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RESEARCH ARTICLE

Sequelae and post-thrombotic syndrome after venous thromboembolism in acute lymphoblastic leukemia survivors treated on the NOPHO ALL2008 protocol

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Abstract

The treatment of acute lymphoblastic leukemia (ALL) is frequently complicated by toxicity, including venous thromboembolism (VTE) affecting roughly 8% of patients. VTE can lead to post-thrombotic syndrome (PTS), a group of signs and symptoms developed as a complication to deep venous thrombosis (DVT), imposing risk of permanent disability and reduced quality of life (QoL). PTS prevalence ranges from 0% to 70%, reflecting very heterogenous cohorts and assessment tools. We aimed to estimate sequelae, including PTS and QoL in children and adults (<45 years old) who had a DVT during ALL treatment. PTS and QoL scores were obtained through use of Villalta and Modified Villalta Scale, PedsQL, and Short Form-36 questionnaires. The cohort comprised 20 children (<18 years) and seven adults (median age: 12.9 years, range: 2–44 years) at the time of DVT diagnosis. In total, 25 ALL survivors underwent PTS examination. The examination took place when survivors were 7–48 years (median age: 20.3 years, median follow-up time 6.8 years). QoL was assessed correlating cases with three matching ALL survivors without VTE. Two adults (15.4%) showed mild or moderate PTS. Eight children (66.7%) were diagnosed with mild PTS, while three cases had collaterals as sole symptoms. Pain or symptoms affecting daily life were reported

Abbreviations: ALL, acute lymphoblastic leukemia; CVL, central venous line; DVT, deep venous thrombosis; mVS, Modified Villalta Scale; NOPHO, Nordic Society of Pediatric Hematology and Oncology; PE, pulmonary embolism; PTS, post-thrombotic syndrome; QoL, quality of life; VS, Villalta Scale; VTE, venous thromboembolism.

by 16%. No difference in QoL was found ($p = .9$). This study underscores the need for comprehensive population-based investigations with validation of PTS instruments in ALL survivors.

1 | INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common cancer in children. The treatment is effective and survival rates are high.[1–3] Anti-leukemic therapies carry significant risks of acute and long-term toxicities, which adversely may affect the physical and mental well-being of patients during and after treatment.[4,5] PEG-asparaginase, a key component of ALL treatment, has been associated with an increased risk of venous thromboembolism (VTE) due to its effect on asparagine levels. Reduced serum asparagine levels can disrupt hepatic protein synthesis, affecting blood coagulation proteins. This imbalance, primarily characterized by a reduction in antithrombin III, diminishes anticoagulant and fibrinolytic factors while elevating pro-coagulant factors, resulting in heightened thrombin formation and an elevated risk of blood clot formation.[6–10] Factors such as PEG-asparaginase, glucocorticoids, central venous lines (CVL), immobilization, the leukemia itself, and endothelial dysfunction are contributors to the increased risk of VTE during treatment for ALL.[11–14] VTE includes deep venous thrombosis (DVT), pulmonary embolism (PE), and cerebral sinus venous thrombosis (CSVT).[15,16] Rank et al. reported a risk of VTE of 7.9% after 2.5 years of follow-up in 1- to 45-year-old patients with ALL treated on the Nordic Society of Pediatric Hematology and Oncology (NOPHO) ALL2008 protocol. Thus, VTE is one of the most frequent toxicities during treatment for ALL, and more frequent in ALL compared with other pediatric cancers.[17,18]

Post-thrombotic syndrome (PTS) is a condition with varying degrees of venous insufficiency[19] and the most common long-term complication of DVT.[20–22] It is a burdensome condition where patients can experience chronic pain, edema, and heaviness of affected limb.[23,24] All potentially leading to severe disability and poor quality of life (QoL),[23,25] particularly in children who have a substantial portion of their lifespan ahead. The existing evidence presents small study-cohorts and very heterogeneous groups of patients.[24,26–28] The literature suggests that age, body mass index, proximal DVT, infection, and increased levels of inflammation markers at the time of DVT are all associated with the risk of developing PTS.[21,22,24]

The reported prevalence of PTS has shown significant variability, spanning from 0% to 70% in published studies. These studies typically encompass individuals across various age groups with diverse underlying medical conditions,[24,29,30] underscoring the limited research in children and adolescents in general, and specifically in pediatric ALL survivors. Additionally, only a very limited number of investigations have specifically examined the sequelae and incidence of PTS in survivors who were diagnosed with DVT during treatment for ALL. Furthermore, there are even fewer studies that utilize grading scales to assess the severity of PTS in this patient population.[21]

The observed variation in incidence underscores the pressing need for further research dedicated to exploring PTS in survivors who have experienced VTE as a result of their ALL diagnosis and treatment.[31]

The objective of this study was to elucidate the characteristics, occurrence, and severity of complications arising from DVT, which included PTS and QoL, in survivors who developed DVT while undergoing anti-leukemic therapy as per the NOPHO ALL2008 protocol. The main aim was to provide insights that could aid healthcare practitioners in effectively communicating with survivors and their parents or caregivers regarding potential complications associated with DVT during ALL treatment. Additionally, the research sought to underscore the significance of tailored follow-up care for the subset of survivors who experienced treatment-related DVT.

2 | METHODS

2.1 | Design and participants

This study employed a cohort study design and included survivors who were previously diagnosed with Philadelphia chromosome-negative ALL, and received treatment according to the NOPHO ALL2008 protocol from 2008 to 2020. This protocol covered individuals aged 1.0–45.0 years at the time of their ALL diagnosis. Cases were diagnosed with DVT during their treatment, while the controls did not experience DVT during their ALL treatment. Ultrasound was utilized in cases where DVT was suspected, leading to the confirmation of diagnosis. The cases received treatment in Denmark, Iceland, Lithuania, Estonia, or Norway. All controls were treated in Denmark and participated in the ongoing Danish ALL-STAR study[32] about late effects and QoL after treatment on the NOPHO ALL2008 protocol, and thus a collaboration about QoL was established. The diagnosis of DVT adhered to the criteria outlined by the Ponte di Legno Consensus Definitions of severe acute toxicities.[33] To be included, survivors had to be alive, available for examination, and meet the aforementioned criteria. DVT were categorized as "lower" if the involvement encompassed lower extremity or pelvic vessels, and "upper" if it related to atrial, upper extremity, or neck vessels. Identification of eligible cases was carried out using the NOPHO database, and additionally involving researchers within NOPHO who had published relevant thromboembolism data about survivors diagnosed with DVT before 2016 ($n = 14$).[13] Ethical guidelines were adhered to in contacting survivors, obtaining informed consent during or before clinic visits, or through mail correspondence. Tailored information was provided to adolescents aged 15–17.

Demographic information, characteristics of ALL, and treatment details were gathered from the NOPHO database. Further specific

TABLE 1 Villalta Scale[56] and Modified Villalta Scale.[24]

	Modified Villata Scale <18 years	Villalta Scale ≥18
Symptoms		
Pain	0–1	0–3
Abnormal use	0–1	
Swelling	0–1	
Cramps		0–3
Heaviness		0–3
Parastesia		0–3
Pruritus		0–3
Signs		
Edema	0–1	0–3
Skin induration		0–3
Hyperpigmentation		0–3
Change in skin color	0–1	
Pain during calf compression	0–1	0–3
Venous ectasia		0–3
Redness		0–3
Increase in limb circumference (>3%)	0–1	
Edema of the head	0–1	
Varicosities	0–1	
Venous ulcer	0 or 8	
Collaterals	0–1	

Note: Villalta Scale for individuals aged 18 years and above. Ratings ranged from none (0 points) to severe (3 points), while mild and moderate were assigned 1 and 2 points, respectively. The Modified Villalta Scale was applied to survivors under 18 years of age. Ratings indicated presence (1 point) or absence (0 points) of findings. The presence of a venous ulcer added 8 points to the score. Diagnosis of post-thrombotic syndrome (PTS): Villalta Scale score 0—4 = no PTS; 5—14 = mild PTS; ≥15 or presence of ulcer = severe PTS. Modified Villalta Scale: 0 = no PTS; 1—3 = mild PTS; 4—8 = moderate PTS; >8 = severe PTS.

data, including age at DVT diagnosis and occurrences of recurrent DVT, were extracted from patient charts or previously collected data.

2.2 | Outcomes

2.2.1 | Post-thrombotic syndrome

PTS can be diagnosed according to various scoring tools.[23,24] In this study, adults (≥18 years) were evaluated by means of Villalta Scale (VS).[34] Ratings ranged from none (0 points) to severe (3 points), while mild and moderate were assigned 1 and 2 points, respectively. A VS of 5–9 was denoted mild, 10—14 moderate, and ≥15 severe PTS (Table 1).

PTS in children (<18 years) was assessed by Modified Villalta Scale (mVS). Ratings indicated presence (1 point) or absence (0 points) of findings. The presence of a venous ulcer added 8 points to the score. A mVS of 1—3 indicated mild, 4—8 was classified as moderate PTS, and scores greater than 8 were categorized as severe PTS (Table 1). Examinations were conducted by clinicians responsible for the study or clinicians at the treating centers after thorough introduction to the examination tool and approach. Following VS and mVS guidelines, the examination included inquiries about pain and limb functionality, along with a physical assessment involving skin inspection, clinical evaluation, and limb circumference measurements on both affected and collateral limbs. Circumference measurements were obtained at the mid-thigh (at a midpoint between the anterior superior iliac spine and the tibial tuberosity in a fully extended and relaxed limb),[35,36] midpoint-calf (halfway between the tibial tuberosity and ankle), midpoint-forearm (halfway between the elbow and wrist), and mid-upper arm (mid-length of the humerus in a fully extended relaxed limb).[37]

2.2.2 | Phenotype of sequelae and subsequent thrombosis

All participating survivors underwent evaluation using a validated tool (VS or mVS). Additionally, they were questioned about any occurrences of subsequent thrombosis or any suspicions leading to medical evaluation. In the case of adult survivors, examinations for collaterals and circumference were performed, even though they did not contribute points to the VS.

2.2.3 | Quality of life

Survivor, parents, or guardians were asked to report QoL by a previously validated questionnaire Pediatric QoL inventory, version 4 (PedsQL 4.0, age adapted). For adults, a similarly validated QoL questionnaire was used; Short Form 36.[38] Both QoL questionnaires encompass distinct domains that cover various aspects, including physical, emotional, social, and school/work-related. Responses to the questions are provided on a scale ranging from "never" to "always" with options such as "almost never," "sometimes," and "often" in between. All cases and their three corresponding controls completed age-appropriate QoL questionnaires.

2.2.4 | Statistics and ethics

Descriptive statistics were employed using Stata (StataCorp. 2021, Stata Statistical Software: Release 17) to assess the phenotype of potential sequalae from DVT, risk of subsequent thrombosis, incidence, and severity of PTS. For QoL analysis, each case was paired with three controls. Random matching was conducted within the same age group, allowing for a maximum age difference of 1 year at the time of assessment. Optimal matches were further selected based on the duration since ALL diagnosis, ensuring the closest possible correspondence between cases and their respective controls. Subsequently, *t*-test and conditional logistic regression were employed to compare individual

cases with a group of three matched controls, both within the entire cohort and within three specific age groups. Significance was defined as $p < .05$.

All data management adhered to Good Clinical Practice guidelines. Prior to study initiation, approval was obtained from the Scientific Ethics Committee (N1-10-72-163-20). Informed consent was obtained from all participants or their caregivers, and the study consistently upheld the principles outlined in the Helsinki Declaration throughout its duration.

3 | RESULTS

We examined 27 survivors diagnosed with DVT during the NOPHO ALL2008 protocol, representing 41.8% of eligible survivors. Almost all survivors (25/27, 92.6%) completed the PTS examination, and their details are outlined in Table 2. Median age at PTS assessment was 21.9 years (range: 7–48), including 13 adults and 12 children (10 females, seven males). DVT was diagnosed at a median age of 12.9 years (range: 2–44), with assessments conducted after a median of 6.9 years from ALL diagnosis. Predominantly upper DVT related to CVL (64%), 12% lower extremity DVT, and 12% had DVT in multiple locations. Thrombophilia was investigated in 11 patients. One patient was found heterozygote for factor V Leiden mutation (Table 2).

3.1 | Post-thrombotic syndrome

Among the 25 survivors who underwent PTS assessment and were evaluated using the VS or mVS, eight children and two adults met the defined point threshold for a PTS diagnosis, accounting for 40% (95% CI: 22.4%–57.1%) of all cases.

In the pediatric subgroup, which included 12 survivors, eight had a PTS score ≥1, which indicated the presence of PTS at a rate of 66.7% (95% CI: 44.4–86.3). All eight pediatric survivors had mild PTS. The most prevalent sign on the mVS was the presence of collaterals, which was observed in six pediatric survivors (75%) of whom three experienced collaterals as their sole symptom, while one survivor had a change in skin color without reporting any additional symptoms (PTS score = 1). Additionally, two pediatric survivors with collaterals experienced pain associated with exercise, and one of them also experienced pain even when not exercising. Furthermore, one pediatric survivor exhibited both edema and increased limb circumference in conjunction with collaterals. Two pediatric survivors had an increase in limb circumference of the affected limb exceeding 3% (1 point).

Of the 13 adult survivors, four had objective signs of PTS and four reported symptoms of PTS. Signs of edema and pain on calf palpation were found in three adult survivors (23.1%). Two adult survivors had a VS ≥5 (PTS score 7 and 10), reflecting mild and moderate PTS (15.4%, 95% CI: 3.8–36.8).

Notably, none of the adults diagnosed with DVT during childhood ALL treatment accumulated any points in the PTS assessment. Among the adults who were treated for ALL at or above the age of 18, the incidence of PTS was 28.6% (95% CI: 6.6–51.9), calculated as two out of seven survivors.

3.2 | Non-point-scoring signs or symptoms and re-thrombosis

Phenotypical manifestations, which did not contribute points to the VS, included collaterals and difference in circumference. Among the adult survivors, two exhibited collaterals, and one had an increased circumference of more than 3%. Besides the assessment of PTS scoring, the study also evaluated the occurrence of subsequent thrombosis in both pediatric and adult survivors. Three cases of subsequent VTE were identified in the adult survivor cohort. The initial presentation of the first case involved lower DVT, which progressed over time. Subsequently, a PE was diagnosed 1 month later during the course of treatment. The second case developed multiple thrombi during treatment, and was diagnosed with a subsequent lower DVT 1.5 years after the initial DVT. Lastly, the third case experienced a subsequent upper DVT 6 months after the primary DVT, during a period when anticoagulation had been discontinued following completion of PEG-asparaginase treatment.

Remarkably, no pediatric survivor had been diagnosed with subsequent DVT, and only one had sought medical attention due to suspicion of subsequent DVT.

3.3 | Quality of life

QoL was assessed in 22 of 27 cases (81.5%), and each case was compared with three survivors who did not experience DVT during their treatment for ALL. This assessment was conducted using the provided QoL scoring instruments. The score from QoL had an approximately normal distribution. For both cases and controls, the QoL assessment was conducted at approximately 7 years from ALL diagnosis (cases 6.9 years and controls 7.3 years). Additionally, age at PTS examination was 21.0 years (7.0–48.1) in the case-group and 21.1 years in the control-group (6.6–49.1). The QoL score for controls was 75.9 (range: 35.9–100.0), and 76.5 points (range: 37.0–97.7) for cases. The *p*-value was .9, indicating no significant difference between the two groups. Survivors were stratified in following age groups: less than 13, 13–17, and ≥18 years. Cases aged less than 13 scored 71.5 compared to 76.1 in the controls less than 13. The mean difference was 4.6 points, with a *p*-value of .57. Among survivors aged 13–17 and ≥18, no differences (0.032 and 1.25) in scores were found (13–17: 83.3/83.2, $p = .997$; ≥18: 74.1/72.9, $p = .83$).

4 | DISCUSSION

This study aimed to explore sequalae of DVT by studying incidence and severity of PTS in 1- to 45-year-old survivors treated according to NOPHO ALL2008 protocol.

TABLE 2 Case by case PTS score.

Age		Localization				PTS	
DVT	PTS examination	Upper/lower	Thrombophilia	Signs	Symptoms	Score	Diagnosis
Years							
1.9	11.2	U[a]	0	Collaterals		1	Mild
2	10.67	U[a]	0	Collaterals		1	Mild
3.2	7.09	U[a]	N/A	Change in skin color		1	Mild
3.4	7.39	U[a]	N/A			1	Mild
4.2	11.04	U[a]	0	Collaterals		1	Mild
5.6	17.84	U	0			0	
5.9	11.83	L, bilat	0	Collaterals	Abnormal use, pain	2	Mild
6.4	16.01	U	N/A			0	
6.4	16.29	L	N/A			0	
8.1	14.05	U[a]	0	Collaterals	Pain	2	Mild
12.9	15.41	U[a]	N/A			0	
12.9	16.95	U[a]	N/A	Edema, collaterals		3	Mild
11.4	21.56	U	0			0	
12.9	25.37	U, L, PE[a]	N/A	Collaterals		0	
13.3	20.26	U[a]	1 (factor V Leiden)			0	
16.7	21.26	U[a]	0			0	
17.1	21.64	U[a]	0			0	
17.9	23.60	U[a]	0			0	
24	27.67	U[a]	N/A		Pain, cramps	2	
24.3	32.23	U[a]	N/A		[b]	0	
28.2	31.78	U**	N/A	Edema		1	
29.5	33.08	L	N/A	Edema (moderate), redness, pigmentation (moderate), pain on palpation (moderate), venous ectasia	Cramps (moderate)	10	Moderate
35.1	44.46	L, PE	N/A			0	
38.2	41.14	U[a]	N/A		Pain (moderate)	2	
43.8	48.01	U, L, PE	N/A[c]	Pain on palpation, cramps (moderate), heaviness, pruritus, collaterals	Pain (moderate)	7	Mild

Note: Patients are separated according to age at DVT diagnosis and PTS assessment. The top section represents survivors who were children at the time of DVT diagnosis and PTS assessment, the middle section represents survivors who were children at the time of DVT diagnosis but had become adults by the time of PTS assessment, and the bottom section represents survivors aged ≥18 at both the time of DVT diagnosis and PTS assessment.

Abbreviations: DVT, deep venous thrombosis; L, lower DVT (lower extremity and pelvic vessels); MC, mid-calf; MF, mid-forearm; MT, mid-thigh; MU, mid-upper arm; N/A, not investigated; PE, pulmonary embolism; PTS, post-thrombotic syndrome; U, upper DVT (atrial, upper extremity or neck vessels).

[a]Central venous line related.

[b]Atherosclerosis reported from survivor. Found on ultrasound imaging.

[c]Family history of thrombus.

**Unknown.

The incidence of PTS was 40% (95% CI: 22.4%–57.1%) depending on age. The broad confidence interval reflects the significant variability in the observed frequency. We found that adults had a lower incidence of PTS diagnosis (15.4%) compared to children (66.7%).[26,34]

PTS has been characterized as a condition with significant challenges.[23,39,40] Interestingly, the pediatric survivors in this study who had a PTS diagnosis did not seem to carry a noticeable burden. This observation was supported by the fact that the QoL scores were consistent between the group of pediatric ALL survivors with DVT and those without. Several children seemed to have moved past their initial DVT experience and did not encounter any limitations in their daily lives, despite the presence of collaterals on their skin. However,

all pediatric survivors with an mVS score ≥1 were diagnosed with mild PTS. No assessments were conducted on controls, thereby rendering it impossible to differentiate whether the observed collaterals in patients with DVT were a result of the DVT itself or from CVL in general. Conversely to children, survivors diagnosed with DVT during adulthood experienced a more pronounced impact stemming from the initial DVT. Notably, only one adult survivor reported a lack of PTS signs or symptoms associated with DVT. Overall PTS score in the adult survivors was higher compared to the pediatric survivors (1 point/child, 1.6 points/adult). A VS ≥5 has been validated to distinguish clinical meaningful PTS in adults,[34,41] which explains why fewer adult survivors received a PTS diagnosis. Six pediatric survivors had collaterals (50%) (1 point), only three of these survivors had another symptom and ended up with two or three points. Previous studies reported lower incidences of PTS in pediatric patients (5.3%[42] and 24%[26]), also highlighting low overall PTS scores and collaterals as predominant PTS symptoms. This study, as well as other studies examining PTS in children with cancer, found a lower incidence of clinical meaningful PTS (despite a potentially high PTS diagnosis rate)[26,43] compared to studies involving pediatric non-oncologic patients with PTS.[27,44,45] Upon dividing the adult survivors based on their age at the time of DVT diagnosis—distinguishing between those who were adults and those who were children during their DVT diagnosis—it appears that the burden of PTS is predominantly observed in those who were adults at the time of their DVT diagnosis. On the contrary, children who experienced DVT and were adults at the time of PTS assessment did not show any discernible PTS-related findings.

The mVS, along with the Manco–Johnson scale,[46] is frequently employed for assessing PTS in pediatric populations. However, it is important to emphasize that while these tools are commonly used, there is no universally accepted gold standard for PTS assessment in the pediatric population. The mVS was chosen for evaluation because it incorporates clinical symptoms and objective signs of PTS and has been validated in the pediatric population, primarily within cardiac conditions, demonstrating reliability in screening but some limitations in diagnostics.[36] As far as we are aware, there has been no validation of the use of mVS in children with ALL up to this point.[47] In a recent review by Jones et al., the discussion focused on defining clinically significant PTS in children.[43] The review emphasized the necessity for more sensitive and specific pediatric PTS assessment tools to precisely ascertain the clinical and functional significance of PTS in children.[43] The optimal approach to studying PTS in children is a topic of ongoing discussion, considering both the Manco–Johnson and mVS.[47–50]

Collaterals were the predominant symptoms significantly contributing to the mVS score, which is consistent with findings from other studies.[39] Notably, collaterals are not considered when assigning points on the VS, as the presence of venous ectasia is necessary for point allocation. One survivor showed venous ectasia, and nine of 25 survivors had collaterals. This suggests that collaterals could progress to venous ectasia, emphasizing the need for ongoing targeted follow-up due to the dynamic nature of venous conditions.[51]

It is worth noting that the Manco–Johnson scoring tool does not assign points to collateral symptoms, which resulted in three children in the current study not meeting the criteria for a PTS diagnosis. Additionally, most adult survivors showed PTS symptoms from DVT, but only two met formal PTS diagnosis criteria. Recent reviews highlight the need for a thorough clinical assessment beyond PTS scoring scales.[52,53]

Quality of Life was examined in a substantial portion of the cohort (22 out of 27 survivors), revealing no significant statistical disparity between survivors with ALL who experienced DVT during treatment and those who did not. This assessment utilized two well-established questionnaire tools, and all participants successfully answered all the questions. Despite the low power of analyses, no significant difference between the groups was observed. Furthermore, no notable distinctions emerged within the overall cohort or when stratified by age groups. These findings contrast with certain prior studies that have reported a correlation between PTS and diminished QoL.[39] Conversely, alternative research has indicated that QoL is significantly affected in those with moderate and severe PTS. This might explain the absence of a noticeable difference in QoL within this study, where the majority had mild PTS.[25]

The cohort examined in this study exhibits a high degree of homogeneity, as all survivors were diagnosed with ALL and treated according to same protocol. Furthermore, they all underwent comprehensive assessments for both PTS and QoL. A limitation of this study was the small sample size, rendering comprehensive statistical analyses to establish associations between risk factors and PTS development infeasible and potentially introducing selection bias. This restricts the generalization of study findings, underscoring the need for larger epidemiological studies focused on PTS in the pediatric and oncologic populations even though limited sample size is inevitable in rare diseases like ALL with uncommon toxicities like DVT. However, it was possible to observe a tendency for adults (age ≥18 at the time of DVT and PTS assessment) to have a higher burden of sequelae after their DVT, which also could be explained by the severity and location of the primary VTE.[53] This is in line with findings from Kahn et al. who identified several risk factors in adults that increase the likelihood of developing PTS.[19] The incidence of DVT during treatment may be uncertain. There were no screenings for DVT conducted within the protocol, which could lead to asymptomatic DVT cases potentially being overlooked. It is suspected that the incidence of DVT is higher among patients with T-ALL and lymphoma compared to those with B-cell ALL.[13,54,55] In addition, the increased risk of DVT in adults might also be explained by a potential decline in anticoagulant and fibrinolytic parameters associated with aging.[10]

The absence of blinding for the investigator, who possessed knowledge regarding the primary location of DVT in all cases is a limiting factor as well. This might have influenced the assessment, measurement of, for example, circumference and scoring of PTS in both directions and is a potential source of bias.

Unfortunately, the QoL analyses did not encompass all survivors, resulting in a further reduction of the sample size and introducing considerable variability. Additionally, two adult survivors lacked one of three suitable matches, whereby a single control matched in both cases, were differing more than 4 years in time since diagnosis. Despite this no significant difference in QoL score was found.

Creary et al. found fluctuation in PTS score over time.[44] In contrast, our study only assessed survivors at a single time point, with varying intervals from primary DVT to PTS assessment, potentially causing some symptoms to resolve or emerge in the future. In addition, examination assessment was designed according to VS and mVS, and no survivor was evaluated by Manco–Johnson scale subsequently.

5 | CONCLUSION

To conclude, we assessed sequalae and PTS in survivors who had DVT during treatment for ALL. Mild and moderate PTS was diagnosed in two adult survivors, and mild PTS was diagnosed in eight pediatric survivors with collaterals being the most common symptom of PTS in children. The QoL in the group of survivors with DVT during ALL treatment was similar to that of survivors without DVT.

The majority of ALL survivors receive ongoing follow-up care, emphasizing the importance of specific assessment for survivors who developed DVT during their ALL treatment. This assessment is vital for tracking any potential advancement in symptoms and signs, even in cases where only collateral blood vessels are evident.[51] Recognizing the disparity in symptom severity and PTS scoring between pediatric and adult survivors becomes crucial, especially when evaluating individuals across both age groups. Importantly, the lack of self-reported symptoms in pediatric survivors offers reassurance, aligning with the similarity in QoL scores across children, adolescents, and adults. This valuable insight can be applied in clinical settings to provide patients and/or their parents with comprehensive understanding of the potential consequences of DVT.

AUTHOR CONTRIBUTIONS

Birgitte Klug Albertsen and Ruta Tuckuviene conceived and designed the study. Merete Dam collected and analyzed data. Merete Dam, Line Stensig Lynggaard, Ruta Tuckuviene, and Birgitte Klug Albertsen wrote the manuscript, and all authors gave final approval.

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CONFLICT OF INTEREST STATEMENT

Birgitte Klug Albertsen serves on Jazz Pharmaceutical's advisory board. Kirsten Jarvis participated in a Bayer expert panel in 2021. All other authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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