Thromboembolism Incidence and Risk Factors in Children with Cancer: A Population-Based Cohort Study

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Thromb Haemost 2018;118:1646–1655.

Abstract

There is conflicting information about the epidemiology of thromboembolism (TE) in paediatric oncology. Objectives were to describe the incidence and risk factors of TE in children with cancer. We included all children with cancer less than 15 years of age diagnosed from 2001 to 2016, treated at one of the 12 Canadian paediatric centres outside of Ontario and entered into the Cancer in Young People-Canada database. Potential risk factors for TE were evaluated using Cox proportional hazards regression stratified by haematological malignancies versus solid tumours. Factors associated with vascular access- and non-vascular access-related TE were compared using chi-square or Fisher's exact tests. Of the 7,471 children included, 283 experienced TE requiring medical intervention; cumulative incidence of TE at 5 years was $3.8 \pm 0.2\%$ and $0.36\% \pm 0.07\%$ for life-threatening or fatal TE. For haematological malignancies, the following factors were associated with TE in multivariable regression: age $<$ 1 year, 5 to 9.99 years and 10 to 14.99 years (relative to age 1–4.99 years), haematopoietic stem cell transplant (hazard ratio [HR] $=$ 1.49, 95% confidence interval [CI], 1.00–2.32), anthracyclines (HR $=$ 2.21, 95% CI, 1.12–4.37) and asparaginase (HR $=$ 1.68, 95% CI, 1.15–2.44). For solid tumours, obesity (HR $=$ 1.92, 95% CI, 1.01–3.68), surgery (HR $=$ 2.70, 95% CI, 1.44–5.08), radiation (HR $=$ 47.51, 95% CI, 24.01–94.01), anthracyclines (HR $=$ 2.74, 95% CI, 1.29–5.82) and platinum agents (HR $=$ 2.26, 95% CI, 1.19–4.28) were associated with TE. Life-threatening and fatal TEs were more common among non-vascular access TEs (14.5% vs. 3.3% $p = 0.001$). In a population-based cohort, 4% of children with cancer developed a clinically significant TE. Accurate risk stratification tools are needed specific to malignancy type.

Keywords
- paediatric haemostasis
- thrombosis
- cancer
- epidemiology

received
May 2, 2018
accepted after revision
July 11, 2018

DOI https://doi.org/10.1055/s-0038-1668543.
ISSN 0340-6245.

Introduction

Thromboembolism (TE) is a well-recognized complication in children and adults with cancer. TEs are associated with chronic morbidity,[1–3] delay or modification of treatment,[4] adverse events associated with anticoagulation[5] and rarely mortality.[6] While its epidemiology is well described in adult populations, many areas of uncertainty remain in understanding the incidence and risk factors of TE in children with cancer. Previous studies have reported a TE incidence of between 2.1 and 16% for symptomatic events in children with cancer, and up to 40% when accounting for asymptomatic events.[7–18]

Several risk factors have been proposed for TE in children with cancer. Previously described patient-specific factors include older age, higher body mass index (BMI), presence of thrombophilia and non-O blood group.[7,11,15,17–19] Disease and treatment-related factors include haematological malignancies and sarcomas, specific chemotherapy agents, namely, asparaginase and steroids, immobilization and surgery.[15,16,20] The presence of a central venous catheter (CVC) has been associated with thrombosis, with varying rates of TEs depending of the type of catheter used and the presence of CVC-related complications such as infection or occlusion.[8,13] Haematopoietic stem cell transplant (HSCT) has been shown to create a state of acquired thrombophilia,[21] and a recent study has shown that TEs are a clinically relevant complication of HSCT in children and young adults.[22]

Published data in children are mostly limited to single-centre, single disease retrospective studies or prospective studies consisting of children with acute lymphoblastic leukaemia (ALL).[7,8,11,13–19,22–27] A large multi-institutional study that includes all paediatric cancer types is important to improve our understanding of risk factors for TE, and to have a sufficiently large sample size allowing for robust modelling and improved precision in estimates. Therefore, our objectives were to describe the incidence of thrombosis and to identify risk factors for thrombosis among Canadian cancer patients less than 15 years of age using a population-based approach.

Materials and Methods

We conducted a retrospective, population-based study using the Cancer in Young People-Canada (CYP-C) database.

Study Population

We included patients who were: (1) less than 15 years of age at cancer diagnosis; (2) diagnosed with cancer between 1 January 2001 and 31 December 2016; (3) diagnosed with a neoplasm included in the International Classification of Childhood Cancer (ICCC), third edition;[28] and (4) diagnosed and treated at one of the 12 paediatric oncology centres in Canada outside Ontario and entered into CYP-C. ICCC includes malignant neoplasms as well as non-malignant central nervous system (CNS) tumours. We excluded patients from the five Ontario centres, whose information was provided to CYP-C from the Pediatric Oncology Group of Ontario Network Information System (POGONIS), because TE events were not collected systematically over the study period in POGONIS. Collection of data in CYP-C was approved by the Research Ethics Boards of all 12 participating sites. The Research Ethics Board at The Hospital for Sick Children approved this analysis. The requirement for informed consent was waived given the retrospective nature of the study.

Data Source

CYP-C is a population-based registry that captures all paediatric cancers diagnosed and treated in one of the 17 paediatric oncology centres of Canada for children up to 15 years of age. Almost all patients < 15 years old with cancer are treated in one of these hospitals. Application for utilization of data was submitted through the C17 Council website (available at: http://www.c17.ca/index.php?cID=70). Data are abstracted at each participating site from the medical records by trained clinical research assistants or data managers and, for the 12 centres included in this study, the data are entered directly into CYP-C. Data consist of demographics features, diagnostic details, treatment information and outcomes. Data also include specific treatment-related complications that are abstracted from the medical records. If present, grade and date of onset are recorded. Data are collected until 5 years after the primary neoplasm or any subsequent malignancies.

Multiple approaches have been taken to ensure high quality data and these approaches have been previously reported.[29] In brief, data managers meet monthly by teleconference and annually in person for education and training. Each site's data are also audited regularly.

Outcomes

The primary outcome of TE was defined as an occlusion of a blood vessel and graded using the Common Terminology Criteria for Adverse Events (CTCAE), versions 3 or 4. TEs of grade 3 to 5 were included where grade 3 refers to a TE requiring medical intervention, grade 4 refers to a TE associated with haemodynamic or neurologic instability requiring an urgent intervention and grade 5 refers to a TE leading to death. TEs were categorized as either vascular access-related, if the thrombus or embolus could be attributed to the presence of a peripheral or central catheter and had developed in the region of the catheter, or not vascular access-related. Type of catheter and method of insertion were not available; thus, all vascular access-related TEs are analysed together.

Exposure Variables

Potential risk factors for TE included age at cancer diagnosis, sex, obesity, malignancy type, diagnostic era, intensity of treatment, chemotherapy (anthracyclines, asparaginase, methotrexate, platinum agents, steroids), radiation, surgery and HSCT. In addition, we did not include race or ethnicity in the analysis. Age at cancer diagnosis was divided into four categories: less than 1 year, 1 to 4.99 years, 5 to 9.99 years and 10 to 14.99 years. BMI percentile at diagnosis was calculated for all patients 2 years or older using the World Health Organization growth reference standards for BMI z score (zBMI). Obesity was defined as BMI $>$ 99.9 percentile for age (zBMI > 3) in children 2 to 4.99 years and $>$ 97 percentile for

age (zBMI > 2) in children 5 years and above.[30] Diagnostic era was divided between 'early', if the cancer diagnosis occurred on or before 31 December 2006 and 'late' if the diagnosis was made after 31 December 2006. This date threshold, used in a previous study based on CYP-C data,[29] was retained to facilitate comparisons. Intensity of treatment was classified as per the Intensity of Treatment Rating scale (ITR-3.0),[31] a standardized and reliable method to classify intensity of cancer treatment protocols. Possible levels range from 0 to 4, from 'least' to 'most intensive' treatments. Level 2, 'moderately intensive', and 3, 'very intensive', treatments were combined, based on similarity of included diagnosis and treatment modalities. Surgery was considered as a risk factor for TE if it occurred within the preceding 30 days, based on biological evidence of activation of the coagulation system for at least 4 weeks after an operation.[32] All surgeries, regardless of the purpose of the intervention (oncological vs. non-oncological) were considered. Chemotherapy was captured as a dichotomous variable, if the patient was exposed to at least one dose of any chemotherapy agent. The exposure to any dose of the following agents was also collected, because of previously reported associations with TE:[33] anthracyclines, asparaginase (including all formulations of asparaginase), methotrexate, platinum agents and steroids. HSCT was considered a dichotomous variable. For radiation therapy, the risk window for TE started with the first day of radiation; we did not set an end date to the risk window as there is evidence that radiation-induced vascular damage is persistent.[34] Because of the systemic changes induced by radiation therapy,[34] we did not discriminate between sites of radiation therapy.

Statistical Plan

Analyses were performed on data available as of 1 August 2017. Population characteristics were summarized descriptively. Univariate and multivariable Cox proportional hazards regression analyses were performed to explore the relationship between potential predictors variables and the cumulative incidence of TE. Analyses were stratified by type of malignancy (haematological malignancies vs. solid tumours) given substantial differences in rates of exposure to treatment-related risk factors, such as surgery, radiation or specific chemotherapy agents between the two groups. Haematological malignancies included leukaemias, myeloproliferative diseases, myelodysplastic diseases and lymphomas and reticuloendothelial neoplasms. Solid tumours included intra-cranial and intra-spinal neoplasms as well as extra-cranial solid tumours (neuroblastomas and other peripheral nervous cell tumours, retinoblastomas, renal tumours, hepatic tumours, malignant bone tumours, soft tissue and extraosseous sarcomas, germ cell tumours, malignant epithelial neoplasms and other malignant tumours), as defined in ICCC.[28] Time to TE was defined as the number of days from first cancer diagnosis to occurrence of the first TE. For those without a TE, patients were censored on the date of last contact and death was considered a competing event. In the Cox proportional hazards models, surgery and radiation were treated as time-dependent covariates. Impact of these variables were described using hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). We examined Pearson's correlations coefficients to evaluate collinearity which guided multivariable models.

We performed a sub-group analysis among children with TE to compare factors associated with vascular-related and non-vascular-related events using Wilcoxon rank sum test, chi-square or Fisher's exact test, as appropriate. All tests were two-tailed with a p-value of < 0.05 considered statistically significant. All analysis were conducted using SAS (Version 9.4, Cary, North Carolina, United States).

Results

Overall, 7,471 patients were included; ►**Fig. 1** illustrates the number of potential cases identified in CYP-C, the number excluded and the reasons for exclusion. Their clinical characteristics are listed in ►**Table 1** stratified by haematological

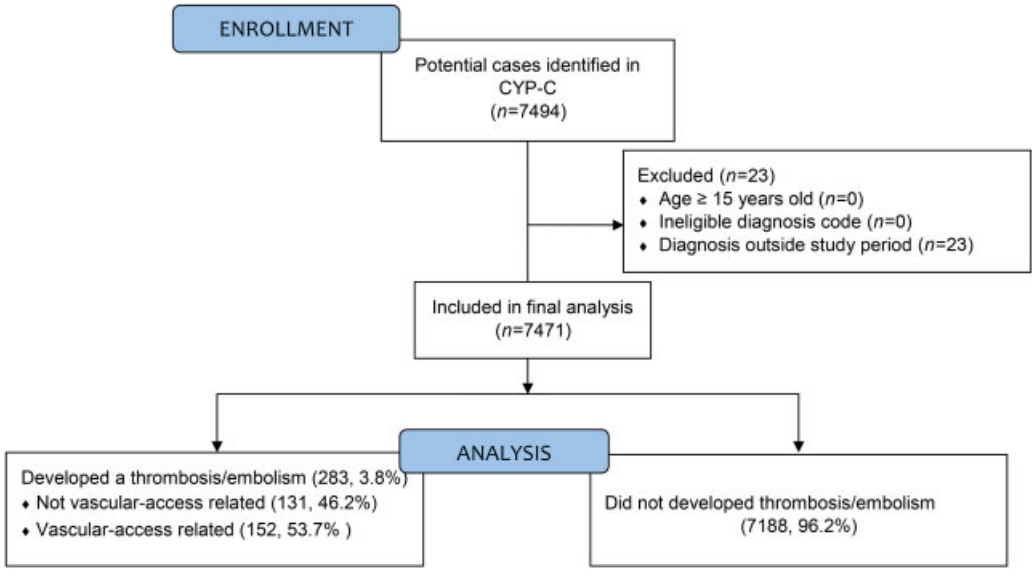

Fig. 1 Flow diagram of case identification and selection.

Table 1 Patients characteristics[a]

Characteristics	All patients *n* = 7,471 *n* (%)	Haematological malignancies *n* = 3,369 *n* (%)	Solid tumours *n* = 4,102 *n* (%)
Age, y			
Less than 1	796 (10.7)	195 (5.8)	601 (14.7)
1–4.99	2,822 (37.8)	1,378 (40.9)	1,444 (35.2)
5–9.99	1,907 (25.5)	901 (26.7)	1,006 (24.5)
10–14.99	1,946 (26.0)	895 (26.6)	1,051 (25.6)
Male sex	4,034 (54.0)	1,916 (56.9)	2,118 (51.6)
Diagnostic era			
Early	3,005 (40.2)	1,376 (40.8)	1,629 (39.7)
Late	4,466 (59.8)	1,993 (59.2)	2,473 (60.3)
Obesity at diagnosis[b]	487/5,192 (9.4)	247/2,789 (8.9)	240/2,403 (10.0)
Primary diagnosis			
Leukaemia	2,406 (32.2)	2,406 (71.4)	–
ALL	1,937 (25.9)	1,937 (57.5)	
AML	317 (4.2)	317 (9.3)	
Lymphoma	963 (12.9)	963 (28.6)	–
HD	289 (3.9)	289 (8.6)	
NHL (incl. Burkitt)	426 (5.7)	426 (12.6)	
CNS tumours	1,689 (22.6)	–	1,689 (41.2)
Astrocytoma	683 (9.1)		683 (16.7)
Ependymoma	185 (2.5)		185 (4.5)
Medulloblastoma	340 (4.6)		340 (10.1)
Extra-cranial solid tumours	2,413 (32.3)	–	2,413 (58.8)
Ewing sarcoma	121 (1.6)		121 (2.9)
Hepatoblastoma	94 (1.3)		94 (2.3)
Neuroblastoma	604 (8.1)		604 (14.7)
Osteosarcoma	166 (2.2)		166 (4.0)
Rhabdomyosarcoma	223 (3.0)		223 (5.4)
Wilms tumour	396 (5.3)		396 (9.7)
ITR			
0	305 (4.1)	111 (3.3)	194 (4.7)
1	878 (11.7)	87 (2.6)	791 (19.3)
2/3	4,927 (66.0)	2,478 (73.5)	2,449 (59.7)
4	1,361 (18.2)	693 (20.6)	668 (16.3)
Radiation therapy	2,059 (27.6)	521 (15.5)	1,538 (37.5)
Surgery	3,900 (52.2)	469 (13.9)	3,431 (83.6)
HSCT	771 (10.3)	410 (12.2)	361 (8.8)
Chemotherapy (any agents)	5,888 (78.8)	3,173 (94.2)	2,715 (66.2)
Anthracyclines	3,904 (52.3)	2,795 (83.0)	1,109 (27.0)
Asparaginase	2,116 (28.3)	2,112 (62.7)	< 5
Steroids	4,179 (55.9)	2,883 (85.6)	1,296 (31.6)
Systemic methotrexate	2,523 (33.8)	2,270 (67.4)	253 (6.2)
Platinum compounds	941 (12.6)	23 (0.7)	918 (22.4)

Abbreviations: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CNS, central nervous system; HD, Hodgkin lymphoma; HSCT, haematopoietic stem cell transplantation; ITR, Intensity Treatment Rating; NHL, non-Hodgkin lymphoma.
[a]Small cell sizes suppressed and listed as < 5.
[b]Obesity assessed in those 2 years of age and older with height and weight available at diagnosis.

malignancies versus solid tumours. The median age at diagnosis of the total cohort was 5.0 years (range: 0.0–14.9) and was similar in patients with haematological malignancies (median [range]: 5.0 years [0.0–14.9]) and solid tumours (median [range]: 5 years [0.0–14.9]). Among the entire cohort, 283 patients developed at least one TE. Most TEs were grade 3 (259, 91.5%), with 18 (6.4%) grade 4 and 6 (2.1%) grade 5. One patient was not included in cumulative incidence analyses because the date of TE was missing. The cumulative incidence of TE (± standard error [SE]) at 5 years from cancer diagnosis was 3.8 ± 0.2%. The median interval (interquartile range) between date of cancer diagnosis and development of TE was 77 days (18–166 days). The cumulative incidence (±SE) of life-threatening or fatal TE (i.e. TE grade 4 or 5) was 0.36 ± 0.07% at 5 years. Five out of the six TE-related deaths were not vascular access-related and occurred in patients older than 10 years old, with either haematological malignancies or CNS tumours.

The proportion of patients with TE was highest in children with leukaemia (135/2,406, 5.6%), lowest in children with CNS tumours (17/1,689, 1.0%) and intermediate in children with lymphomas (4.4%, 42/963) and extra-cranial solid tumours (89/2,413, 3.7%). The extra-cranial solid tumours most commonly associated with TEs were neuroblastomas ($n = 20$), nephroblastomas ($n = 19$) and osteosarcomas ($n = 14$).

Risk Factors for Thrombosis

►**Table 2** shows the results of univariate and multivariable Cox proportional hazards regression for 3,368 patients with 177 TEs among those with haematological malignancies. In univariate analysis, the following factors were significantly associated with TE: age at cancer diagnosis, HSCT, ITR, anthracyclines, asparaginase, methotrexate and steroids. A total of 580 (17.2%) patients had missing BMI values, either because they were aged < 2 years or because either weight or height at diagnosis were missing. We therefore conducted a secondary multivariable regression analysis among the 2,788 patients with available BMI data to identify whether omitting obesity would affect study results. Obesity was not significantly predictive of TE (HR, 1.27, 95% CI, 0.77–2.09) and inclusion of obesity did not affect the β coefficients for

Table 2 Risk factors for thromboembolism in haematological malignancies

	Univariate Cox regression			Multivariable Cox regression[a] ($n = 3,368$)		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Patient-related variables						
Age, y						
Less than 1	1.96	1.01–3.79	0.045	2.51	1.28–4.92	0.008
1–4.99	Ref	–	–	Ref	–	–
5–9.99	1.72	1.15–2.57	0.001	1.77	1.18–2.65	0.006
10–14.99	2.46	1.69–3.57	< 0.001	2.78	1.88–4.11	< 0.001
Sex, male versus female	0.97	0.71–1.31	0.842	0.97	0.72–1.31	0.040
Malignancy type, leukaemia versus lymphoma	1.29	0.92–1.83	0.144	–	–	–
Obesity[b]	1.52	0.94–2.46	0.089	–	–	–
Diagnostic era, late versus early	1.21	0.89–1.65	0.222	1.23	0.91–1.67	0.185
Treatment-related variables						
ITR						
0	0.22	0.03–1.55	0.130	–	–	–
1	0.23	0.03–1.70	0.150	–	–	–
2/3	Ref	–	–	–	–	–
4	1.79	1.30–2.46	< 0.001	–	–	–
HSCT	1.51	1.02–2.23	0.040	1.49	1.00–2.32	0.050
Anthracyclines	3.26	1.72–6.17	< 0.001	2.21	1.12–4.37	0.023
Asparaginase	1.58	1.13–2.21	0.007	1.68	1.15–2.44	0.008
Methotrexate	1.44	1.19–1.75	< 0.001	–	–	–
Platinum agents	1.69	0.42–6.79	0.463	1.29	0.31–5.32	0.730
Steroids	2.20	1.22–3.95	0.008	1.43	0.76–2.69	0.270

Abbreviations: CI, confidence interval; HR, hazard ratio; HSCT, haematopoietic stem cell transplant; ITR, Intensity of Treatment Rating scale.
[a]Because of collinearity, leukaemia, methotrexate and ITR were not included in the multivariable model.
[b]Obesity was not included given the high rate of missing data. It was not significantly predictive of TE and inclusion of obesity did not affect the β coefficients for the other predictor variables substantially.

the other predictor variables substantially (data not shown). Thus, obesity was omitted from the main multivariable Cox regression model. There was collinearity between the diagnosis of leukaemia and asparaginase and methotrexate ($r = 0.66$ and $r = 0.41$, respectively), between methotrexate and asparaginase and steroids ($r = 0.58$ and $r = 0.46$, respectively), and between ITR and HSCT ($r = 0.66$). Thus, leukaemia, methotrexate and ITR were not included in multivariable regression. Age < 1 year, 5 to 9.99 years and 10 to 14.99 years (relative to age, 1–4.99 years), anthracyclines, asparaginase and HSCT were significant independent positive predictors of TE in the multivariable regression.

►**Table 3** shows the results of univariate and multivariable Cox proportional hazards model regression for patients with solid tumours. Among these 4,102 patients, 106 experienced a TE. In univariate analysis, the following variables were predictive of TE: metastatic status, obesity, ITR (4 vs. 2/3), surgery, radiation, anthracyclines, methotrexate, steroids and platinum agents, while CNS tumour was protective against TE. There was collinearity between ITR and HSCT and platinum agents ($r = 0.58$ and $r = 0.43$, respectively). Thus, ITR was not included in the multivariable regression. Within the solid tumour group, we again created a secondary multivariable analysis to evaluate the effect of obesity among the 2,403 patients (66 TEs) with available BMI data. Obesity remained predictive of TE (HR, 1.92, 95% CI, 1.01–3.68). Thus, ►**Table 3** presents two multivariable models, one (Model 1) including all solid tumour patients but not including obesity and the second (Model 2) including obesity. In Model 1 multivariable analysis ($n = 4,102$), surgery, radiation, anthracyclines and platinum agents were predictive of TE. In Model 2 ($n = 2,403$), surgery, radiation, anthracyclines and platinum agents were similarly significantly associated with TE and, in addition, obesity remained significantly associated with TE.

We then further explored the relationship between TE and HSCT. Forty-five of 283 patients with TE received a HSCT (15.9%) versus 726/7,188 patients without TE (10.1%). However, thrombosis preceded HSCT in 36/45 cases (80.0%); 5/36 (13.9%) patients sustained a TE recurrence after the HSCT.

Table 3 Risk factors for thromboembolism in solid tumours

	Univariable Cox regression			Multivariable Cox regression			Multivariable Cox regression		
				Model 1–without obesity ($n = 4,102$)			Model 2–with obesity ($n = 2,403$)		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Patient-related variables									
Age, y									
Less than 1	0.88	0.48–1.62	0.687	0.90	0.47–1.73	0.758	–	–	–
1–4.99	Ref	–	–	Ref	–	–	Ref	–	–
5–9.99	0.69	0.40–1.20	0.188	0.88	0.49–1.56	0.652	1.25	0.62–2.54	0.536
10–14.99	1.19	0.75–1.88	0.465	1.13	0.67–1.92	0.651	1.53	0.78–3.03	0.219
Sex, male vs. female	0.84	0.58–1.24	0.384	0.88	0.60–1.30	0.530	0.79	0.48-1.30	0.353
Diagnostic era, late vs. early	0.98	0.67–1.44	0.917	0.92	0.61–1.37	0.667	1.02	0.61–1.71	0.928
Location, CNS vs. extra-cranial	0.28	0.16–0.46	< 0.001	0.65	0.33–1.27	0.209	0.51	0.21–1.26	0.147
Metastatic status	2.49	1.70–3.67	< 0.001	1.03	0.65–1.62	0.908	0.93	0.51–1.67	0.803
Obesity[a]	2.03	1.08–3.79	0.027	–	–	–	1.92	1.01–3.68	0.048
Treatment-related variables									
ITR									
1	0.73	0.42–1.28	0.27	–	–	–	–	–	–
2/3	Ref	–	–	–	–	–	–	–	–
4	1.7	1.09–2.63	0.02	–	–	–	–	–	–
Surgery	2.26	1.48–3.43	< 0.001	3.98	2.50–6.23	< 0.001	2.70	1.44–5.08	0.002
Radiation	61.13	38.09–98.05	< 0.001	48.40	28.60–81.89	< 0.001	47.51	24.01–94.01	< 0.001
HSCT	1.56	0.89–2.73	0.12	0.70	0.37–1.34	0.282	0.66	0.27–1.60	0.357
Anthracyclines	5.77	3.84–8.68	< 0.001	3.15	1.79–5.54	< 0.001	2.74	1.29–5.82	0.009
Methotrexate	1.72	1.33–2.23	< 0.001	1.10	0.78–1.57	0.578	1.00	0.65–1.54	0.984
Steroids	1.77	1.21–2.60	0.004	1.21	0.80–1.82	0.375	1.20	0.71–2.02	0.490
Platinum agents	3.01	2.05–4.40	< 0.001	2.13	1.29–3.52	0.003	2.26	1.19–4.28	0.013

Abbreviations: CI, confidence interval; CNS, central system nervous; HR, hazard ratio; HSCT, haematopoietic stem cell transplant; ITR, Intensity Treatment Rating scale.

[a]Obesity at time of diagnosis was determined for patients > 2 years of age with available height and weight.

Table 4 Comparison between vascular access- and non-vascular access-related thromboembolism

	Vascular access-related TE $N = 152$ *n* (%)	Non-vascular access-related TE $N = 131$ *n* (%)	*p*-Value
Median age at diagnosis, years (range)	6.7 (0.0–14.0)	7.2 (0.0–14.0)	0.413
Male sex	88 (54.3)	74 (56.5)	0.812
Diagnostic era			0.693
Early	58 (38.2)	53 (40.5)	
Late	94 (61.8)	78 (59.5)	
Primary diagnosis			0.050
Leukaemia	79 (52.0)	56 (42.8)	
Lymphoma	26 (17.1)	16 (12.2)	
CNS tumours	5 (3.3)	12 (9.2)	
Extra-cranial solid tumours	42 (27.6)	47 (35.8)	
Grade			0.001
3	147 (96.7)	112 (85.5)	
4 and 5	5 (3.3)	19 (14.5)	
Radiation	53 (34.9)	56 (42.8)	0.174
Chemotherapy	149 (98.0)	126 (96.2)	0.478
Surgery (within 30 d)	11 (7.2)	27 (20.6)	0.001
HSCT	28 (18.4)	17 (13.0)	0.212
Thrombosis recurrence	10 (6.6)	7 (5.3)	0.663

Abbreviations: CNS, central nervous system; HSCT, haematopoietic stem cell transplantation; TE, thromboembolism.

Comparison between vascular access and non-vascular access-related TE

Among all TEs, 53.7% were vascular access-related. ►**Table 4** shows the comparison between vascular access-related and non-vascular access-related TEs. Recent surgery and higher CTCAE grades of TE were associated with non-vascular access-related TEs. Nineteen recurrences of thrombosis were reported in 17 patients (recurrence rate of TE: 6.0%); recurrence risk was not different between vascular access and non-vascular access-related TE.

Discussion

In this study, approximately 4% of children less than 15 years of age diagnosed with cancer developed a clinically significant TE, of which about half were vascular access-related. TEs were most common in children with leukaemia, and least common in children with CNS tumours. In children with haematological malignancies, risk factors for TEs were younger and older age relative to age 1 to 4.99 years, HSCT and exposure to anthracyclines and asparaginase. In children with solid tumours, risk factors for TEs were obesity, surgery, radiation and exposure to anthracyclines and platinum agents.

TEs are associated with increase in morbidity and mortality, as well as increased utilization of health resources, even after consideration of cancer type and stage.[6,22,35] TEs can also delay or truncate cancer treatment[18] and lead to CVC replacements.[4] Anti-thrombotic therapy for TE is associated with adverse effects, such as increased risk of major bleeding, reported to occur between 0.3 and 24% of patients.[5] TEs can also lead to chronic morbidities, such as post-thrombotic syndrome[1] or, in the case of CNS thrombosis, neuro-developmental disabilities.[2,3] As survival rates are increasing for most paediatric cancers, prevention of long-term morbidity is gaining greater importance. While primary thromboprophylaxis has been shown to be effective in hospitalized and ambulatory adults with cancer,[36,37] these findings have not been replicated in children to date.[26,38] As emphasized in our study, the incidence of TE varies depending on factors such as age, the type of cancer and treatment-related variables, and these factors appear to vary based on the underlying malignancy type. Accurate risk stratification will help to identify patients at high risk of TE and may guide clinical decision making such as when to consider thromboprophylaxis.

Our TE cumulative incidence rate falls at the lower end of previously reported incidence of symptomatic TE (between 2 and 16%). This finding may be reflective of our stringent outcome definition, namely, TE requiring medical intervention, as well as factors specific to the Canadian paediatric oncology population, which might include the ethnic mix of patients, approaches to detection methods and cancer treatment protocols. Our incidence rate is likely to reflect the incidence rate observed in clinical settings where screening for TE in asymptomatic patients is not standard of care. However, it is possible that asymptomatic TEs may have been included in the study, if these patients received medical intervention despite the lack of symptoms.

Important inconsistencies exist in the current literature regarding TE risk factors. Several potential risk factors for TEs such as sex, diagnostic era and presence of metastatic or intra-thoracic disease had variable impact in different settings. For example, Lipay et al had identified male sex as a risk factor of TEs in cancer,[11] while another study observed a non-statistically significant increase of TEs in female HSCT recipients[22] and some studies found no impact of sex on TEs.[17,18] Our study reaffirms the contribution of certain risk factors such as older age and underlying type of malignancy.[7,11,15,17–19] In patients with haematological malignancies, TEs followed a bimodal incidence peak, with highest risk among infants and older children, compared with children 1 to 4.99 years of age. Of note, age was not significantly associated with TEs in patients in solid tumours. Given very few reports have looked specifically at children with CNS and extra-cranial solid tumours, this observation will require confirmation in other cohorts. TEs were most frequent among patients with leukaemia, and least frequent in patients with CNS tumours, although TE-related fatalities were prominent in the CNS tumour group. Likewise, surgery was a statistically significant risk factor for TE, as previously

demonstrated in cancer and non-cancer patients.[39] We observed a strong association between radiation therapy and thrombosis in children with solid tumours that has not been reported before, although radiation therapy is known to induce endothelial inflammatory pro-thrombotic process[40] leading to persistent endothelial damage.[34] In a recent report from a registry of adults with cancer, 13% of TEs occurred during or after radiation.[41]

In our population, anthracyclines, asparaginase (haematological malignancies) and platinum agents (solid tumours) were associated with TE. The pro-thrombotic biological effects of asparaginase, by depletion of natural anticoagulants,[42,43] have been well established. Anthracyclines have also been previously identified as risk factors for thrombosis.[20] Although the mechanism is not fully elucidated, anthracyclines are associated with increased expression of pro-coagulant tissue factor and exposure to phosphatidylserine[44] and increased cell-free deoxyribonucleic acid,[45] resulting in increased thrombin–anti-thrombin complexes and increased thrombin generation. To our knowledge, platinum agents have not been previously reported as risk factors for thrombosis in the paediatric population, but increased thrombotic risk is described in adult patients exposed to platinums.[33,46]

Conversely, some risk factors were not statistically significant in our population, including the influence of sex and diagnostic era.[17,27,47] Steroids, which have also been reported as a risk factor for TE in children with leukaemia,[20] were not associated with TE in multivariable Cox regression. It is possible that not only is the specific agent important in increasing the risk of TE but that combination of chemotherapeutic agents may contribute to increasing TE risk. For example, steroids have been described as more potent pro-thrombotic agents while given concurrently with asparaginase,[12] but this could not be evaluated using the available data.

Interestingly, a higher proportion of patients with TE underwent HSCT, compared with patients without TE. Exploration of the data revealed that the majority of patients sustained their first TE before their HSCT, with a substantial proportion of them experiencing a TE recurrence following HSCT. Limited evidence suggests TE is a low frequency event after paediatric HSCT,[48] despite the HSCT-induced pro-thrombotic state.[21] Our data suggest that children who were more likely to develop a TE, based on individual predisposition or treatment-related factors, did so before the HSCT.

Our results suggest that clinically relevant TE is not a rare complication of childhood cancer, and is life-threatening or fatal in almost 10% of cases. Our findings provide an important insight into epidemiology and risk factors of thrombosis because the use of a population-based database allows for unbiased reporting of risk factors and outcomes. Our study also provides important information on cancers other than ALL, that are often too rare to be evaluated in single-centre studies.

Strengths of our study includes our large and population-based sample size as well as the quality of information provided. In particular, the CYP-C database provided a unique richness of data regarding diagnostic and treatment information. Also, our outcome, namely, TEs requiring medical intervention, is clinically meaningful. Lastly, our study provides important information about TEs in cancer other than leukaemias, which has been previously addressed mostly in small and retrospective studies. However, our study must be interpreted in light of its limitations. Our study was limited by the paucity of information regarding thrombosis-related details. Another limitation is that CYP-C does not distinguish between arterial and venous TEs. While we believe that the majority of the events were venous TE, our sample may include arterial TEs. Also, other known risk factors of thrombosis such as blood group, recent immobilization or presence of an inherited thrombophilia were not available, and there was no information regarding use of anti-thrombotic agents. Therefore, it is unclear whether the incidence and low recurrence rates of TE are reflective, in part, of primary or secondary thromboprophylaxis. However, as primary thromboprophylaxis is currently not standard of care for any paediatric cancer patients, our estimates of the cumulative incidence of TE should be generalizable. Lastly, as with any database analysis, there is a risk of misclassification or miscoding of outcomes or predictor variables. However, CYP-C has pro-actively attempted to minimize such errors by extensive training of data abstracters and regular data audits.

In conclusion, approximately 4% of children less than 15 years of age diagnosed with cancer developed a clinically significant TE within 5 years. TEs were most common in children with leukaemia, and least common in children with CNS tumours. Among children with haematological malignancies, age at cancer diagnosis, anthracyclines and asparaginase were associated with TE, while obesity, radiation therapy, surgery, anthracyclines and platinum agents were risk factors of TEs in children with solid tumours. Surgery was more commonly associated with non-vascular access-related TE. Future efforts should aim towards the creation and validation of clinical prediction models to target patients at high risk of TE.

What is known about this topic?

- Thromboembolism (TE) is a well-recognized complication of cancer.
- There is conflicting information about the epidemiology of TE in children with cancer.

What does this paper add?

- The cumulative incidence at 5 years of TE requiring medical intervention was 3.8 $\pm$ 0.2% and 0.36% $\pm$ 0.07% for life-threatening or fatal TE, in a population-based study.
- In children with haematological malignancies, age, haematopoietic stem cell transplant, anthracyclines and asparaginase were associated with TE.
- In children with solid tumours, obesity, surgery, radiotherapy, anthracyclines and platinum agents were associated with TE.

Conflict of Interest
None of the authors have competing interest to disclose. Dr. Marie-Claude Pelland-Marcotte's fellowship at the Hospital for Sick Children (Toronto, Canada) was supported by Shire Endowment Fund for Training in Pediatric Hemostasis.

Acknowledgements
The authors gratefully acknowledge the contributions of study participants, the participating paediatric oncology centres, members of the Cancer in Young People in Canada (CYP-C) Management and Steering Committees, the Pediatric Oncology Group of Ontario (POGO) and the five POGO Hospital Partners. The CYP-C is fully funded by the Public Health Agency of Canada. The authors would like to thank Randy Barber, Jaskiran Kaur and Mylène Fréchette for their help.

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