

Epidemiology of venous thrombosis in children with cancer

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Summary

There has been an extensive body of research focusing on the epidemiology of thrombosis in adult cancer populations; however, there is significantly less knowledge about thrombosis in paediatric cancer populations. Thrombosis is diagnosed with increasing frequency in children being treated for cancer, and there is an urgent need to increase our understanding of the epidemiology of thrombosis in this population. Currently, there are no guidelines for identification of high-risk groups, prophylaxis or management of thrombotic complications in paediatric cancer patients. We reviewed the available literature regarding the epidemiology, mechanisms, risk factors, prophylaxis and outcomes of thrombosis in children with cancer and identified areas that require further research. The reported incidence of symptomatic venous thromboembolism (VTE) in children with cancer ranges between 2.1% and 16%, while the incidence of asymptomatic events is approximately 40%. Approximately 30% of VTE in this population is

associated with central venous lines (CVL). The most common location of VTE is upper and lower extremity deep venous thrombosis (43 to 50% of events, respectively), while 50% of events in ALL patients occur in the central nervous system. Key characteristics that increase the risk of thrombosis include the type of cancer, age of the patient, the presence of a CVL, presence of pulmonary/intra thoracic disease, as well as the type of chemotherapy. Outcomes for paediatric cancer patients with VTE include post-thrombotic syndrome, pulmonary embolism, recurrent thromboembolism, destruction of upper venous system and death. Prospective studies aimed at enabling risk stratification of patients are required to facilitate development of paediatric specific recommendations related to thromboprophylaxis in this population.

Keywords

Cancer, child, epidemiology, incidence, thrombosis, paediatrics

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Introduction

The majority of studies investigating epidemiology of thrombosis in the setting of cancer have focused on adult populations, with thromboembolic complications being the second leading cause of death in cancer patients (1). In comparison, little is known about the pathophysiology and epidemiology of thromboembolism in the paediatric cancer populations.

The incidence of venous thromboembolism (VTE) is approximately 0.7 to 1.4 events per 100,000 children and 53 events per 100,000 hospital admissions (2-4). This is significantly lower compared to adults, with the incidence of VTE ranging between 71 to 117 events per 100,000 individuals (2). In addition, 95% of VTE events that occur in children are secondary to underlying diseases such as cancer, trauma, surgery and congenital heart disease (2, 5).

This paper reviews the literature available from January 1990 to November 2013 regarding the epidemiology, mechanisms, risk factors, prophylaxis and outcomes of thrombosis in children with cancer and critical areas where more research is needed. The ultimate aim of this review is to provide the basis for prospective studies in this population that will facilitate the establishment of

guidelines for identification of high-risk groups, prophylaxis and management of thrombotic complications in children with cancer.

Method

A PubMed search was performed by one author and verified by a second author using key words: cancer, children, epidemiology, paediatric, thrombosis, and thromboembolism. The search was limited to humans, English and papers published between January 1990 and November 2013. Case series were excluded from this study.

Characteristics of published studies

This review included 47 studies, 14 (30%) of which were retrospective and 25 (53%) were prospective, with one meta-analysis and seven reviews, accounting for the remaining 17% of the studies (► Figure 1). There was a significant heterogeneity in the studies identified. Despite this, the majority of the studies were prospec-

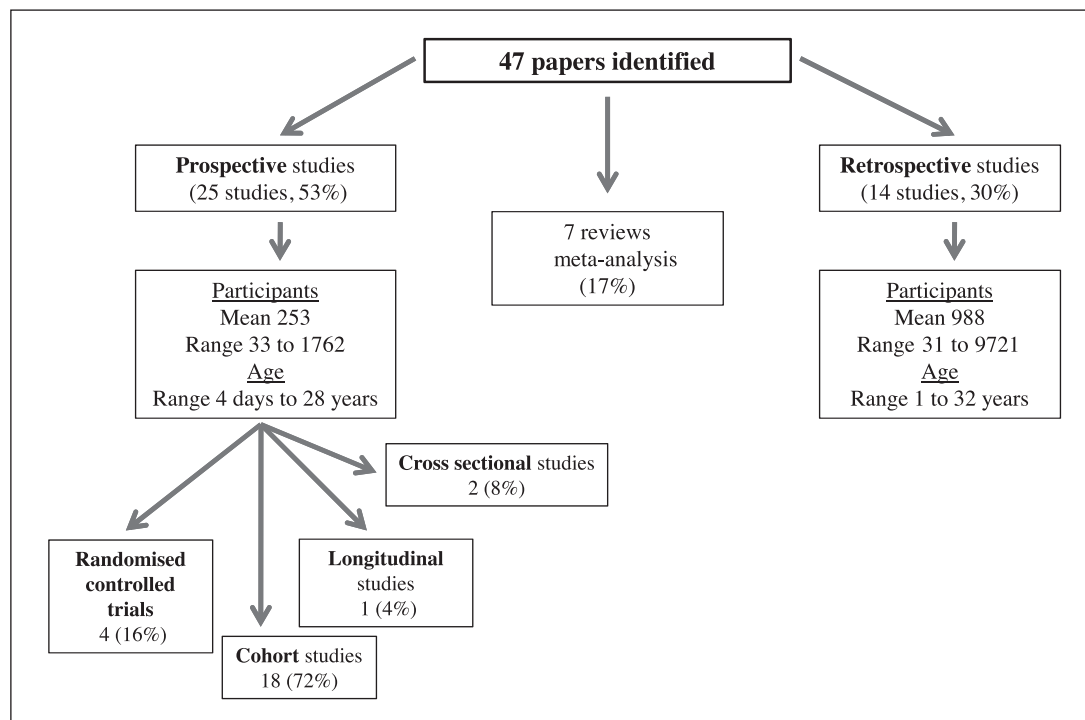


Figure 1: Summary of the studies identified in this review.

tive. The mean number of participants for all studies was 567 (range 31 to 9,721). For retrospective studies, there was a mean of 988 participants (range 31 to 9,721); while for prospective studies the mean number of participants was 253 (range 33 to 1,762). The participants for all studies were aged between four days to 32 years (1 to 32 years for retrospective; 4 days to 28 years for prospective). The majority of the studies included children only, with two studies including some adult data up to 32 years of age. Overall, 43% of the studies focused on paediatric patients with acute lymphoblastic leukemia (ALL), 11% on solid tumours or sarcomas, 5% on paediatric haematological malignancies, while 41% were based on paediatric patients with all types of cancer.

It is important to note that only one publication referred to arterial thrombosis, with the incidence of thrombotic events being between 2% and 3.6% (6). Hence, this review will focus on venous thrombosis.

Incidence of VTE in children with cancer

The overall incidence of symptomatic VTE in children with cancer was 2.1 to 16% (6-9), while the incidence of asymptomatic VTE was significantly higher, at approximately 40% (9, 10). The incidence of symptomatic VTE is based on a number of both retrospective and prospective studies where the number of participants for specific studies ranged from 44 to 9,721. The methods for the diagnosis of VTE also varied, with studies utilising radiographic tests, clinical symptoms, laboratory tests or a combination of these. The variability in the number of patients, differences in study design and the way in which VTE was detected could contribute to

the variation in the incidence of symptomatic VTE. The most common location of VTE in paediatric cancer patients is upper and lower extremity deep venous thrombosis (DVT), accounting for 43 to 50% of events (2, 8). In addition, 75% of the VTE in children with cancer are central venous line (CVL)-associated (7). The incidence of pulmonary embolism (PE) is not well defined, with reports varying between 2% and almost 20% of all VTEs in children with cancer (6).

Risk factors involved in developing TE

Cancer type

The summary of the effect of cancer type on the risk of thrombosis is presented in ► Table 1. Athale et al. demonstrated that the prevalence of TE in paediatric patients across all cancer types was 7.9% (8). Interestingly, while adult studies have shown that individuals with brain tumours have a high incidence of TE, such events are highly uncommon in paediatric patients with brain tumours (11). Therefore, excluding brain tumours, the prevalence of TE across all other cancer types in children was found to be significantly higher at 10.7% (8). In paediatric cancers excluding ALL, the overall incidence of TE is 16% (12). In patients with ALL, the rate of asymptomatic VTE is 30–70% and the rate of symptomatic VTE is 5%, with 50% of these events located in the upper venous system (13). Central nervous system (CNS) thrombosis is a common occurrence in children with ALL in approximately 50% of children with symptomatic thrombosis (14). Approximately 52% of ALL patients with CNS thrombosis had sinovenous thrombosis (14). In children with ALL treated on BFM ALL 90/95 proto-

Table 1: Effect of type of cancer on risk of thrombosis in children.

Cancer type	Incidence of TE	Location of TE	Chemotherapy increased risk	CVL increased risk	Other risk factors
ALL	Symptomatic: 1–5.2% [30, 43] Asymptomatic: 30–70% [30]	CNS (up to 53%) [16, 30] Upper and lower deep venous system 42.8% [16]	Yes, concomitant use of L-asparaginase and corticosteroids [17, 26–28] 90% of VTE's occur during induction therapy [30]	37% of asymptomatic TE associated with CVL [17] Symptomatic TE unknown	T-immunophenotype associated with higher risk [44]
Sarcoma	Symptomatic: 14% Asymptomatic: ~8% [45]	43% DVT, 22% PE, 17% inferior vena cava, 35% tumour compression [45]	Not applicable	30–50% of TE associated with CVL [45]	Incidence of TE: rhabdo- myosarcoma (15%), Ewing sarcoma (13%) and osteosarcoma (10%) [45]
Lymphoma	Symptomatic: 4.1–12% [7, 18] Asymptomatic: Not available	Upper venous DVT (75%) [17] PE (2.6%)[18]	No, study suggests devel- opment of TE related to mechanical factors rather than biology of disease and chemotherapy [18]	~68% of TE associated with CVLs [18] All patients with CVL-re- lated TE had mediastinal mass lymphadenopathy [18]	Older children (>12 years) and advanced stage dis- ease associated with higher risk [18]
AML/APL	AML: Symptomatic 6% [7] Asymptomatic: Not available APL: Symptomatic 14.3% [7] Asymptomatic: Not available	Not available	AML: Yes APL: Same as ALL [7]	Not available	Not available

ALL, acute lymphoblastic lymphoma; AML, acute myeloid leukaemia; APL, acute promyelocytic leukaemia; CVL, central venous line; DVT, deep venous thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

col, there was a 6% incidence of cerebral sinus venous thrombosis (SVT) (15).

Age

Older paediatric cancer patients have a higher risk of developing TE (8, 16), with the median age of patients with VTE being 13.5 compared to the median age of patients without VTE being 9.2 years old (7), while the highest risk of VTE for children receiving chemotherapy observed in 10- to 17-year-olds (8, 16). In a retrospective review, however, with cancer patients aged 15 to 24 years, the increased risk of VTE was highest in the range of 18 to 24 years, where 236 (46.18%) had non-superficial VTE (6). Unfortunately, this study did not include children below the age of 15, and thus further studies that encompass a broader age range need to be done in order to confirm the age range at which VTE risk is highest. The current hypothesis is that post-pubescent children/adolescents in this setting may be more prone to VTE due to differences in the epidemiology of cancer with respect to different age groups, as well as the more aggressive therapy used in older paediatric patients, particularly in the setting of ALL (17). Another hypothesis is that the higher risk in adolescents is due to the fact that their haemostatic system may more closely resemble that of adults, who are more prone to thrombosis.

Central venous lines (CVLs)

A significant number of individuals who developed TE also had CVLs, indicating that the presence of a CVL is a confounding factor to the role of cancer type in children (7, 8, 18). Catheter-related thrombosis has been demonstrated as prevalent among all cancer types (8). The presence of a CVL is an important factor that has been strongly associated with causing upper venous thrombosis (8, 9, 15, 19–23) with one study identifying 43% of catheter-related DVT as asymptomatic (24). The incidence of CVL occlusion in children with cancer is estimated at 1.35 per 1,000 catheter days, while the incidence of CVL-DVT is 0.13 per 1,000 catheter days (23). These incidences were found to increase significantly if the catheter was inserted in an angiography suite rather than surgically (23). It was also demonstrated that paediatric cancer patients who developed DVT (7%) had on average more catheters placed than those without DVT (25). In the setting of ALL, 30% of symptomatic VTE events are associated with CVLs (10). The risk of thrombosis increases significantly when CVLs are present in conjunction with L-asparaginase treatment, a scenario that results in 25% to 100% vessel occlusion (13).

In terms of CVL-related VTE and other associated complications, Journeycake et al. found that 73% of total catheters placed in the children who developed DVT were associated with at least one episode of occlusion or infection (6.4 times higher risk), with

90% of the patients with DVT experiencing at least one catheter occlusion and 47% experiencing CVL-related bacteraemia (25). Additionally, having multiple episodes of occlusion and infection were associated with unidentified DVT (25).

Pulmonary/ intra-thoracic disease

There is a high incidence of TE in paediatric patients with concurrent pulmonary or intra-thoracic disease. Athale et al. concluded that 26.1% of paediatric sarcoma patients with pulmonary disease had TE as compared to 8.5% of those without pulmonary disease. (21). The same study observed that five of the six patients with upper venous system DVT had pulmonary disease (21).

Chemotherapy

One of the major risk factors for children with cancer is the potential for the chemotherapy itself to induce a prothrombotic state and cause thrombosis. This may be caused by the direct effect on proteins involved in haemostasis, endothelial cell damage or by complications such as infections and immunosuppression (17).

Chemotherapy also plays a significant role in increasing the risk of TE, particularly in the setting of paediatric patients with ALL, where the concomitant administration of L-asparaginase and corticosteroids increases the risk of thrombosis (17, 26–28). This is because L-asparaginase causes suppression of natural anticoagulants such as Antithrombin, while corticosteroids increase the levels of procoagulant factors (Factor II, VIII) and induce a hypofibrinolytic state (increased plasminogen activator inhibitor type 1, reduced alpha-2-macroglobulin and tissue type plasminogen activator) (17, 29). Specifically, the risk of thrombosis in paediatric patients with ALL receiving both L-asparaginase and corticosteroids increases by up to 10-fold, with 90% of events occurring during induction therapy, with the remaining 10% occurring during consolidation therapy (16, 26, 30). Paediatric patients with ALL reach a hypercoagulable state just four weeks after the start of dexamethasone treatment (26), with VTE events occurring at approximately the 8th week of treatment of ALL (7).

Other treatment options such as growth factors (i.e. anthracyclines) have also been observed to increase the risk of TE in children in the setting of ALL, acute myeloid leukaemia (AML) and lymphomas (7). In addition, in ALL patients that there is an increased risk of VTE in patients being treated with anthracyclines (6.1%), compared to those without (2.7%) (16).

The PARKAA study, with a population of 60 children with ALL who had CVLs and were undergoing chemotherapy with L-asparaginase (13), demonstrated that the prevalence of TE was high at 36.7%, that 40% of collaterals were categorised as major and that the majority of TEs were located in the upper central venous system (95.5%). In this study, of the 22 patients with TEs, three patients had TEs in the right atrium placing them at risk for PE, while three patients were found to be clinically symptomatic (13). From this study, it can be concluded that the presence of both risk factors of chemotherapy and the presence of CVLs in a patient population, present a significantly high risk and should be targeted for further investigation.

Inherited prothrombotic defects

While some studies have determined a correlation between inherited prothrombotic defects and thrombosis in paediatric oncology patients, this link is not very clear (13, 31, 32).

One study demonstrated that while prothrombotic defects were prevalent among the paediatric population with malignancies, only 3.2% actually developed thrombosis. It should be noted that, the study population consisted of only 31 native Cretan children and therefore no major conclusions can be drawn from this study (33). The PARKAA prospective cohort study demonstrated that there was no association between VTE and thrombophilia in children with ALL where no children with TEs were positive for FV G1691A mutation or the prothrombin G20210A mutation (13).

However, Knofler et al. demonstrated that prothrombotic risk factors (such as hyperlipoproteinaemia, heterozygous FV G1691A mutation, prothrombin G20210A mutation and protein C deficiency type I, protein S deficiency) were found in 17 (23%) patients in a study population of 77 paediatric oncologic patients with CVLs (22). Of seven of the 11 patients that had CVL-related thrombosis, four of the children had a single defect and three patients had combined prothrombotic defects suggesting that inherited thrombophilia may play a significant role in the development of thrombosis in paediatric oncologic patients with CVLs (22). This conclusion was also supported in a multicentre, prospective study that evaluated the risk of TE in children with ALL that had at least one inherited prothrombotic defect (34). With regard to prophylactic use of LMWH in paediatric ALL patients with prothrombotic defects, a study by Harlev et al. demonstrated that those with prothrombin gene mutation may have a higher risk of TE than those with FV Leiden mutation (35).

The prevalence of prothrombotic defects in children with: haematological malignancies, particularly ALL, with FV Leiden mutation G1691A ranges between 3.3–18.5% (13, 15, 34, 36, 37); prothrombin G20210A mutation and MTHR T677T mutation are 2–11.1% and 7.6–18.5%, respectively (13, 15, 34, 36, 37). While the prevalence of prothrombotic defects in children diagnosed with ALL appeared similar to that of the general population, Nowak-Gottl et al. demonstrated that a significantly higher proportion of children with ALL and prothrombotic defects developed VTE (46.5%), compared to children with ALL but without prothrombotic defects (2.2%), and additionally, 29.6% of the 27 patients with VTE and inherited prothrombotic defects had combined defects (34). In addition, patients with ALL with at least one biological abnormality had lower “thrombosis-free survival” compared to patients without that abnormality (34). This study indicates that while the overall incidence of VTE in paediatric cancer patients is low, the incidence of VTE in the setting of ALL is much higher and that inherited prothrombotic defects may be a significant contributing factor in VTE development. However, amongst the studies investigating the role of prothrombotic defects in paediatric cancer patients, only the study by Nowak-Gottl et al. demonstrated that there was a significant correlation between the incidence of TE and the presence of at least one prothrombotic defect (34).

Patients with ALL that have at least one prothrombotic defect, exhibit increased levels of thrombin and fibrin formation, fibrinolysis inhibition, decreased inflammatory cytokine levels as well as endothelial activation (28). These results become more pronounced during steroid administration (26), suggesting that a prothrombotic condition may not be an independent risk factor for the development of TE but may interact with other risk factors such as the specific chemotherapy used in ALL patients.

It can be suggested from the above data that before or shortly after CVL insertion and/or steroid administration, particularly in ALL patients, testing should occur for the presence of factor V G1691A mutation, and prothrombin G20210A variants.

Biomarkers and haemostatic alterations in paediatric cancer patients

A recent study by Giordano et al. suggested that certain biomarkers might be able to predict the tendency for a hypercoagulable state in paediatric patients with cancer (28). Specifically, biomarkers such as D-dimer and thrombin-antithrombin complex (TAT) were high at diagnosis with ALL (indicative of increased thrombin generation and fibrin formation), but decreased during induction therapy towards normal values. This trend was also observed in the inflammatory cytokines, tumour necrosis factor- α and interleukin 6, suggesting that the reduction of the tumour correlates with the normalisation of the hypercoagulable state (28). Plasminogen activator inhibitor 1, von Willebrand factor antigen and P-selectin levels were also high at diagnosis (indicative of fibrinolysis inhibition and endothelial activation, respectively). These markers, however, increased significantly during induction therapy, suggesting that chemotherapy plays a role in causing injury to the vascular endothelium. While two symptomatic VTE episodes occurred during induction therapy in the study by Giordano et al., there was no conclusion of a specific association between a prothrombotic marker and the thrombotic outcome (28). Therefore, the clinical relevance of prothrombotic biomarkers remains to be established and should be investigated further, as they may be able to provide an accurate prediction of the risk of TE in the paediatric cancer population (28).

While the pathogenesis of VTE in adult cancer patients is well understood, the exact pathogenesis and molecular mechanisms involved in the development of VTE in paediatric cancer patients is not clearly defined (12). It has been documented in children with ALL that there is an increased thrombin activation and thrombin generation, inferring that this may be an important factor in the pathogenesis of VTE in ALL patients (12, 38).

In addition, mechanical factors such as venous stasis are considered important factors in the development of VTE and large tumours are likely to compress the vessels which consequently alter venous flow (8, 12). However, this hypothesis is yet to be confirmed and more research is needed in this area.

Prophylaxis

Catheter maintenance

CVLs increase the risk of TE through various mechanical and biochemical effects including changes in the venous flow, trauma to the endothelium or by hyperosmolar substances infused through the CVL (10, 39). As a result, it is of utmost importance that the patency of the CVL is maintained. When comparing the efficacy of standard unfractionated heparin (UFH) and saline, it was found that UFH was superior at maintaining catheter patency and reducing infection in CVLs (17).

Primary prophylaxis

It has been suggested that patients with inherited prothrombotic defects undergoing intensive therapy such as L-asparaginase, adolescent patients undergoing major surgery and patients with a prior episode of TE should be considered for primary thromboprophylaxis. However, there have been no clear guidelines about the use of thromboprophylaxis in paediatric cancer patients.

LMWH vs UFH

There have been several prospective studies that investigate primary prophylaxis in the general paediatric setting. LMWH was compared to the standard of care, which was UFH flush, or infusion (<3 U/kg/hour) in children with CVLs, demonstrating that there was no difference in the rate of VTEs between the two treatment arms (40). However, while this study included 186 participants, only 51.1% and 50% of children had cancer in the LMWH and UFH treatment arms, respectively (40). In paediatric sarcoma patients undergoing major surgery LMWH has been shown to be effective for primary prophylaxis (41). LMWH also seems to be an effective prophylactic agent in children with ALL that are undergoing L-asparaginase therapy who also have inherited prothrombotic defects; however, the study only provides pilot data for future randomised trials investigating LMWH as a primary prophylactic agent during ALL therapy (37).

Antithrombin (AT) concentrate

The use of AT concentrate for primary prophylaxis in paediatric ALL cancer patients undergoing L-asparaginase therapy has increased and demonstrated a trend for a beneficial effect; however, the result was not statistically significant, potentially due to the low sample size (13).

Warfarin

The use of low-dose oral warfarin for primary thromboprophylaxis in a study population of 62 paediatric oncologic patients with CVLs was investigated in a randomised controlled study (35). In this study, 80% of the children had international normalised ratios (INRs) in the target range (INR 1.3–1.9) for more than 50% of the study period. However, the dose to achieve this fluctuated a lot due

to significant inter- and intra-individual variations (35). Additionally, none of the patients had the intended level of INR for the whole study period (35). They found that incidences of CVL-related VTE that occurred in the jugular vein (where CVLs were placed) were equally as frequent in the children on low-dose warfarin compared to those who were not (35). Therefore, there were no benefits observed of warfarin in children with malignancies to prevent asymptomatic VTE associated with CVL use.

Outcomes of thrombosis in children with cancer

Outcomes for paediatric cancer patients who have suffered TEs are highly variable (► Table 2) and could reflect the heterogeneity of the population. As a consequence of these TE-related complications, chemotherapy is often interrupted which is known to reduce the chances of treating the cancer (9, 42). In patients with ALL and thrombosis, over 50% of TEs are reported in potentially life-threatening sites such as the CNS, right atrium and in the lungs (PE) (14). In children with lymphoma, 44.4% have recurrent TE while 33.3% have signs and symptoms of post-thrombotic syndrome (18). In paediatric patients with sarcoma, 60% of children that had a TE had an adverse outcome (21).

Areas that require further research

There are many different aspects related to TEs in paediatric cancer patients that require further research. One of the major areas that need to be explored further is the pathogenesis of TE in the paediatric cancer population. Gaining knowledge in this area will assist in the development of risk stratification of patients and thus improve the outcomes of paediatric cancer patients at risk of thrombosis. These insights can also then facilitate further areas of research such as thromboprophylaxis and treatment of TEs within this population. Currently, the guidelines for thromboprophylaxis in paediatric cancer patients are unclear and thus determining the efficacy and safety of anticoagulants in sub-populations and/or specific risk groups is essential. There have also been no prospective studies that successfully evaluate the relationship between TE

and infection and this is therefore another important area that needs to be investigated.

After detailed review of the available studies that investigate TE in children with cancer, the two groups of patients that are at the highest risk of developing thrombosis are ALL patients undergoing concomitant L-asparaginase and corticosteroid therapy and the overall use of CVLs. Therefore, other treatment options for paediatric patients with ALL may need to be further investigated due to the high incidence of TEs that occur in patients subjected to this type of chemotherapy.

Other areas of research that should be explored further include studies that compare the survival rates of paediatric cancer patients who have had a TE to those who have not had a TE. This kind of information is important because it is currently not known how TE events impact the outcomes of this population. The notion that biomarkers could facilitate prediction of TEs in paediatric cancer patients is also interesting and potentially beneficial. Hence, directed studies should investigate potential biomarkers that could be used in this setting. Most of the retrospective studies examined in this review focus on TEs in children across all types of cancers whereas prospective studies have focused largely on TEs in ALL paediatric patients; therefore, there is a need for more large randomised trials that focus on the whole paediatric cancer population.

Conclusion

TE is a common complication in the paediatric oncology population, with a number of biochemical and mechanistic risk factors playing a role in development of thrombosis in this population. Accurate identification of children at high risk of thrombosis in this setting remains problematic, and prospective cohort studies and clinical trials are required to better understand the aetiology and define the risk factors. This will in turn allow for development of age-specific guidelines for risk stratification of patients and hence better directed individualised prophylaxis and treatment that will improve the outcomes of children with cancer who are at risk of thrombosis.

Conflicts of interest

None declared.

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Table 2: Outcomes for paediatric patients with VTE.

CVL-associated TE outcomes	Incidence
Infection	22–40% [8, 9]
Post-thrombotic syndrome	15–35% [8, 9]
Patients with ALL and CVLs VTE outcomes	Incidence
Recurrent VTE	4–19% [30, 46, 47]
Post-thrombotic syndrome	5–25% [30, 46, 47]
PE	8–15% [30, 46, 47]
Death	2–4.8% [30, 46, 47]

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