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Full Length Article

Venous thromboembolism in children with Hodgkin lymphoma – A population-based study in Sweden, Finland, and Denmark

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ABSTRACT

Background: Children and adolescents with Hodgkin lymphoma (HL) are susceptible to developing venous thromboembolism (VTE) due to several predisposing factors such as cancer itself, central venous catheter use, mediastinal mass, and glucocorticoid therapy, yet reports on the topic are scarce.
Aim: To study incidence, risk factors, and treatment of VTE, and the use of thromboprophylaxis, in a retrospective clinical study on pediatric HL.
Methods: Children under 18, diagnosed with HL 2005–2019 in Sweden, Denmark, and Finland were included. Data on patient characteristics, treatment, thrombotic events and follow up were collected from patients' medical records.
Results: A total of 490 children were identified and data were assessed for 489. The cumulative 2-year incidence of VTE was 8.1 % (42/489). Older age at diagnosis ($p = 0.004$), mediastinal involvement ($p = 0.024$), and HL stage III + IV ($p = 0.036$) were significant risk factors for VTE. Children over 15 with mediastinal mass and HL stage III or IV had a 1-year cumulative incidence of VTE of 18 % and a nearly three-fold risk of developing VTE compared to all other patients (OR 2.94, 95 % CI 1.47–5.88, $p = 0.002$). The majority (39/42; 92.9 %) were treated with low-molecular-weight heparin. Four (9.5 %) patients developed post-thrombotic syndrome. Thromboprophylaxis was given to 18/489 (3.7 %) patients with HL, two of whom developed VTE.
Conclusion: VTE is a common complication in adolescents treated for HL with large tumor burden at diagnosis. Prospective studies should focus on identifying patients who would benefit from thromboprophylaxis.

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1. Introduction

Venous thromboembolism (VTE) is a well-known complication to cancer and anti-cancer therapy in both children and adults [1–4]. Symptoms of VTE vary depending on the location of the thrombosis, but typically include pain and swelling when localized in the extremities, breathing difficulties in the case of pulmonary embolism, and neurological symptoms when the sinus venous system in the central nervous system (CNS) is involved [3,5,6]. Children and young adults with Hodgkin lymphoma (HL) are susceptible to developing VTE due to known risk factors such as the prothrombotic condition of the cancer itself, central venous catheter (CVC) use, bulky disease (mediastinal bulky lymphadenopathy), and glucocorticoid (GC) treatment [4,6–8]. VTE can be life threatening and lead to treatment delays [9,10]. Chronic venous insufficiency after VTE can lead to post-thrombotic syndrome (PTS), characterized by chronic pain and swelling [11–13]. As the 5-year survival rate of HL is approaching 100 %, focus lies in adjusting treatment to reduce complications including VTE [14,15]. Previous studies on VTE in pediatric HL have reported incidences between 7.7 and 11.5 %, but these studies have included small cohorts, or focused on the population of a single institution, resulting in contradictive results regarding risk factors for VTE such as age and tumor burden [5,6,16].

Management of VTE in children and adolescents with cancer is comprised of anticoagulation with heparin (unfractionated heparin (UFH), low-molecular-weight heparin (LMWH)) or, more seldom, vitamin K antagonists (VKA) [17,18] or thrombectomy. Anticoagulants have several limitations such as subcutaneous administration (LMWH), risk for bleeding, food and drug interactions (VKA), and the need of monitoring [19,20]. Thromboprophylaxis is not routinely recommended for pediatric HL patients. Two direct oral anticoagulants (DOACs) have been approved by both European Medicines Agency and U.S. Food and Drug Administration for treatment and secondary prevention of VTE in children, thus providing an attractive alternative for primary VTE prophylaxis in the future [21–24]. However, general guidelines concerning thromboprophylaxis in pediatric HL are lacking, and initiation of VTE prophylaxis in children with HL is based on individual clinical risk factors and recommendations from adult cancer care.

Since studies on VTE in children with HL are scarce, we aimed to assess incidence, risk factors, treatment, and outcome of VTE in a large population-based cohort of children and adolescents with HL. We hypothesized that patients with older age and larger disease burden at diagnosis are at higher risk of developing VTE. Another aim was to examine the extent of the use of thromboprophylaxis in this group, and to identify which patients could benefit of VTE prophylaxis.

2. Methods

2.1. Study design

All patients under 18 years old when diagnosed with HL in Sweden, Finland and Denmark between 2005 and 2019 were eligible for the study. The International Classification of Disease (ICD-10) for HL (C81.0-C81.9) was used to identify patients from either the National Childhood Cancer Registry (Sweden and Denmark) or hospital medical records (Finland). We included all subgroups of HL described by the World Health Organization (WHO) classification of HL, including classic nodular sclerosis HL, lymphocyte rich classical HL, mixed cellularity HL, lymphocyte depleted HL, and nodular lymphocyte-predominant HL (NLPHL) [25]. All data collection and analysis were managed according to the Declaration of Helsinki and the study was approved by an Ethical Review Authority in each participating country (Sweden: 2020-00174, 2023-01174-02; Finland: 271/2019; Denmark: R-20073404).

2.2. Data collection

Data on patient characteristics (i.e. age, body mass index (BMI), pubertal status, country), details of the HL disease (e.g., date of diagnosis, stage and type of HL, mediastinal involvement, treatment, VTE prophylaxis, date of last follow-up), as well as details of the VTE (e.g., symptoms, date of VTE and diagnostic measure of the VTE, treatment, radiological/clinical follow-up and genetic predisposition to thrombosis such as Factor V Leiden and prothrombin G20210A mutations), were collected manually from patients' medical records by a local clinician or research nurse. Only radiologically verified thrombotic events were included. All data were collected between 2020 and 2022 using a standardized clinical report form.

From medical records, information on pubertal status were categorized as "not in puberty" and "in puberty/completed puberty". When information about pubertal status was missing (N = 99; 20.2 %), it was estimated based on age: girls who were eight years or younger and boys nine years or younger, were registered as "not in puberty", girls who were 13 years or older, and boys who were 14 years or older, were registered as "in/completed puberty", and all others remained as unknown pubertal status (N = 28).

As the cut offs for BMI in children differs from adults, the International Obesity Task Force (IOTF) BMI cut offs were used to assess BMI using height and weight that were obtained at start and end of treatment. Three BMI categories were used in the analyses; "underweight" (BMI below 17 kg/m^2), "normal" (BMI 17–25 kg/m^2), "overweight" (BMI above 25 kg/m^2) [26]. BMI was also transformed to standard deviation scores (SDS) to facilitate comparisons between BMI at different time points [27]. BMI could not be calculated for 24 patients at diagnosis and 97 patients at end of treatment due to missing information on height and/or weight.

Total cumulative GC doses given during the whole first line HL treatment were calculated as prednisolone equivalents [28]. Information regarding cumulative GC dose before VTE was lacking.

Reported complications due to anticoagulant treatment were described according to the International Society on Thrombosis and Haemostasis (ISTH) definition as either major bleeding (i.e. fatal or symptomatic bleeding in critical areas/organs, or hemoglobin fall of $\geq$2 g/dl (1.24 mmol/l)) or minor bleeding (i.e. all non-major bleedings) [29].

Time to VTE was assessed as the time from HL diagnosis to the date of radiological confirmation of the VTE. Patients diagnosed 0–3 days prior to HL diagnosis were registered as "0" days to VTE (N = 3). All patients who developed VTE from diagnosis to 15 days after end of therapy (EOT) were included in the group "VTE during HL treatment". All patients with symptoms leading to radiological assessment and diagnosis of VTE, such as breathing problems, swelling, redness or pain, were categorized as "symptomatic VTE". Patients who were diagnosed with VTE incidentally, for example at routine follow-up of HL, were categorized as "asymptomatic VTE". Most often, VTE was stated as "related to CVC" in medical records. In four patients, this information was missing but as the VTE was located in the same vein as the CVC, it was registered as "related to CVC" in the final analysis. Radiological definitions of VTE at follow-up were categorized as: complete response and fully resolved VTE with normal blood flow (CR), partial response with significant reduction of thrombus burden and improvement of blood flow compared to baseline imaging (PR), stable disease with no significant change of thrombus size and persistent obstruction of the blood flow (SD), or progressive disease with increased thrombus burden or new thrombus formation and worsening obstruction of blood flow (PD). Severity of PTS symptoms and time from VTE diagnosis to developing PTS were missing in medical records, hence, only the presence of PTS symptoms was reported in this study. Time to last follow-up was registered as the time from HL diagnosis to the date of last contact with a healthcare provider at the local treatment center. Missing dates for last follow-up were replaced with date for EOT for six patients.

2.3. Data analysis and statistics

The IBM Statistical Product and Service Solutions (SPSS) Statistics, version 28.0.1.0 was used for storage, management, and analysis of data. Patient characteristics were presented as categorical and continuous data and comparisons between groups were made with the Chi square test and the Mann Whitney Wilcoxon *U* test respectively, presented with two-sided *p*-values. Simple and multiple logistic regressions were used to analyze the risk factors for VTE. All independent variables (age at diagnosis, mediastinal involvement, HL stage and pubertal status) were analyzed separately to get unadjusted results (simple regression). In the multiple regression we adjusted for age and HL stage. Cumulative incidence of VTE in different HL stage groups, as well as a specific group combining the three risk factors age ≥ 15 years, HL stage III/IV, and mediastinal involvement, was estimated with 95 % confidence intervals (CI) using Kaplan Meier time-to-event analyses. Significance was determined for associations with *p*-values below 0.05.

3. Results

There were 490 children eligible for the study. Data were available for all but one individual, thus data from 489 included patients were analyzed. Descriptives of the whole cohort are presented in Table 1 and details on patients with VTE in Table 2.

3.1. VTE incidence and location

In total, 8.6 % (42/489) of the patients developed VTE, and two thirds (66.7 %, 28/42) of them had a symptomatic VTE (5.7 % of the entire cohort). The cumulative 2-year incidence of VTE was 8.1 % (95 % CI 5.7–10.5). Time to VTE is shown in Fig. 1. Median time to VTE was 62 days (interquartile range (IQR) 28–140 days); time to VTE was missing for one patient who had VTE after EOT. The majority, 83.3 % (35/42), were diagnosed with VTE during HL therapy, or within one month after EOT. Nine patients developed VTE >5 months (range 5.3–25.1 months) after HL diagnosis, of which all were off treatment (median 64 days from EOT, range 0–577 days from EOT). Among these nine patients, four presented with asymptomatic VTE and five with symptomatic VTE.

The most common location for VTE was in the upper venous system (internal jugular vein n = 14, subclavian vein n = 12). Pulmonary embolism occurred in seven patients and atrial thrombosis in five patients. Among the 29 patients with symptomatic VTE, most common symptoms were swollen extremity and/or pain (n = 18, respectively), followed by breathing difficulties (n = 7), and/or redness of the extremity (n = 4). One patient with sinus thrombosis presented with seizures. Eleven patients with VTE were asymptomatic and diagnosed at follow-up imaging for HL. Data on symptoms were missing for two patients.

3.2. Risk factors for VTE

As presented in Table 1, patients who developed VTE were older at diagnosis compared to those who did not develop VTE (15.2 ± 2.22 vs 13.74 ± 3.18, $p = 0.004$). Mediastinal involvement of any kind was more common in patients who developed VTE ($p = 0.024$). In the simple regression model presented in Table 3, the odds for developing VTE increased with 21 % with each added year of life from diagnosis (odds ratio (OR) 1.21, 95 % CI 1.05–1.39, $p = 0.007$). There were no differences in developing VTE between the four different HL stages. However, when dividing HL stages into two groups in a logistic regression analysis adjusted for age, there was two-fold higher odds for VTE in patients with more advanced HL (stage III/IV) compared to HL stage I/II (OR 2.01, 95 % CI 1.05–3.84, $p = 0.034$). Furthermore, patients aged ≥15 with HL stage III/IV and mediastinal involvement of any kind, had three-fold higher odds of developing VTE, compared to those who did not have all these risk factors at the same time (OR 2.94, 95 % CI 1.47–5.88, $p = 0.002$). The group with three combined risk factors had a cumulative 1-

Table 1
Descriptives of the cohort.

	All (N = 489)		No VTE (N = 447)		VTE (N = 42)		*P-value*[a]
	Mean	SD	Mean	SD	Mean	SD	
Age at diagnosis (years)	13.86	±3.13	13.74	±3.18	15.12	±2.22	0.004
BMI SDS at diagnosis[b]	0.26	±1.18	0.24	±1.16	0.50	±1.34	0.171

	All (N = 489)		No VTE (N = 447)		VTE (N = 42)		*P-value*[a]
	N	%	N	%	N	%	
Sex							0.165
Male	271	55.4 %	252	56.4 %	19	45.2 %	
Female	218	44.6 %	195	43.6 %	23	54.8 %	
Country							0.32
Sweden	254	51.9 %	231	51.7 %	23	54.8 %	
Denmark	113	23.1 %	107	23.9 %	6	14.3 %	
Finland	122	24.9 %	109	24.4 %	13	31.0 %	
Subtype							0.133
Nodular sclerosis	357	73.0 %	320	71.6 %	37	88.1 %	
Mixed cellularity	51	10.4 %	49	11.0 %	2	4.8 %	
NLPHL	45	9.2 %	44	9.8 %	1	2.4 %	
HL NOS	36	7.4 %	34	7.6 %	2	4.8 %	
HL stage							0.238
Stage I	36	7.4 %	35	7.8 %	1	2.4 %	
Stage II	246	50.3 %	229	51.2 %	17	40.5 %	
Stage III	100	20.4 %	88	19.7 %	12	28.6 %	
Stage IV	103	21.1 %	91	20.4 %	12	28.6 %	
N/A	4	0.8 %	4	0.9 %	0	0.0 %	
Treatment protocol							0.095
EuroNet PHL C1/C2	362	74.0 %	323	72.3 %	39	92.9 %	
GPOH 95/2002	66	13.5 %	65	14.5 %	1	2.4 %	
ABVD	23	4.7 %	22	4.9 %	1	2.4 %	
EuroNet PHL-LP1	12	2.5 %	11	2.5 %	1	2.4 %	
Other	23	4.7 %	23	5.1 %	0	0.0 %	
N/A	3	0.6 %	3	0.7 %	0	0.0 %	
GC treatment							0.153
Yes	463	94.7 %	421	94.2 %	42	100 %	
No	25	5.1 %	25	5.6 %	0	0 %	
Missing	1	0.2 %	1	0.2 %	0	0 %	
Estimated pubertal status at diagnosis							0.033
Not in puberty	112	22.9 %	108	24.2 %	4	9.5 %	
In/completed puberty	349	71.4 %	314	70.2 %	35	83.3 %	
N/A	28	5.7 %	25	5.6 %	3	7.1 %	
Mediastinal involvement							0.024
No	100	20.5 %	96	21.5 %	3	7.1 %	
Yes	385	78.7 %	347	77.6 %	39	92.9 %	
N/A	4	0.8 %	4	0.9 %	0	0.0 %	
Radiotherapy treatment							0.059
Yes	184	37.6 %	174	38.9 %	10	23.8 %	

(*continued on next page*)

Table 1 (*continued*)

	All (N = 489)		No VTE (N = 447)		VTE (N = 42)		*P-value*[a]
	N	%	N	%	N	%	
No	299	61.2 %	268	60.0 %	31	73.8 %	
N/A	6	1.2 %	5	1.1 %	1	2.4 %	
Relapse							0.812
Yes	64	13.1 %	59	13.2 %	4	9.5 %	
No	425	86.9 %	388	86.8 %	38	90.5 %	
Overall survival							0.974
Alive	477	97.5 %	436	97.5 %	41	97.6 %	
Dead	12	2.5 %	11	2.5 %	1	2.4 %	

ABVD: doxorubicin hydrochloride (adriamycin), bleomycin sulfate, vinblastine sulfate, and dacarbazine; BMI SDS: Body mass index standard deviation score; EuroNet PHL: European Network Pediatric Hodgkin Lymphoma Study Group; GC: Glucocorticoids; GPOH-HD: The *German* Society of *Pediatric* Oncology and Hematology –Hodgkin's Disease; HL: Hodgkin lymphoma; N/A: Not answered; NLPHL: Nodular lymphocyte predominant Hodgkin Lymphoma; NOS: not otherwise specified; SD: Standard deviation; VTE: Venous thromboembolism.

[a] Significance level $p < 0.05$, comparison between "No VTE" and "VTE" with Mann Whitney U or Chi^2 test.

[b] Data available for 464 patients.

year incidence of VTE of 17.9 % (95 % CI 9.47–26.33), compared to a cumulative 1-year incidence of VTE of 6.1 % (95 % CI 3.75–8.45) in all other patients (Fig. 2). The difference between these two groups was significantly different when running a log rank test ($p = 0.001$). The distribution of VTE in different HL stages and ages of the patients is visualized in Fig. 3.

Patients with VTE were more often in, or had completed, puberty compared to those with no VTE ($p = 0.033$). Furthermore, those who were in or had completed puberty had a three-fold higher risk of developing VTE (OR 3.01, 95 % CI 1.05–8.66, $p = 0.41$). There were no differences in sex, BMI SDS or HL subtype between patients with and without VTE. In the whole cohort, most patients received GC as part of HL treatment (463; 94.7 %) and all patients with VTE were treated with GC. There was no difference in risk of developing VTE between patients with and without GC treatment. Among those who were diagnosed with VTE and received radiotherapy during treatment for HL (n = 10), eight developed VTE before starting radiotherapy, one developed VTE 12 days prior to EOT, and one was diagnosed with VTE 394 days after EOT.

In 24/42 (57.1 %) patients, VTE was related to the CVC, missing information for nine patients.

3.3. VTE management and follow-up

The most common method for diagnosing VTE was ultrasound, followed by computed tomography, angiography, and magnetic resonance imaging, as presented in Table 2.

There were implications to HL treatment due to VTE in 12/42 (28.6 %) patients. Five (11.9 %) patients needed a removal of CVC and treatment was delayed in four (9.5 %) patients (missing data for type of implication in three patients).

Thrombophilia investigation for Factor V Leiden G1691A and prothrombin G20210A mutations was carried out, in 27/42 (64.3 %) patients with thrombosis. As seen in Table 2, abnormal results were shown in seven patients, four with Factor V Leiden mutation (two heterozygous, two homozygous) and three with prothrombin mutation (all heterozygous).

VTE treatment with LMWH was initiated for 39/42 (92.9 %) patients. Duration of LMWH treatment varied between four days and six months, with 15 patients receiving LMWH for ≤3 months, 13 patients for 4–6 months and one patient continued treatment for one year

Table 2
Descriptives of patients with venous thromboembolism (VTE).

	All VTE patients (N = 42)
	Median (IQR)
Time to VTE (days)[a]	62 (28–140)
Time to last follow-up (years)	5 (2.8–8.1)

		All VTE patients	
		N (42)	%
VTE prophylaxis	Yes	2	4.8 %
	No	40	95.2 %
VTE during HL treatment[b]	Yes	35	83.3 %
	No	7	16.7 %
Symptoms of VTE[c]	Yes	29	69.0 %
	No	11	26.2 %
	N/A	2	4.8 %
Diagnostic method	Ultrasound	26	61.9 %
	Computed tomography	11	26.2 %
	Magnetic resonance imaging	1	2.4 %
	Angiography	3	7.1 %
	N/A	1	2.4 %
VTE related to CVC	Yes	24	57.1 %
	No	9	21.4 %
	N/A	9	21.4 %
Change of CVC	Yes	17	40.5 %
	No	25	59.5 %
Treatment modification due to VTE	Yes	12	28.6 %
	No	29	69.0 %
	N/A	1	2.4 %
Ongoing antibiotics	Yes	16	38.1 %
	No	21	50.0 %
	N/A	5	11.9 %
Thrombophilia investigation[c]	Factor V Leiden mutation	4	9.5 %
	Prothrombin G20210A mutation	3	7.1 %
	No factor V Leiden/Prothrombin G20210A mutation	20	47.6 %
	Not evaluated	11	26.2 %
	N/A	4	9.5 %
LMWH treatment for VTE	Yes	39	92.9 %
	No	3	7.1 %
Status at last follow-up	Complete regression	28	66.7 %
	Progression	2	4.8 %
	Partial regression	5	11.9 %
	No change	4	9.5 %
	N/A	3	7.1 %
Post-thrombotic syndrome	Yes	4	9.5 %
	No	36	85.7 %
	N/A	2	4.8 %

HL: Hodgkin lymphoma, CVC: central venous catheter, LMWH: Low molecular weight heparin, N/A: not answered.

[a] Data available for 41 patients.
[b] All VTE from diagnosis of HL to one month after end of HL treatment.
[c] Percentage adds up to 99.9 % due to rounding off.

(missing data n = 9). Of the three patients who were not treated with anticoagulation, one was asymptomatic (VTE in vena iliaca interna), one was first misdiagnosed as pneumonia, and one was treated for a VTE in the left atrium only with removal of CVC. Anticoagulation treatment was well tolerated. Only one patient experienced minor nose bleeding as a complication to the anticoagulation treatment.

Median time to last clinical follow-up was 5 years (IQR 2.8–8.1 years). At radiological follow-up of the VTE, 33 (78.6 %) patients had partial or complete resolution of the thrombosis, four (9.5 %) had no change, and in two (4.8 %) patients the thrombosis had progressed (missing data n = 3). Four (9.5 %) of the 42 patients with VTE developed PTS with symptoms of edema and chronic pain in upper or lower extremities. Four (9.5 %) patients with VTE relapsed 0.2–6.6 years after EOT, which did not differ from the number of relapses in those without VTE. One patient with VTE died of unknown cause at two years after treatment. There were no reported recurrent VTEs.

3.4. Thromboprophylaxis

In the whole cohort, thromboprophylaxis with LMWH was given to 3.7 % (18/489) of the patients. Reasons stated for thromboprophylaxis were bulky tumor (n = 12), smoking, family history for thrombosis, known factor V Leiden mutation, and treatment at intensive care unit. Two of the patients who received thromboprophylaxis, one with Factor V Leiden mutation (heterozygous), and one with bulky tumor, developed VTE. There were no reported complications due to VTE prophylaxis.

4. Discussion

In this retrospective, observational cohort study, we found a crude VTE incidence of 8.6 % in 489 children treated for HL between 2005 and 2019 in Sweden, Finland, and Denmark. We identified adolescents 15 years and older with advanced stage HL and mediastinal involvement as a high-risk group for VTE, with a one-year cumulative incidence of VTE of nearly 18 %. The majority of patients with VTE were treated with LMWH (92.9 %) with no severe complications. However, almost 10 % of the patients with VTE experienced delayed HL treatment and developed PTS, respectively. Thromboprophylaxis in patients with HL was uncommon and two patients developed VTE despite prophylaxis.

Most studies reporting on VTE in pediatric cancer include several types of malignancies in the same cohort [1,30–36]. Other studies focus mainly on VTE in pediatric acute lymphoblastic leukemia (ALL), and even though both ALL and HL treatment contain high doses of GC, a major thrombotic risk factor in ALL is the exposure to asparaginase [36–40]. Older age is a known risk factor for VTE in children with ALL [36,41], who are generally younger than the most often adolescent patients with HL. Only a few studies report on VTE specifically in children with HL and the incidence has varied from 7.7 % to 11.5 % [5,6,16,42,43]. Schönning et al. reported a crude incidence of VTE of 7.7 % in a cohort of 163 Swedish HL patients under 18 years of age, partially overlapping with the current study cohort [5]. Athale et al. presented a VTE incidence of 11.5 % in 52 HL patients, among 75 children (<18 years old) with lymphoma [6]. In a retrospective study on CVC complications, van den Bosch found catheter-associated thrombosis in 10 % of the 98 included patients under 15 years with HL [42]. In a single-center study including 330 patients under 21 years of age with

Table 3
Analysis of risk factors for venous thromboembolism.

	Unadjusted			Adjusted		
	OR	95 % CI	*P-value*[a]	OR	95 % CI	*P-value*[a]
Age at diagnosis	1.21	1.05–1.39	0.007	1.21	1.05–1.39	0.007
HL stage III + IV	1.97	1.04–3.73	0.038	2.01	1.05–3.84	0.034
Mediastinal involvement	3.65	1.10–12.05	0.034		–	
During/ completed puberty	3.01	1.05–8.66	0.041		–	
Age ≥ 15, HL stage III + IV, and mediastinal involvement	2.94	1.47–5.88	0.002		–	

Unadjusted results analyzed with simple logistic regression. Adjusted results analyzed with multiple logistic regression.
[a] Significance level $p < 0.05$; HL stage: Hodgkin lymphoma disease stage; OR: odds ratio; CI: confidence interval.

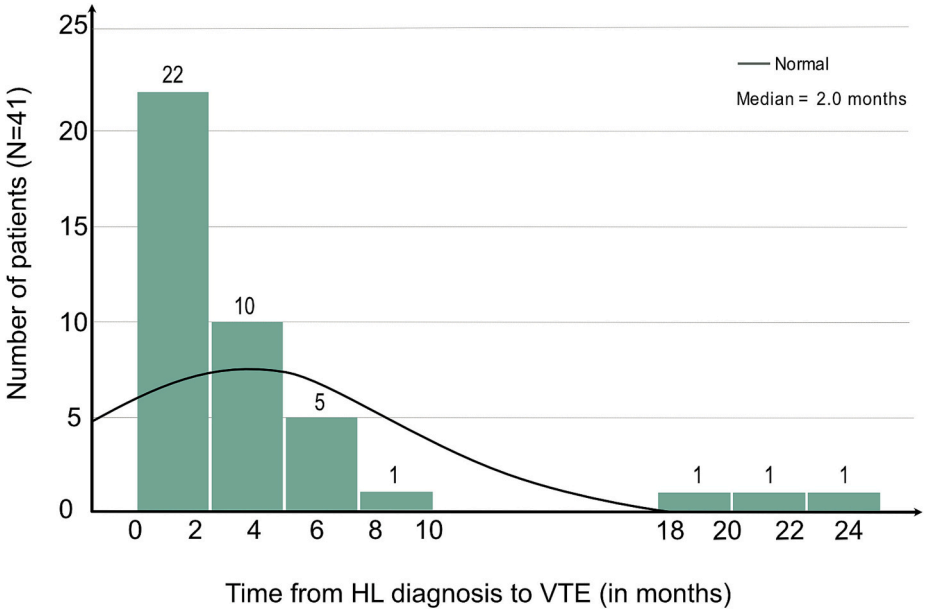

Fig. 1. Time to VTE.

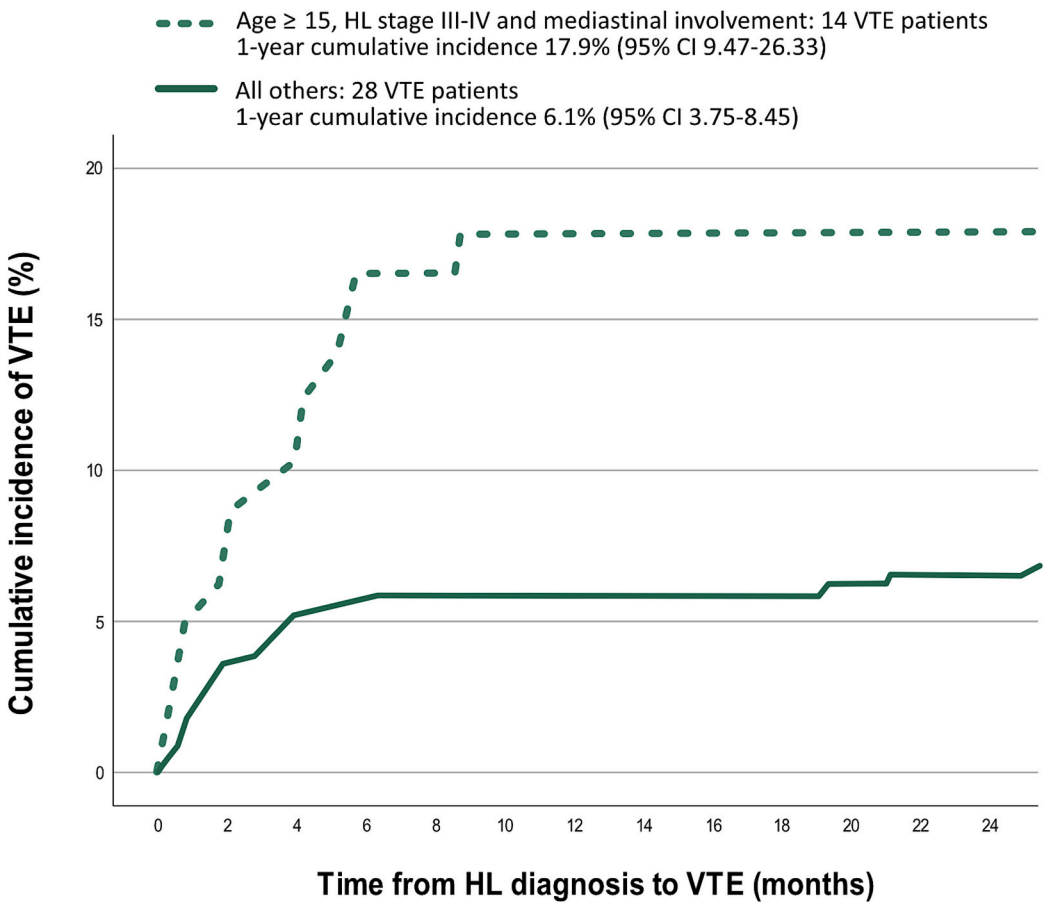

Fig. 2. Cumulative incidence of VTE in the specific risk group "Age ≥ 15, HL stage III-IV and mediastinal involvement".

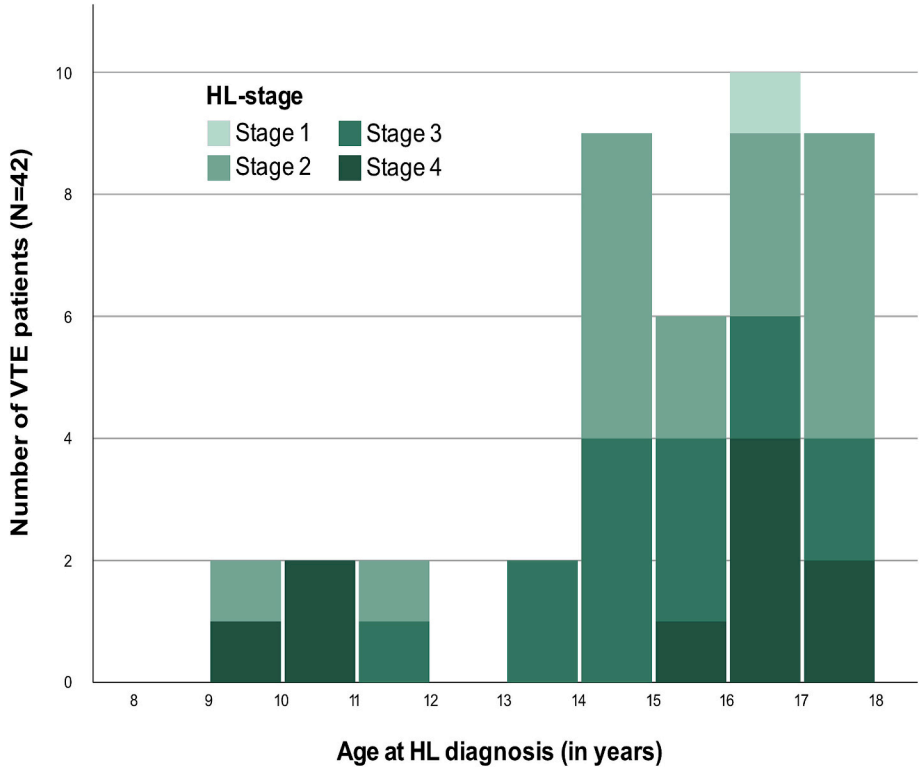

Fig. 3. Distribution of VTE in different HL stages and ages of the patients.

non-lymphoblastic lymphoma, Gartrell et al. reported a VTE incidence similar to ours, 8.7 %, among 228 patients with HL [16]. Adult studies on VTE and HL are more common [2,10,44,45]. Two large adult studies from USA and Germany have reported a considerably lower VTE incidence, of 4.6 % and 3 %, respectively [2,45]. However, these studies were based on toxicity reports, with considerable risks of lacking data. Also, the treatment protocols differed from those used in this study, especially when it comes to the inclusion of steroids. In a recently published paper, Kendel et al. retrospectively studied 3034 patients aged 0–39 years with HL, and found that 5.9 % (178/3034) developed VTE in the whole group, and the incidence was higher, 7.5 % (132/1759) in the age group 15–39 years [43].

Identified risk factors for VTE in this study were older age, advanced HL stage, being in or after puberty and mediastinal involvement. Mediastinal lymphadenopathy was presented as a risk factor for VTE in the study by Athale et al., however they did not clearly define the criteria used for mediastinal involvement [6]. A study on adult patients with HL by Borchman et al. showed that large mediastinal involvement was not a risk factor for VTE [2]. Furthermore, Gartrell et al., did not identify mediastinal involvement as a risk factor for VTE in their study on patients with non-lymphoblastic lymphoma, and rather found that vena cava compression of >25 % was twice as common in patients who developed VTE, compared to those with <25 % vena cava compression (14 % vs 7 %) [16]. Perhaps compression of large veins could be of more importance in the development in VTE than the size of mediastinal mass, and a risk factor to consider when making decisions about prophylactic anticoagulation treatment.

In line with our study, studies by Gartrell et al. and Kendel et al. found higher age at diagnosis was a risk factor for VTE [16,43]. Even though obesity is a documented risk factor for VTE, especially in adults [46–48], higher BMI at diagnosis was not a risk factor in our study, which is supported by results from the study by Gartrell et al. This may be due to other competing risk factors, and that relatively few patients in our cohort were obese.

In the present study, more than half of the patients with VTE were tested for thrombophilia on clinical basis, and seven (27 %) of them showed abnormal results, which was more than expected compared to the general population. Yet, thrombosis in patients with cancer is often caused by acquired risk factors and there is no evidence to support routine genetic screening in children with VTE and cancer, especially in CVC-related VTEs [49,50]. American Society of Hematology 2023 guidelines recommend thrombophilia testing for ambulatory patients with cancer receiving systemic therapy, and thromboprophylaxis for patients with thrombophilia [51]. Thrombosis is more common in adults than in children, and the incidence increases in puberty, as demonstrated in our cohort [3]. In the light of current knowledge and evidence, we recommend genetic testing based on clinical judgement primarily in patients diagnosed with cancer and VTE who have a family history of VTE [51].

Most patients with VTE in this study were treated with LMWH for three months or less, in line with current recommendations on VTE management in children [19]. Longer treatment can, however, be considered if the patient has active malignancy or if the CVC is still in place [52]. Treatment with LMWH was safe with no complications other than one minor bleeding.

Bleeding is the main complication of anticoagulation therapy in patients with cancer, which affects decisions concerning prophylactic treatment [53]. For adults, there are predictive models for chemotherapy induced VTE in outpatients, including factors such as obesity, abnormal laboratory results at diagnosis, and tumor site. There are also recommendations for prophylactic anticoagulation treatment in patients with cancer who are immobilized or undergoing surgery [54,55]. No such guidelines exist for children with cancer, and few studies have shown that LMWH and VKA can be effective and safe measures to reduce the risk of CVC-induced VTE [56,57]. Furthermore, recent studies have not been able to prove that CVC-induced VTE is frequent enough to motivate prophylactic treatment with LMWH or VKA [58–60]. As the VTE cohort in the present study was small and lacking details on the indications for prophylactic treatment, we could not identify any specific patient group that would benefit from thromboprophylaxis. However, our results, in combination with adult experiences, support that HL patients with older age, more advance disease and mediastinal mass should be considered for VTE prophylaxis, especially in case of additional risk factors such as i.e. long-term immobilization and extensive surgery.

There are, however, many challenges with LMWH treatment in children, especially subcutaneous administration [61]. For these reasons, new emerging treatments, such as DOACs are seen as potential and preferred substitutes. In adult patients with VTE and non-gastrointestinal malignancies, DOACs have shown similar results on the effect on recurrent VTE and bleedings as LMWH [62–64]. Current recommendations now state that both prophylaxis and treatment with DOACs can be offered to adults with cancer, however the choice of anticoagulant should be based on the type of cancer and risk of bleeding as well as drug/drug interactions [65]. In recent years, studies on DOACs have also come to include pediatric populations [66–71], and the U.S Food and Drug Administration has approved rivaroxaban and dabigatran for treatment of VTE and secondary prevention in children [21]. However, a recent randomized, controlled study on 512 children with ALL and lymphoblastic lymphoma, could not show any statistically significant treatment benefit of receiving VTE prophylaxis with another DOAC, apixaban, compared to no anticoagulation treatment [69]. Furthermore, in the mentioned study, both minor and clinically relevant non-major bleedings were more common in patients receiving apixaban.

The main strength of this study is the population-based approach where we have included all but one pediatric HL patient in three Nordic countries during the study period, eliminating selection bias. Furthermore, health care systems and treatment regimens used in Sweden, Finland and Denmark were similar and the majority GC based. Despite the retrospective design, information bias was limited due to data collection conducted by trained professionals. Our data is however susceptible to e.g. change in reporting routines over time, transition from paper to electronic medical records and national legislation on requirements for reporting in medical records, resulting in missing detailed information of the mediastinal mass and BMI data for a proportion of patients. Furthermore, GC doses were based on the whole treatment period and the information about doses until development of VTE were not available. Also, this study did not include any data on vessel compression. Lastly, as this was conducted as a retrospective study with no standard VTE prophylaxis given to the patients, it is not possible to estimate numbers needed to treat with prophylactic anticoagulation.

In conclusion, we show that VTE in pediatric HL is common in adolescents with advanced stage HL and mediastinal involvement. As there are limited studies exploring VTE in pediatric HL, the current study adds new and important data, relevant for future studies on prophylactic VTE treatment and HL protocol development. Future studies should aim at evaluating the efficacy and safety of both first line treatment and prophylactic anticoagulation therapy with DOACs in randomized, controlled settings, preferably focusing on adolescents with high stage HL.

CRediT authorship contribution statement

Mia Giertz: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Henri Aarnivala:** Writing – review & editing, Validation, Project administration, Methodology, Investigation, Conceptualization. **Sascha W. Michelsen:** Writing – review & editing, Project administration, Methodology, Investigation. **Caroline Björklund:** Writing – review & editing, Investigation. **Marika Grönroos:** Writing – review & editing, Investigation. **Lisa L. Hjalgrim:** Writing – review & editing, Funding acquisition. **Pasi Huttunen:** Writing – review & editing, Investigation. **Riitta Niinimäki:** Writing – review & editing, Supervision, Conceptualization. **Tuuli Pöyhönen:** Writing – review & editing, Investigation. **Päivi Raittinen:** Writing – review & editing, Investigation. **Susanna Ranta:** Writing – review & editing, Investigation, Conceptualization. **Johan E. Svahn:** Writing – review & editing, Investigation. **Lisa Törnudd:** Writing – review & editing, Investigation. **Annika Englund:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Arja Harila:** Writing – review & editing, Validation, Supervision, Resources, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2025.109287.

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