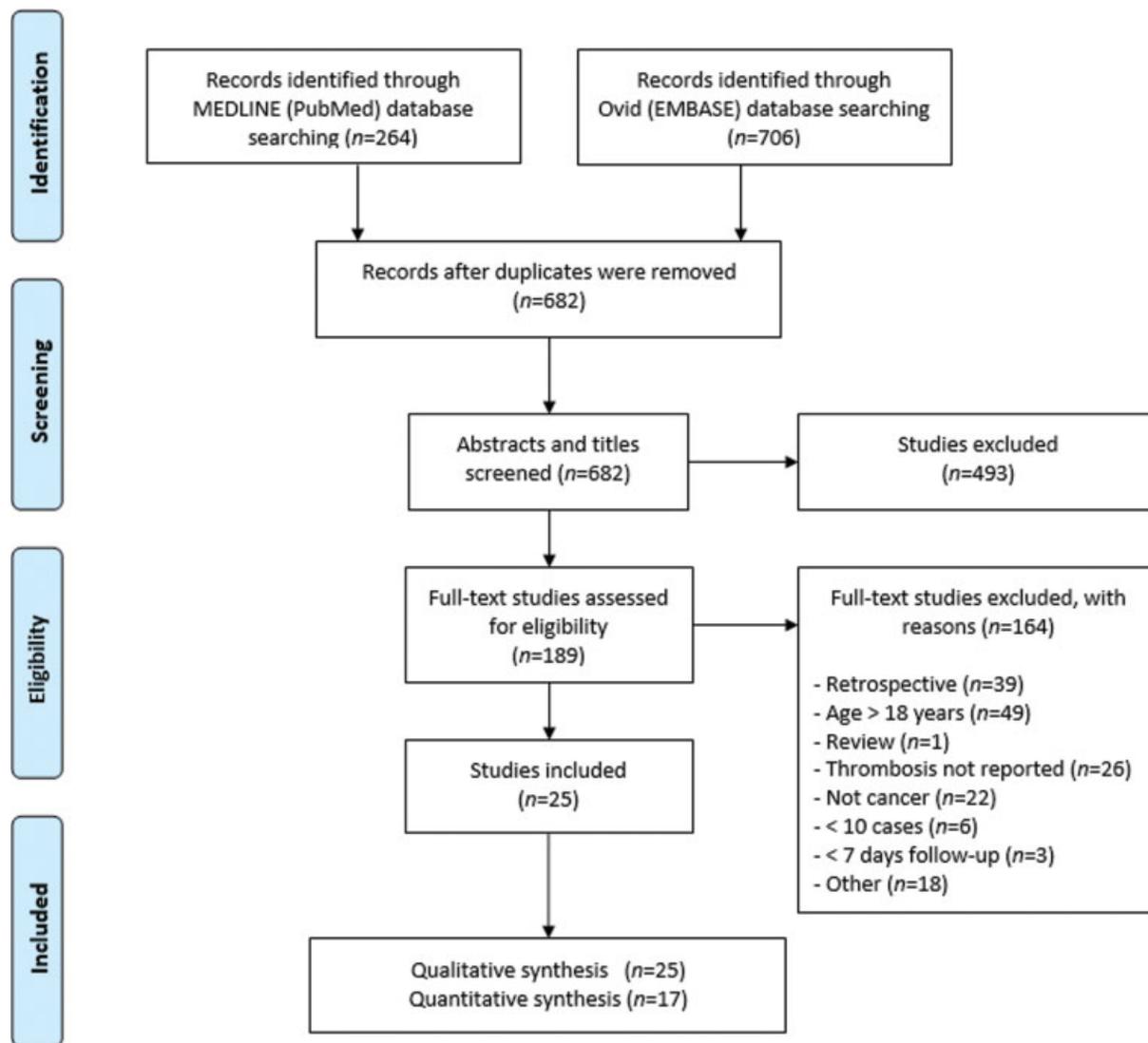


Fig. 1 PRISMA flow diagram of the inclusion and exclusion process of articles.¹¹

was asymmetric for both children with ALL and solid tumors studies (► **Fig. 3A, B**) indicating low publication bias. The I^2 for ALL studies was 95% and for solid tumors studies it was 88%, indicating considerable heterogeneity between included studies.¹⁴

Catheter Care and Thromboprophylaxis

Half of the included studies described how the indwelled catheters were cared for.^{17,20,25–27,29,30,33–35,37,39}

Catheter care consisted of heparin lock^{17,25,34} or flushes^{20,26,27,30,34,35,37,39} in 10 studies (976 children),^{17,20,25–27,30,34,35,37,39} urokinase instillation in one study (18 children),³³ and heparin flushes plus urokinase instillation in two studies (46 children).^{20,29} Despite catheter care, VTE was diagnosed in 130 (13%) children with heparin, 11 (61%) patients with urokinase, and eight (17%) children with heparin flushes plus urokinase instillation as localized catheter care.

Schoot et al¹⁷ compared 70% ethanol with 100 IU/mL heparin as lock solution and found no statistically significant difference (three symptomatic VTE in 152 children with ethanol as lock solution vs. no symptomatic VTE in 153 children with heparin as lock solution ($p = 0.25$)). In addition,

2% of children with ethanol as lock solution versus 5% of children with heparin as lock solution were diagnosed with asymptomatic VTE ($p = 0.17$). Additionally, Kalmanti et al²⁰ compared intraluminal urokinase in addition to heparin (study) versus standard heparin care (control) and found asymptomatic VTE in seven of 19 study children and nine of 11 control children ($p = 0.047$).

Three studies investigated thromboprophylaxis in addition to lock solution.^{18,23,37} Ruud et al¹⁸ compared warfarin (intended INR range 1.3–1.9) with no prophylaxis and found no difference in number of VTE ($p = 0.44$). Mitchell et al²³ compared enoxaparin (1 mg/kg) before catheter insertion ($n = 8$) to no prophylaxis before catheter insertion ($n = 11$) in high-risk ALL patients and found that one child receiving enoxaparin 1 mg/kg experienced a VTE compared with eight VTE cases out of 11 children without prophylaxis ($p = 0.023$). Abate et al³⁷ provided low-molecular weight heparin (LMWH) to 85 of 155 included children and reported that one out of the 85 children receiving LMWH suffered symptomatic VTE. However, asymptomatic VTE was not reported by Abate et al.³⁷

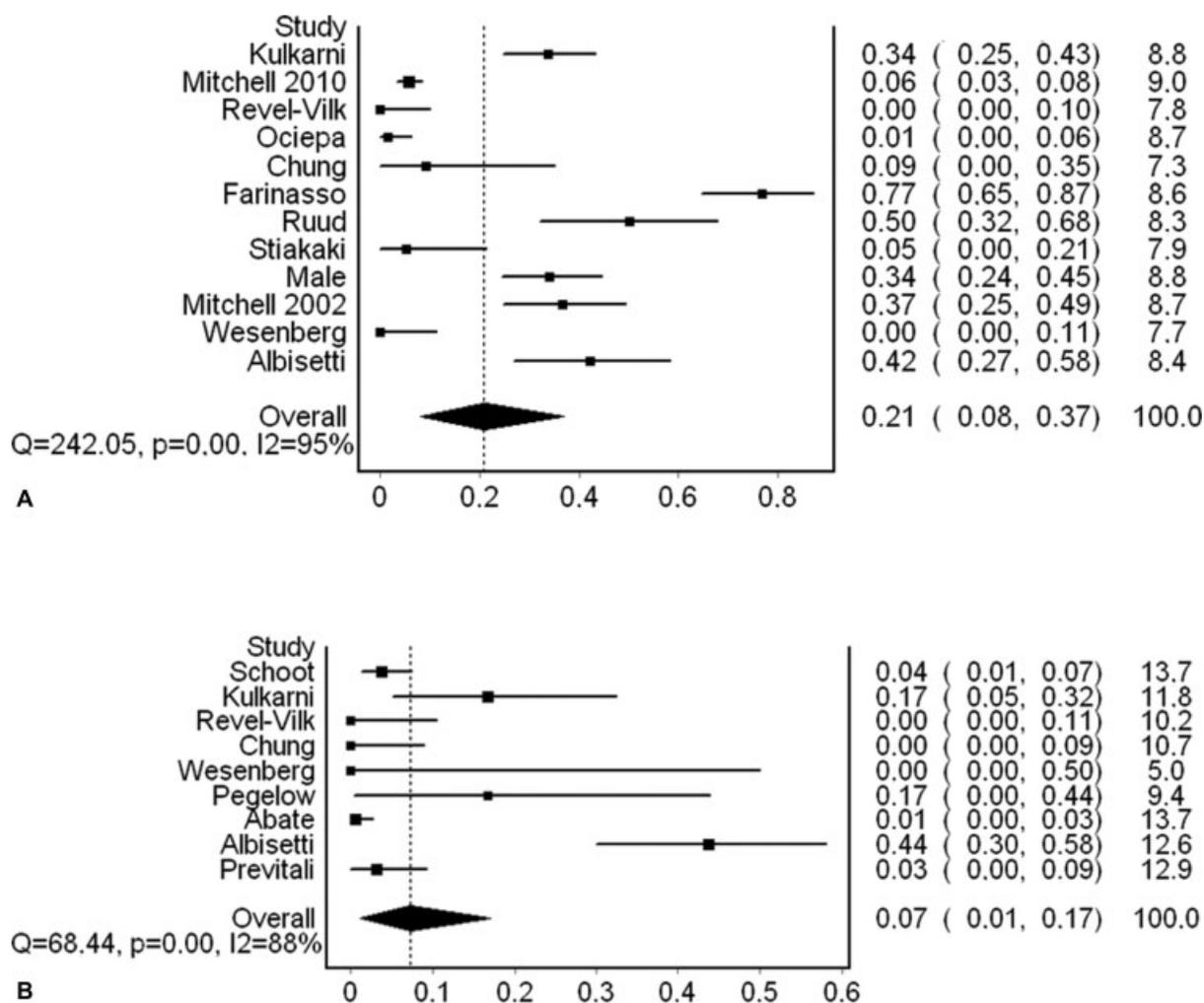


Fig. 2 Forest plots of incidence of symptomatic or asymptomatic venous thromboembolism in children suffering from acute lymphoblastic leukemia, based on 12 studies (A), or solid tumors, based on nine studies (B).

Thrombophilia

Eight studies investigated thrombophilia (→ **Supplementary Table S1**, available in the online version only).^{18,19,22,26,29–31,38} Six of 11 (55%) children with persistent antiphospholipid antibodies,^{19,30} three of 15 (20%) children with the factor V Leiden variation,^{19,29,30,38} and one of 25 (4%) children with the methylenetetrahydrofolate reductase variation²⁶ suffered a VTE. None of the children with the factor II variation ($n = 7$),^{19,26,29,30,38} protein C deficiency ($n = 2$),²⁶ or protein S deficiency ($n = 1$)²⁶ suffered a VTE. Three of 75 (4%) children without thrombophilia suffered a VTE.^{18,26,29} However, Revel-Vilk et al only investigated thrombophilia in children suffering VTE ($n = 13$), and found that eight (62%) children with VTE did not have thrombophilia.²² None of the eight studies reported a significant association between the presence of thrombophilia and VTE.

Discussion

To the best of our knowledge, this is the first systematic review to disclose the literature on VTE in pediatric cancer patients with CVC inserted. From 25 studies including a total of 2,318 pediatric cancer patients with a catheter inserted,

we found that 400 (17%) were diagnosed with VTE. From 15 studies specifically reporting CVC-related VTE an incidence of 11% was found. The overall estimated VTE incidence was substantially higher in children with ALL (21%) than children with solid tumors (7%). Additionally, children with tunneled or nontunneled CVC were more likely to suffer from VTE than children with implantable ports.

Of the 25 included studies, 13 had acceptable quality (rating *good* or *fair*). Of the 12 studies with *poor* quality, the majority lacked information on sample size, power calculation, outcome assessment, or study population. Altogether, a *good* or *fair* quality in 52% of included studies is acceptable, but it should be taken into account when interpreting the results and conclusion of this review.

To reach a compromise between sufficient sample size and reduction of heterogeneity, we divided the study population into ALL, non-ALL hematological cancer, solid tumors, any cancer and any hematological cancer if the number of ALL cases was not specified. The solid tumor group constituted a wide range of cancer diagnosis, which limits its usefulness for specific diagnosis and increases its heterogeneity but increases the generalizability and made a meta-analysis possible.

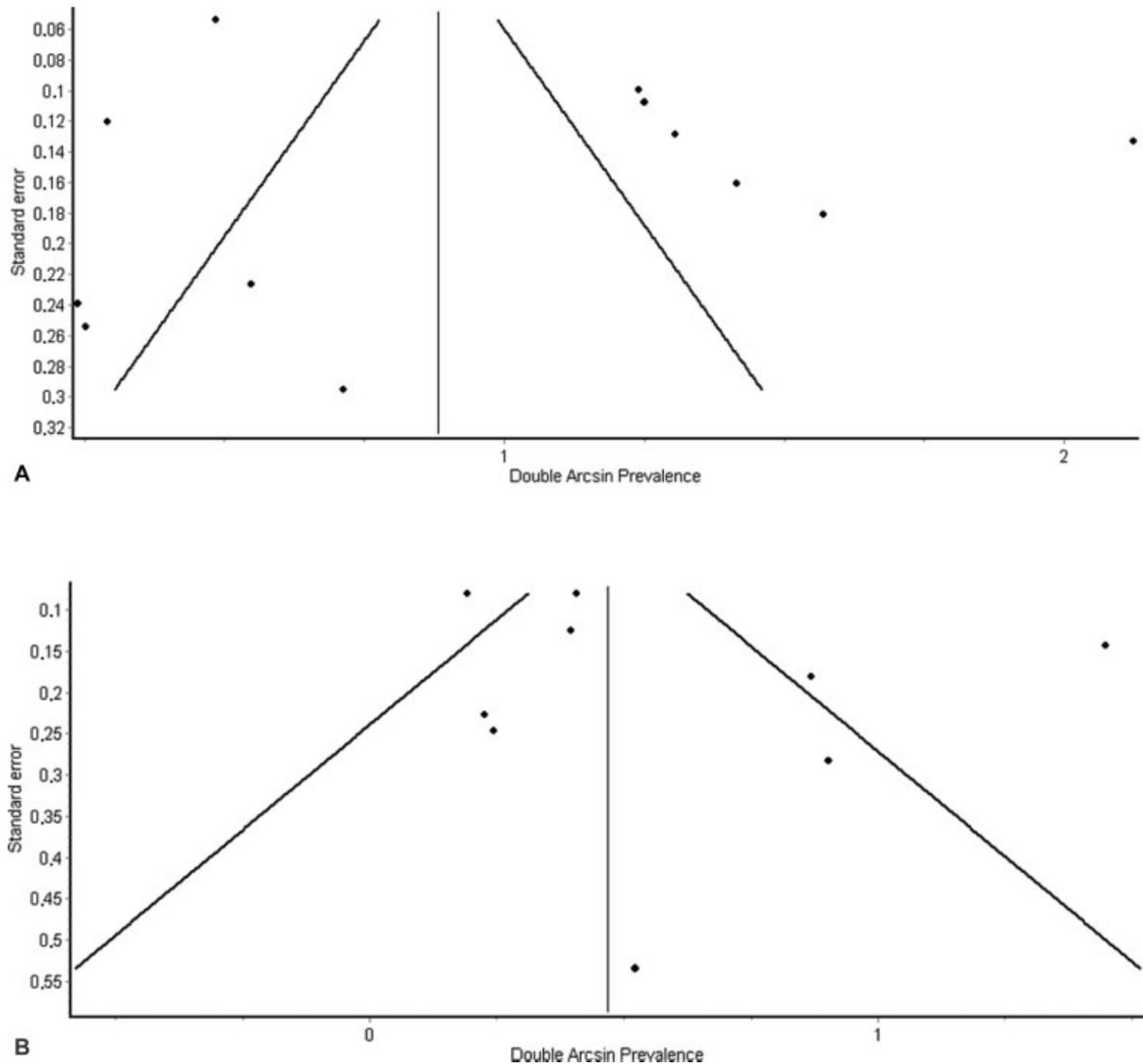


Fig. 3 Funnel plot of incidence of symptomatic or asymptomatic venous thromboembolism in children suffering from acute lymphoblastic leukemia, based on 12 studies (A), or solid tumors, based on nine studies (B).

The incidence of CVC-related VTE in adults with cancer has been reported to range from 0.3 to 28.3%.⁴² We found that 11% of pediatric cancer patients with a catheter inserted suffered from CVC-related VTE, which is considered equal to that of adults.^{9,10} The incidence of CVC-related VTE in adults with ALL has been reported to range from 6.5 to 11.7%,^{43,44} and from 3.8 to 13% in adults with solid tumors and a catheter.^{45,46} Five studies described specifically CVC-related VTE in 459 children with ALL and 69 CVC-related VTE (15%).^{23,27–29,34} Unfortunately, no study described specifically CVC-related VTE in children with solid tumors. The statistical dispersion of our estimated VTE incidence was wide for both ALL and solid tumors, and therefore the VTE estimates should be interpreted with caution. However, the present meta-analyses suggest that children with ALL and a catheter have a higher incidence of VTE than adults with ALL and a catheter.

The VTE incidence in children with ALL and a CVC inserted (21%) is considerably higher than the overall thrombosis rate of 5.2% found in a previous meta-analysis of 1,752 children with

ALL.⁴⁷ However, only few of the studies included by Caruso et al⁴⁷ describe CVC, but 27.5% of the reported symptomatic thrombi were catheter related, which is higher than our finding of 15%. Nevertheless, this supports the fact that CVC indeed is a severe additional thromboembolic risk factor in children with ALL.

Regarding catheter type, the majority of patients had either tunneled CVC, nontunneled CVC or implantable ports inserted, whereas only 2.4% of children had PICC. Revel-Vilk et al²² found eight PICC-related VTE in 211 patients, but the number of PICC in the 211 patients was not reported. Thus, the VTE risk of PICC cannot be concluded from that study.

Catheter care was only reported explicitly in half of the included studies.^{17,20,25–27,29,30,33–35,37,39} Among these, 976 of 1,040 children received heparin as catheter care. Although we found a VTE incidence of 61% in children with urokinase as catheter care, and only 13% in children with heparin as catheter care, we render that studies with direct comparison of different catheter care regimens are warranted to conclude which regimen is superior to the others.

Testing for inherited thrombophilia in children is in general debatable.⁴⁸ However, several studies have found that inherited thrombophilia does not increase the risk of CVC-related VTE in children.⁴⁸ Accordingly, none of the eight studies we identified investigating thrombophilia in pediatric cancer patients reported a significant association between the presence of thrombophilia and VTE.^{18,19,22,26,29–31,38} Altogether, thrombophilia testing does not seem recommendable in pediatric cancer patients with CVC and VTE.

The strengths of the present systematic review are the comprehensive literature search and the inclusion of a high number of pediatric cancer patients. Consequently, the number of VTE was sufficient for statistical purposes. We only included prospective studies, which ensured systematic data collection. Studies included in the meta-analysis were evenly distributed in the funnel plot, especially the one for ALL indicating a low publication bias of the included studies.

However, some limitations must be considered. The included studies were quite heterogeneous, indicated by I^2 at 95% for ALL studies and 88% for solid tumor studies. Not all studies reported asymptomatic VTE, which is much more incident than symptomatic VTE,²⁷ and therefore the VTE incidence could be underestimated. This is due to the design of the included studies, where only nine studies performed systematic imaging investigations for VTE. We reported VTE per patient, since the total number of included catheters could not be calculated. As some patients may need catheter replacement, VTE per catheter would have been useful information. Rubie et al³⁹ did only report VTE per catheter and found that 16 of 180 (9%) tunneled or nontunneled CVC catheters had VTE. Partially overlapping study populations existed between Male et al³⁰ and Mitchell et al.¹⁹ Moreover, there was potential overlap of three study populations included from the same hospital and by the same author,^{18,28,31} with two of them also including patients from the same time period.^{18,28} In case of overlapping study populations, children are counted twice, and consequently drive the results in the same direction and thereby introduce bias.

Conclusion

Children with ALL and CVC hold a higher VTE incidence compared with children with solid tumors and CVC. Importantly, pediatric cancer patients with implantable port catheters probably have lower risk of VTE than children with tunneled or nontunneled CVC. Investigation for thrombophilia does not seem relevant in pediatric cancer patients with CVC and VTE. Intensified catheter care is recommended, especially in children with ALL. Finally, implantable port catheter should be preferred to reduce the VTE risk.

Funding

None.

Conflict of Interest

A.-M.H. reports other from CSL Behring, other from CSL Behring, Bayer, Boehringer Ingelheim, Astellas, outside the submitted work.

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