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Clinical Care of Pediatric Patients with or At-Risk of Post-Thrombotic Syndrome: Guidance from the Pediatric and Neonatal Thrombosis and Haemostasis SSC of the ISTH

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Introduction

The incidence of pediatric venous thromboembolism (VTE) is rising [1–4]. Although VTE is perceived as an acute event, chronic complications such as a lack of thrombus resolution, recurrence, post-thrombotic syndrome (PTS), and post-pulmonary embolism (PE) syndrome

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are now better recognized [5,6]. PTS, a form of chronic venous insufficiency, develops in one-third of children after extremity deep venous thrombosis (DVT) [5,7–10]. PTS is clinically significant because of its impact on functioning and health-related quality of life [11].

There is scarce evidence to guide the management of pediatric PTS, resulting in heterogeneous clinical management. Additionally, the presentation of pediatric PTS is variable over time, leading to under-recognition and variation in care. This led the Post-Thrombotic Sequelae Working Group (WG) of the Scientific and Standardization Subcommittee (SSC) on Pediatric and Neonatal Thrombosis and Haemostasis within the International Society on Thrombosis and Haemostasis (ISTH) to launch a project to provide guidance on key areas related to the care of pediatric PTS. This document summarizes the available evidence on PTS risk factors, PTS evaluation tools, prevention, and the treatment of pediatric PTS to guide clinicians regarding PTS prevention and treatment for children with, or at-risk of, PTS following limb DVT.

Methods

The WG developed the document, anchored on an updated systematic review of pediatric PTS [12]. To guide the systematic review, the WG prioritized ten relevant Population, Intervention, Comparison, Outcome, and Timing (PICOT) questions (Online Supplemental, Tables 1–10). The WG selected outcomes of interest for each question *a priori*. Two WG members were assigned to each question, and a third WG member acted as a mediator for areas of disagreement. A systematic search of publications included in MEDLINE (from 1960 to 5/10/2023), EMBASE (from 1960 to 5/11/2023), and the Cochrane Library (issue 5 of 12, May 2023) was performed. The search strategy was designed in consultation with one librarian experienced in systematic reviews of medical literature. MeSH terms and search strategy terms used were as follows: “Postthrombotic Syndrome” post-thromb* OR postthromb* OR PTS AND all child OR young adults. Relevant references from the papers identified were also reviewed. Case reports, case series, review articles, and conference abstracts were excluded. Following the search, duplicates were removed. Titles and abstracts were screened for assessment against review inclusion criteria for each PICOT question. The full text of selected citations was assessed in detail against the inclusion criteria. Any disagreements that arose between the reviewers were resolved through discussion. Based on the systematic review, the WG summarized the evidence for each of the 10 questions. Lastly, based on the existing data, research priorities were drafted by the WG members.

Summary of Evidence

1. Screening and Diagnosis of Pediatric PTS

1.1 Risk Factors for Pediatric PTS: Question: What clinical and laboratory biomarkers are associated with PTS in pediatric patients with limb DVT?

Evidence Summary: Six studies were included in this question: two systematic reviews, a meta-analysis, two prospective cohorts, a cross-sectional, and a case-control study not already included in the systematic review or meta-analysis (Table 1)[8,12–16]. These studies

included 1,708 patients with extremity DVT, of whom 42% (n=709) were diagnosed with PTS. The most frequently investigated prognostic clinical factors in these studies included patient-related factors (i.e., age at diagnosis, sex, comorbidities) and thrombus-related factors (i.e., degree of thrombus burden, thrombus resolution, thrombus recurrence). In the systematic review and meta-analysis of 12 studies investigating at least one prognostic factor for PTS (n=1076; PTS=434), CVC-associated DVT (pooled OR, 1.8; 95%CI, 1.08–2.98), complete veno-occlusion (pooled OR, 1.89; 95%CI, 1.04–3.46), and residual thrombosis (largely at the end of therapy, pooled OR 2.07, 95%CI 1.4–3.07) were found to be significantly associated with developing PTS [12]. Even though CVC-associated DVT was predictive for PTS in this meta-analysis, the three largest cohorts of patients with CVC and non-CVC DVT have shown that non-CVC-associated DVT confers an approximately three fold higher risk for PTS [7,8,17]. Similarly, the cross-sectional study of children with an extremity DVT (n=150; PTS=96) identified no change or extension of thrombosis (OR 3.96, 95%CI 1.68, 9.30, p=.0016) and >1 vessel involvement (OR 2.05, 95%CI 1.52, 2.77, p<.0001) as prognostic factors for PTS development [14]. Ipsilateral DVT recurrence was significantly associated with PTS (OR 3.36, 95%CI 1.28, 8.82) in a systematic review and individual patient data meta-analysis of pediatric May-Thurner Syndrome patients (n=103; PTS=63) [13]. Longer time from the diagnosis of an extremity DVT to PTS assessment was associated with an increased risk for PTS development in a prospective cohort that included children with CVC-associated DVT (coefficient estimate 0.9, 95%CI 0.4, 1.3, p<.0001), while the cross-sectional study found that with every year of follow-up, the likelihood of having a higher PTS score increased by factor 1.22 (OR 1.22, 95%CI 1.08, 1.39, p=.0019) [8,14]. In addition, older age at the time of DVT diagnosis was associated with the development of PTS in both patients with CVC-related and non-CVC-related thrombosis (coefficient estimate [95%CI]: 0.6 [0.1, 1.2], p=.02 and 1.7 [1.0, 2.4], p<.001, respectively) [8]. Lastly, an analysis of plasma biospecimens collected 6 weeks and 3 months after acute thrombosis in 79 children aged 0–21 years (only 7.5% of the patients were ≥19 years old) found that fibrinolytic activity and serum amyloid A could be potential predictors of PTS development in children [16].

Some of the key challenges in included studies and understanding of the prognostic factors for pediatric PTS include the heterogeneity of the study designs, the patient populations studied, the prognostic factors investigated, and the scoring instruments used to diagnose PTS, which have led to conflicting results and difficulty to generalize findings.

Summary Statement: Every pediatric patient with an extremity DVT is at risk of PTS. Patient- and thrombus-related factors, including older age, DVT provoking factor, thrombus burden, and thrombus persistence and time from DVT diagnosis to PTS assessment, *may* be associated with the development of pediatric PTS. The associations of treatment-related factors and biomarkers with PTS are conflicting and unclear.

1.2 Pediatric PTS Measurement Tools: Question: In pediatric patients with limb DVT, what are the measurement properties of existing pediatric PTS tools for diagnosing pediatric PTS?

Evidence Summary: Nine studies were included in the analysis of this question (Tables 2–4), including five cross-sectional studies [10,18–21] and four prospective cohort studies [22–25]. The total number of children involved across all studies was 886.

Three clinical tools are available for the diagnosis of PTS in children, namely the modified Villalta Scale (MVS)[14], the Manco-Johnson instrument (MJJ)[26], and the index for the Clinical Assessment of PTS in Children (CAPTSure®)[21,27].

The MVS includes two symptoms and nine signs of PTS, rated on a scale of 0–1 or 0–2, depending on the item. Scores for individual items are summed up together to provide a final score, which is categorized as no PTS (0 points), mild PTS (1–3 points), moderate PTS (4–8 points), or severe PTS (≥ 9 points). There is an automatic score of 9 points if a venous ulcer is present [14].

The MJJ considers the assessment of four PTS signs in addition to pain at rest, pain-limiting activities of daily living, and pain-limiting aerobic activities. The Wong-Baker Faces pain scale is used for the assessment of pain. The final score of the instrument is derived from the sum of the physical exam findings (0–4), the pain rating (0–15), and the presence of activity-limiting pain (0–1). The diagnosis of PTS requires a score of one, and functionally significant PTS requires both a physical exam sign and the presence of pain limiting at least one level of activity [26].

CAPTSure® was developed with the input of an international panel of pediatric thrombosis experts and a group of children with diagnosis of PTS. Experts and patients were asked to indicate which signs and symptoms had to be included for diagnosis and severity rating of pediatric PTS. The collected signs and symptoms were then prospectively tested in children at risk for PTS to evaluate their individual diagnostic ability [27]. The results were used to select the final items through a Delphi process involving pediatric thrombosis experts. Lastly, a scoring system was developed with the help of pediatric hematologists, patients, and parents via elicitation of the relative importance of each final sign and symptom using multiple-criteria decision analysis [21]. The final score ranges between 0–100 points, with higher scoring indicating higher PTS severity; a score of 0–10 points indicates no PTS, a score of 11–30 points indicates mild PTS and a score of ≥ 31 points indicate moderate to severe PTS [8].

The measurement properties of each tool are shown in Tables 2–4. All three tools have evidence supporting construct and criterion validity [18–23]. Similarly, the three tools have shown high inter- and intra-rater reliability [10,19,20,22,23,25]. Data on measurement error, minimal detectable change, and responsiveness are available for CAPTSure® [24,25]. Of note, one study compared the performance of the items of the three tools for the discrimination of children with and without PTS according to expert assessment. Results showed that the area under the curve was larger for CAPTSure® than for the MVS or MJJ (Supplemental Online, Table 11), which could be explained by experts using more clinical items to diagnose PTS in children than those included in the MVS and MJJ [21].

Summary Statement: The three tools for diagnosing PTS in children, the MJJ, MVS, and CAPTSure© have been shown to be reliable and valid for assessing pediatric PTS. Selection of the tool depends on the preference of the clinician.

1.3 Required Follow-up to Diagnose PTS: Question: In pediatric patients with limb DVT, what is an adequate duration and frequency of follow-up to diagnose PTS?

Evidence Summary: Five studies were included in the analysis of this question (Table 5) [7,8,17,28,29]. The total number of children involved across all studies was 1,025. A pair of retrospective studies using the MVS in the upper extremity (UE) and lower extremity (LE) DVT demonstrated that median time to PTS diagnosis (defined as MVS score >1) was 1–2 years for children with non-CVC-associated thrombosis (median age ~15 years at the time of DVT diagnosis), 3–5 years for non-neonates with CVC-associated thrombosis (median age ~2 years at the time of DVT), and 10–11 years for neonates with CVC-associated thrombosis (median age ~10 days at the time of DVT) [7,17]. Another study that retrospectively applied the MVS to children with follow-up visits for extremity DVT demonstrated that the median interval between diagnosis of VTE and PTS was 12 months (range 6–18 months) among children aged ~10 years at the time of DVT diagnosis [28]. A study using CAPTSure© during follow-up clinical evaluations of UE and LE imaging confirmed DVT demonstrated that CAPTSure© scores increase over time (0.9 points per year) in children with CVC-associated DVT (median age 3.5 months at the time of DVT diagnosis), further indicating that it may require 5 to 10 years to document clinical findings of PTS in younger patients [8]. In contrast, time from DVT diagnosis to PTS assessment was not an independent predictor of PTS among children with non-CVC-associated DVT (median age 15 years at the time of DVT). The final study, which retrospectively evaluated post-operative thrombosis following cardiac surgery, demonstrated via the MVS that the incidence of PTS increased with time, as freedom from PTS was 97% ± 1% at two years post-surgery and declined to 65% ± 7% at 8 years post-surgery[29]. Most children in the study (84%) were younger than one year at the time of surgery.

Summary Statement: Long-term follow-up of children with limb DVT is important. After the initial assessment for PTS surveillance 6 months after DVT diagnosis, the evaluation for non-neonates could be performed annually (+/- 6 months) for at least five years post-DVT diagnosis. For neonates, evaluation could be performed annually (+/- 6 months) for at least ten years post-DVT diagnosis.

2. Prevention of Pediatric PTS

2.1. Thrombolysis in Preventing PTS: Question: In pediatric patients with limb DVT, should thrombolysis followed by anticoagulation vs. no thrombolysis be used to prevent PTS?

Evidence Summary: We did not find any randomized controlled trials that addressed this question in children. In total, six studies were included in this analysis (five cohort studies [23,30–33] and one patient-level systematic review and meta-analysis [13]). The total number of children involved across all studies was 324. One study compared nine children

from within a longitudinal cohort who underwent a percutaneous thrombolytic regimen and 13 who received standard anticoagulation alone for lower extremity DVT [23]. Patients were followed from diagnosis with serial standardized PTS outcome assessments until 18–24 months after diagnosis. PTS risk was significantly lower for the thrombolytic regimen than for standard anticoagulation (22.2% vs. 76.9%, respectively; $p=.01$). The thrombolytic regimen was associated with a markedly decreased odds of PTS, which persisted after adjustment for significant covariates of age and lag time to therapy (odds ratio [OR] 0.018, 95% confidence interval [CI] < 0.001 – 0.483; $p=.02$). There was one major bleeding in the group undergoing thrombolysis (11%), judged not to be directly related to the procedure. We identified four additional single-arm studies with no comparison that provided the frequency of PTS following thrombolysis. The frequency of PTS in these studies was as follows: 14% (50% moderate and 50% mild PTS) [30], 33% (14% moderate and 86% mild) [31], 59% (3.1% severe, 9.4% moderate and 87.5% mild PTS) [32], 80% (physically and functionally significant PTS 13%; 3/16 patients had upper extremity DVT)[33]. The frequency of major bleeding events ranged between 0% and 3%; the frequency of minor bleeding ranged between 10% and 12%. A recent systematic review and individual patient data meta-analysis investigated outcomes of thrombolysis in patients with May-Thurner Syndrome and DVT[13]. Overall, PTS was seen in 59% (46/78) patients treated with interventional modalities for DVT and in 68% (17/25) treated with anticoagulation alone[13]. In the study, there was no evidence of an effect of interventional vs. non-interventional therapy for PTS prevention, although the use of interventional strategies led to higher odds of thrombus resolution, which was in turn, associated with lower DVT recurrence risk. Minor and major bleeding events were documented in 15% and 4% of children in undergoing image-guided therapy vs 4% and 0% in children receiving anticoagulation only.

Summary Statement: Thrombolysis might indirectly prevent or reduce the risk of PTS in select pediatric patients. However, the indications for thrombolysis in children remain controversial, and the benefit/harm ratio of such procedures for PTS prevention is unknown.

2.2. Elastic Compression Stockings in Preventing PTS: Question: In pediatric patients with limb DVT, should ECS vs. no ECS be used to prevent PTS?

Evidence Summary: No articles addressing the use of compression stockings for the prevention of pediatric PTS were identified in the literature search.

Summary Statement: The role of compression stockings in preventing PTS in children is unknown.

2.3 Exercise Training to Prevent PTS: Question: In pediatric patients with limb DVT, should exercise training or physical therapy be prescribed to prevent PTS?

Evidence Summary: One pilot RCT was found and included 22 children with LE DVT, wherein within-subject changes in PTS scores after prescribed physical activity, measured by an activity tracker, was a secondary objective[34]. The mean difference in total PTS score from baseline to six months was 0 points (SD 0.5) among the physical activity group versus 1.3 points (SD 0.8) among the standard care group, with a between-group difference of

−1.3 points (SD 0.6; $p=.0017$). The study was limited by inadequate adherence to prescribed physical activity and a small sample size.

Summary Statement: Evaluating pediatric patients for exercise training or supervised physical therapy may be considered to prevent PTS. The decision to initiate exercise training should depend on baseline physical activity, patient values and preferences, health services resources, infrastructure and support, underlying conditions, comorbidities, and medications.

3. Management of Pediatric PTS

3.1. Elastic Compression Stockings in Managing PTS: Question: In pediatric patients with limb DVT who have symptomatic PTS, should elastic compression garments vs. no garments be used to manage PTS?

Evidence Summary: One study was included in the analysis [24]. In this prospective observational study, 45 children (median age 13 years) who were prescribed compression garments to manage PTS symptoms were followed up for a median of 5 months. Compression sleeves or socks (starting with a pressure of 15–20 mmHg) for ~8–12 hours/day and ≥ 3 days/week were associated with lower PTS severity at follow-up. Half the patients found compression garments to be helpful. Of those patients who found them unhelpful, 50% mentioned that compression garments were difficult to put on or uncomfortable and only 25% reported PTS worsening with compression garments. Importantly, adherence to therapy was estimated at ~50% but can be enhanced through education and specialized care [35].

Summary Statement: A trial of compression garments (knee-high for LE PTS and sleeves for UE PTS) may be indicated/considered for managing symptomatic PTS, starting with a pressure of 15–20 mmHg at the level of the ankle or wrist to enhance adherence. Compression garments should be worn 8–12 hours a day, during the day, and three or more days a week.

3.2. Exercise Training to Manage PTS: Question: In pediatric patients with limb DVT who have symptomatic PTS, should exercise training or physical therapy be prescribed to manage PTS?

Evidence Summary: A six-month exercise training program designed to increase leg strength, leg flexibility and overall fitness improved venous disease-specific quality of life in adults with PTS [36]. No articles addressing the use of exercise training for managing pediatric PTS were identified in the literature search.

Summary Statement: Although supervised exercise training is considered reasonable in adults with PTS, the role of exercise training in managing symptomatic PTS in children is unknown.

3.3. Venoactive Medications to Manage PTS: Question: In pediatric patients with limb DVT who have symptomatic PTS, should venoactive drugs be prescribed to manage PTS?

Evidence Summary: The WG found no studies investigating venoactive drugs for either the prevention or treatment of PTS in pediatric patients.

Summary Statement: The role of venoactive medications in preventing PTS in children is unknown.

The management of symptoms, particularly pain, in pediatric PTS can be complex and may require a multidisciplinary approach, depending on the severity and response to standard treatment.

4. Impact of PTS

Question: In pediatric patients with PTS, what is the impact of disease severity on function and health-related quality of life?

Evidence Summary: Seven studies reporting on the impact of PTS on function and health-related quality-of-life (HR-QoL) outcomes in children were included (Table 6), including 414 children with PTS or at risk of PTS across all studies[8,11,19,22,37–39]. Overall, the studies found an association between PTS presence and/or severity and impact on function and/or HR-QoL outcomes in children.

Impact on function: A study including two prospective cohorts of children with PTS (n=256) found that patients with higher PTS severity, as measured by the CAPTSure©, reported lower Global Functioning and Happiness scores using the Pediatric Outcome Data Collection Instrument (PODCI) [8]. The authors found that for every point increase in CAPTSure© score, the PODCI Global Functioning scores decreased by 0.2 points (95% CI, -0.3 to -0.1; p = .001) and Happiness scores decreased by 0.3 points (95% CI, -0.6 to 0.0; p = .04) indicating that higher PTS severity is associated with lower overall functioning [8]. A cross-sectional study by the same group found that impaired endurance and pain were the most commonly reported clinical findings (50% and 55%, respectively) in children with PTS, more frequent even than limb tiredness (49%), limb heaviness (40%), and swollen limb (36%) [37]. Another cross-sectional study characterizing the physical and functional abnormalities associated with PTS in children with congenital heart disease (CHD) reported that, while HR-QoL was similar in patients with and without PTS, children with PTS had higher rates of delays in gross motor skills and problem-solving indicators, these differences remained significant after adjusting for type of CHD and other comorbidities [19]. A prospective cohort study of children 8–21 years with UE or LE DVT, with and without PTS, found that, adjusted for age, sex, and underlying condition, increasing PTS severity was associated with lower movement ability, as per the Movement Ability Measure, Computer Adaptive Testing (MAM-CAT), and a wider gap between current and preferred movement ability [38]. Increasing PTS severity was also associated with lower mobility scores, as per the Patient-Reported Outcomes Measurement Information System Pediatric Physical Functioning (PROMIS Pediatric PF), and with slightly higher disability scores, as per the Functional Disability Inventory [38]. Lastly, a case-control proof-of-concept study that used exercise to detect and measure the functional deficit in 10 children with unilateral lower limb DVT and PTS and in 12 sex- and age-matched controls found that 1) calf pump function was compensated in patients with PTS, 2) there was no evidence of impact of

PTS on exercise capacity, power output, or changes in segmental extracellular fluid content during exercise, and 3) there was impaired microvascular function at the muscular level in the PTS-affected leg only, which was worse as the severity of PTS increased [39].

Impact on HR-QoL: The impact of PTS severity in the HR-QoL of children was first reported in a cross-sectional study of 90 children with a history of an extremity DVT[11]. Using the Pediatric Quality of Life Inventory (PedsQL), this study found that patients with moderate to severe PTS (PTS score 4–8 and >9, respectively using a self-administered questionnaire) had statistically significant lower mean total, physical and social HR-QoL scores than those with no or mild PTS, indicating that moderate to severe PTS is associated with worse HR-QoL outcomes [11]. The only study using a pediatric thrombosis-specific instrument to assess QoL in children with VTE (the Peds-VEINES-QoL) found that patients with PTS reporting pain-limiting activity, as specified by the MJI (n = 18), had worse HR-QoL scores as measured by both the PedsQL and the Peds-VEINES-QoL compared to those who did not report pain (n=67) (U = 2.4, p = .02 for PedsQL; U=4.6, p <.001 for Peds-VEINES-QoL)[22].

Summary Statement: Assessment of function and HR-QoL should be considered during the time of follow-up visits, whenever possible, for all pediatric patients with moderate to severe PTS facilitating early recognition of physical functioning, social, psychosocial, emotional and/or school-associated problems, and early implementation of tailored interventions. Several tools can be used for the assessment of pediatric PTS impact on functioning, of which MAM-CAT and PROMIS-Pediatric PF seem most helpful. Both the PedsQL and the Peds-VEINES-QoL can be used for assessing HR-QoL in pediatric VTE at risk of PTS.

Conclusions and Priorities for Research

Adaptation of this guidance will be necessary for local implementation. Priorities for pediatric PTS research studies are shown in Table 12 (Supplementary Online). Although the conduct of RCTs in pediatric thrombosis is not debated, completing RCTs in neonates and children, especially related to antithrombotic therapies, is difficult. While the completion of recent RCTs paves the way for the future[40], the WG strongly recommends collaborative cohort studies to improve the current level of evidence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:
Summary of Studies Investigating Prognostic Factors for Pediatric PTS

Author, year	Study Type	Population (n)	PTS Tool	PTS	Prognostic Factors
Avila 2021	Data from two prospective cohorts	Children 0–18 years with UE/LE DVT (n=256)	CAPTSure©	32% (n=82)	For patients with CVC-related DVT (coefficient estimate [95%CI]): - Age at diagnosis 0.6 (0.1, 1.2) $p=0.02$ - Time from DVT diagnosis to PTS assessment 0.9 (0.4,1.3) $p<0.0001$ For patients with Non-CVC-related DVT (coefficient estimate [95%CI]): - Age at diagnosis 1.7 (1.0, 2.4) $p<0.001$ Not significant: days on therapeutic anticoagulation, DVT burden
Avila 2021	Systematic Review and Meta-analysis	Children 0–18 years with MTS and ipsilateral DVT (n=103)	Multiple: Institutional criteria, MVS, VS, and MJJ	61% (n=63)	Association between PTS and DVT recurrence (adjusted for age and patency) Recurrence (yes vs. no): OR (95%CI) 3.36 (1.28, 8.82)
Betensky 2021	Prospective cohort	Children 0–20 years with DVT (provoked, n=79)	MJJ	34% (n=27)	Multivariable analysis (OR, 95% CI): - Complete veno-occlusion 6 weeks after DVT 3.12 (0.81–11.94), $p=0.097$ - CloFAL FI2 3 months post-DVT 2.71 (0.92–7.97), $p=0.7$ - SAA mn/L 3 months post-DVT 2.85 (0.98–8.34), $p=0.055$
Engel 2020	Systematic Review and Meta-analysis	Children <21 years of age with a radiologically confirmed DVT (n=1076)	Multiple: Institutional criteria, MVS, and MJJ	40.3% (434)	Putative prognostic factors (pooled OR [95% CI]): - CVC-associated DVT 1.8 (1.08–2.98) - Complete veno-occlusion 1.89 (1.04–3.46) - Persistent thrombosis 2.07 (1.4–3.07)
Kuhle 2003	Cross-sectional	Children with extremity DVT (n=150)	MVS	64% (n=96)	At follow-up (OR [95% CI]): - DVT no change or extension vs. normal 3.96 (1.68–9.30) $p=0.0016$ - Number of vessels involved 2.05 (1.52, 2.77) $p<0.001$ - Length of follow-up 1. (1.08–1.39) $p=.0019$
Zia 2020	Case-control	Children 10–18 years with acute VTE and controls (n=44 cases)	MJJ	16% (n=7)	Univariable analysis (Coefficient & [95% CI]): Insufficiently active children (Godin score <24) had higher PTS scores compared to active children (Godin score ≥ 24) 1.23 (0.25, 2.20) $p=0.01$ Not significant in multivariable analysis

n= number of patients; PTS= post-thrombotic syndrome; UE= upper extremity; LE=lower extremity; CVC=central venous catheter; DVT=deep venous thrombosis; MTS= May-Thurner Syndrome; MVS=modified Villalta Scale; MJJ=Manco-Johnson Instrument; CAPTSure© = index for the Clinical Assessment of PTS in children; OR=odds ratio; CI=confidence interval; VTE=venous thromboembolism; CloFAL FI2= Clot Formation and Lysis assay, modified fibrinolytic index; SAA= Serum amyloid A.

Table 2:
Measurement properties of the Modified Villalta Scale

Author, year	Validity			
Raffini 2015	Measurement property assessed	Construct validity, convergent validity		
	Methods, results	Spearman correlation coefficient (rs) - MVS vs. VS rs 0.26 for yes/no, and 0.43 for categories - MVS vs. MJJ rs 0.70 for yes/no and 0.65 for categories		
Manlhiot 2019	Measurement property assessed	Criterion validity Comparison vs. expert opinion		
	Methods, results	Assessment of diagnostic properties: - Accuracy 91% - Sensitivity 93% - Specificity 91%		
Smith 2021	Measurement property assessed	Construct validity, convergent validity Hypotheses: correlations between instruments expected to be high; correlation with age and gender expected to be low	Construct validity, discriminant validity (known group) Hypothesis: scores higher in patients vs. controls	Construct validity, concurrent validity Hypothesis: QOL scores worse for patients with pain
	Methods, results	Pearson correlation coefficient - MVS-PedsQL: -0.40 - MVS-PedsVEINES: 0.59 - MVS-age: 0.16 - MVS-gender: 0.06 - MJJ-MVS: 0.68	Mann-Whitney U test MVS patients vs. controls: all p-values reported to be <0.05	Mann-Whitney U test - MVS pain or abnormal use vs. PedsQL: p<0.05 - MVS pain or abnormal use vs. PedsVEINES: p<0.05
Reliability				
Smith 2021	Measurement property assessed	Inter-rater, ICC Note: Second assessment 5.1 weeks (IQR 3.8–7.7 weeks, range 1.9–13.1 weeks)		
	Methods, results	MVS: ICC 0.92		
Manlhiot 2019	Measurement property assessed	Inter-rater, intra-rater reliability		
	Methods, results	Cohen Kappa (k) - Inter-rater reliability: MVS k value of 0.64 (95% CI, 0.18–0.81; p = 0.002); raw agreement 85% - Intra-rater reliability: MVS k of 0.79 (95% CI, 0.28–0.79; p < 0.001); raw agreement 93%		

MVS=modified Villalta Scale; MJJ=Manco-Johnson Instrument; VS= Villalta Scale; QOL= quality of life; PedsQL= Pediatric Quality of Life Inventory; IQR= interquartile range; ICC= intraclass correlation coefficient; CI= confidence interval

Table 3:
Measurement properties of Manco-Johnson Instrument

Author, year	Validity			
Smith 2021	Measurement property assessed	Construct validity, convergent validity Hypothesis: correlations between instruments expected to be high; correlation with age and gender expected to be low	Construct validity, discriminant validity (known group) Hypothesis: scores higher in patients vs. controls	Construct validity, concurrent validity Hypothesis: QOL scores worse for patients with pain
	Methods, results	Pearson correlation coefficient: - MJI-MVS: 0.68 - MJI-PedsQL: −0.51 - MJI-PedsVEINES: 0.76 - MJI-age: 0.22 - MJI-gender: 0.01	Mann–Whitney U test: MJI patients vs. controls: all p reported to be <0.05	Mann–Whitney U test: - MJ pain-limiting activity vs. PedsQL: p=0.02 - MJ pain-limiting activity vs. PedsVEINES: p<0.001
Raffini 2015	Measurement property assessed	Construct validity, convergent validity		
	Methods, results	Spearman correlation coefficient (rs) - MJI vs. VS rs 0.26 for yes/no and 0.58 for MJI clinically significant vs VS any PTS - MVS vs. MJI rs 0.70 for yes/no and 0.65 for categories		
Goldenberg 2010	Measurement property assessed	Construct validity, discriminant validity (known group) – MJI only, upper extremity only		
	Methods, results	UE DVT: Frequency of PTS in healthy children (0%) and history of CVC (3%)		
Goldenberg 2007	Measurement property assessed	Construct validity, discriminant validity (known group) – Lower extremity only		
	Methods, results	LE DVT: Frequency of PTS in healthy children (0%)		
	Reliability			
Goldenberg 2007	Measurement property assessed	Inter-rater reliability		
	Methods, results	Lower extremity, percent agreement 91%–100%		
Goldenberg 2010	Measurement property assessed	Inter-rater reliability		
	Methods, results	Upper extremity, percent agreement 97%–100%		
Luceri 2015	Measurement property assessed	Inter-rater reliability		
	Methods, results	Kappa: 0.88		
Smith 2021	Measurement property assessed	Inter-rater, ICC Note: Second assessment 5.1 weeks (IQR 3.8–7.7, range 1.9–13.1 weeks)		

	Methods, results	MJI: ICC 0.80
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MVS=Modified Villalta Scale; MJI=Manco-Johnson Instrument; VS = Villalta Scale; PedsQL= Pediatric Quality of Life Inventory; UE= upper extremity; LE=lower extremity; DVT= deep vein thrombosis; PTS= post-thrombotic syndrome; ICC= intraclass correlation coefficient; IQR= interquartile range

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Table 4:

Measurement properties of CAPTSure©

Author, year	Validity			
Avila 2016	Measurement property assessed	Criterion validity		Construct validity, convergent validity
	Methods, results	CAPTSure© vs expert opinion - UE AUC 0.88 (0.78–0.94) - LE AUC 0.83 (0.72–0.91)		CAPTSure© vs parental satisfaction - UE OR 1.06, 95% CI 1.01–1.11) - LE OR 1.07, 95% CI 1.03–1.11)
	Reliability			
Avila 2019	Measurement property assessed	Inter-rater reliability	Intra-rater reliability	Measurement error, minimal detectable change
	Methods, results	Second assessment at a median of 13 days (range, 7–34 days) PTS signs (clinician assessment component), UE (n = 86), ICC 0.89 (0.84–0.93) PTS signs (clinician assessment component), LE (n = 92), ICC 0.88 (0.83–0.92)	PTS symptoms (patient/proxy questionnaire component), UE (n = 60), ICC 0.89 (0.84–0.93) PTS symptoms (patient/proxy questionnaire component), LE (n = 61), ICC 0.92 (0.87–0.95)	Measurement error: - PTS symptoms UE: 4.3 (3.3–5.3) - PTS symptoms LE: 3.6 (2.8–4.4) - PTS signs UE: 1.8 (1.5–2.2) - PTS signs LE: 1.5 (1.2–1.8) - CAPTSure© UE: 4.3 (3.7–5.2) - CAPTSure© LE: 3.8 (3.2–4.6) Minimal detectable change: - UE: 11.9 points LE: 10.5 points
		- CAPTSure©, UE (n = 60), ICC 0.92 (0.87–0.95) - CAPTSure©, LE (n = 61), ICC 0.93 (0.88–0.95)		
	Responsiveness			
Avila 2021	Measurement property assessed	Responsiveness: Score change over time with treatment (compression garments)		
	Methods, results	Linear model For the outcome global functioning (measured using PODCI), for every 10-point increase in CAPTSure© score, there was a –4.1 (–5.5 – –2.7) reduction in PODCI score at follow up (adjusted for baseline PODCI score and age)		

CAPTSure© = index for the Clinical Assessment of PTS in children; PTS= post-thrombotic syndrome; UE= upper extremity; LE=lower extremity; ICC= intraclass correlation coefficient; AUC= Area under the curve; OR= odds ratio; PODCI= Pediatric Outcome Data Collection Instrument

Table 5:

Time from DVT to PTS diagnosis

Author, year	Study Type	Population (n)	PTS tool	PTS %	Patient Groups	Time to PTS
Avila 2014	Retrospective cohort	Image confirmed UE DVT with ≥ 1 PTS assessment ≥ 6 months after DVT diagnosis (n= 158)	MVS (score >1) Time to 50% of group diagnosed with PTS	49% (n=78)	Primary DVT (effort/ idiopathic)	1.0 year (95% CI 0.7–1.1)
					Secondary non-neonate (92% CVC-related)	3.1 years (95% CI 2.8–3.6)
					Secondary neonate (100% CVC-related)	9.7 years (95% CI 3.2–11.0)
Avila 2016	Retrospective cohort	Image confirmed LE DVT with ≥ 1 PTS assessment ≥ 6 months after DVT diagnosis (n=339)	MVS (score >1)	47% (n=339)	Non-CVC related neonate	2.0 years (95% CI 1.1–3.2) 10.5 years (95% CI 7.0- not estimable)
					CVC-related non-neonate	5.1 years (95% CI 4.1–6.5)
					CVC-related neonate	10.5 years (95% CI 7.0 - not estimable)
Avila 2021	Two prospective cohorts	Image confirmed UE and LE DVT with ≥ 1 PTS assessment ≥ 6 months after DVT diagnosis (n=256)	CAPTSure© score >10 points)	32% (n=82)	CVC-related thrombosis	CAPTSure© scores increase 0.9 points per year
					Non-CVC-related thrombosis	No significant impact of time on PTS severity
Creary 2012	Retrospective cohort	Children with extremity DVT with ≥ 2 PTS assessments ≥ 6 months after DVT diagnosis (n=69)	MVS (score >1)	48% (n=33)	NA	12-month median interval from DVT to PTS diagnosis (6–18 months)
Manlhiot 2016	Retrospective cohort	Children with cardiac operations with ≥ 1 occlusive postoperative image confirmed thrombus (n ~ 133)	MVS	~ 17% (n=22)	NA	Freedom from PTS (time from surgery) 2 years: 97% $\pm$ 1% 4 years: 93% $\pm$ 2% 6 years: 83% $\pm$ 4% 8 years: 65% $\pm$ 7%

n= number of patients; PTS= post-thrombotic syndrome; DVT= deep vein thrombosis; MVS=Modified Villalta Scale; CAPTSure© = index for the Clinical Assessment of PTS in children; UE= upper extremity; LE=lower extremity; CI= confidence interval

Table 6:
Impact of PTS Severity on Function and Health-Related Quality-of-Life

Author, year	Study Type	Population (n)	PTS	PTS Tool	Function or HR-QoL Instrument	Instrument Description	Outcomes
Avila 2018	Cross-sectional	Children 10–18 years with UE/LE DVT and PTS (n=78)	100% (n=78)	CAPTSure©	PODCI	Measures aspects of related to the Body Structures and Function, Activities, and Participation components of the ICF-CY. Contains 5 subscales: UE, transfer and basic mobility, sports and physical functioning, pain and comfort, and happiness	Slightly lower PODCI global scores in patients with PTS and pain vs those without pain
Avila 2021	Data from two prospective cohorts	Children 0–18 years with UE/LE DVT (n=256)	32% (n=82)	CAPTSure©	PODCI		Higher PTS severity associated with lower overall functioning (analyzed using generalized estimating equations) For every 10-point increase in CAPTSure© score, PODCI Global Functioning and Happiness scores decreased by 2 and 3 points respectively
Kumar 2014	Cross-sectional	Children 0–18 years with UE/LE DVT (n=90)	72% (n=65)	Self-administered survey Instrument	PedsQL	Multidimensional, 23-item questionnaire. Assesses physical, emotional, social, and school functioning	Compared to no/mild PTS, patients with mod to severe PTS had significantly lower total HR-QoL score (mean $\pm$ SD), 83.4 $\pm$ 14 (no PTS) and 84.8 $\pm$ 14.2 (mild) vs 71.3 $\pm$ 13.4 (mod-severe), p 0.001. Psychosocial, physical, and social functional sub-scores were also significantly impacted, while school and emotional scores were not.
Manlhiot 2019	Cross-sectional	Children >2 years with congenital heart disease and UE/LE DVT (n=33) and controls (n=67)	39% (n=13)	MVS	PedsQL ASQ		PedsQL scores were similar between PTS and no PTS groups but children with PTS had higher rates of delays in gross motor skills and problem-solving indicators.
Smith 2021	Prospective cohort	Children $\leq$ 21 years with LE DVT (n=80) and healthy controls (n=60)	13% (n=10) with MJI, 55% (n=44) with MVS	MJI MVS	Peds-VEINES-QoL PedsQL	Venous disease-specific scale adapted from adult VEINES-QOL	Worse HR-QoL scores in patients w/PTS compared to no PTS, and in those reporting pain-limiting activity on MJI compared to those who did not
Bastas 2023	Prospective cohort	Children 8–21 years with UE/LE DVT (n=87)	43% (n=37)	CAPTSure©	MAM-CAT PROMIS-Pediatric PF Mobility FDI	MAM-CAT: movement ability (current, preferred and gap) PROMIS-Pediatric PF: mobility FDI: functional disability	Lower current mobility scores and wider gap between current and preferred movement ability with increasing PTS severity (adjusted for sex, age, and underlying condition). Lower mobility scores and slightly higher functional disability scores with increasing

Author, year	Study Type	Population (n)	PTS	PTS Tool	Function or HR-QoL Instrument	Instrument Description	Outcomes
							PTS severity (adjusted for sex, age, and underlying condition).
Avila 2023	Case-control	Children 12–21 years with unilateral LE DVT and age and sex matched controls	45% (n=10)	CAPTSure©	Calf pump function and exercise testing	Assessed using acute exercise, near-infrared spectroscopy, bioimpedance spectroscopy	Compensated calf pump function, no evidence of impact on exercise capacity or fluid accumulation, similar power output, impaired microvascular function and responsiveness at the muscular level in the PTS-affected leg

n= number of patients; PTS= post-thrombotic syndrome; HR-QoL= health related quality-of-life; UE= upper extremity; LE= lower extremity; DVT= deep venous thrombosis; PODCI= Pediatric Outcome Data Collection Instrument; ICF-CY= International Classification of Functioning, Disability and Health for Children and Youth; CAPTSure©= index for the Clinical Assessment of Post-Thrombotic Syndrome in Children; MJJ= Manco-Johnson Instrument; MVS= modified Villalta Scale; PedsQL= Pediatric Quality of Life Inventory; ASQ= ages and stages questionnaire; MAM-CAT= Movement Ability Measure Computer Adaptive Testing; PROMIS-Pediatric PF= Patient-Reported Outcomes Measurement Information System Pediatric Physical Functioning; FDI= Functional Disability Inventory