Characterization of Post-Thrombotic Syndrome in Children with Cardiac Disease

Cedric Manlhiot, PhD[1], Brian W. McCrindle, MD, MPH[1], Suzan Williams, MD[2], Ines B. Menjak, MD[1], Sunita O'Shea, BSc[1], Anthony K. Chan, MD[2], and Leonardo R. Brandão, MD, MSc[2]

Objective To assess the validity of existing clinical scales assessing the presence of physical and functional abnormalities for diagnosing post-thrombotic syndrome (PTS) in children, including specific evaluation of use in children with congenital heart disease (CHD).

Study design One hundred children aged >2 years (average age, 6 years), including 33 with CHD and previously proven extremity deep vein thrombosis (DVT), 37 with CHD and no previous DVT, and 30 healthy siblings, were blindly assessed for PTS using the modified Villalta Scale (MVS). All patients aged <6 years underwent neurodevelopmental testing and an age-appropriate quality of life assessment.

Results The MVS identified mild PTS in 20 children and moderate PTS in 1 child (including 14 of 33 [42%] in the CHD/DVT group, 5 of 37 [14%] in the CHD/no DVT group, and 2 of 30 controls [7%]). The diagnosis of PTS was confirmed clinically in 14 patients, all of whom had previous thrombosis and 1 of whom was MVS-negative. MVS had an accuracy of 91% and performed reasonably well as a screening tool but poorly as a diagnostic tool. MVS reliability was acceptable. Children with PTS had similar quality of life as those without PTS but had higher rates of neurodevelopmental delays in gross motor skills (70% vs 24%; $P = .02$) and problem-solving indicators (60% vs 15%; $P = .008$).

Conclusions Using the MVS scale for PTS screening in children with CHD is feasible and reliable, and the scale has good correlation with a clinical diagnosis of PTS despite a high prevalence of false-positive findings. Further research is needed to determine the clinical relevance of PTS in this population. *(J Pediatr 2019;207:42-8).*

Thrombosis, especially venous thrombosis, is being increasingly recognized as a serious and common clinical entity in hospitalized children.[1] Children undergoing cardiac surgery for either congenital or acquired heart disease are at particularly high risk of thrombosis, especially those with single-ventricle physiology.[2-4] Post-thrombotic syndrome (PTS) is an important complication of limb venous thrombosis that has been documented in adults mainly after lower extremity deep vein thrombosis (DVT). PTS results from chronic venous hypertension related to a combination of persistent venous outflow obstruction and venous valve damage with valvular insufficiency.[5,6] Ultimately, hypertension is transmitted from the deep venous system to the superficial venous system and can cause fluid extravasation with varied degrees of inflammation.[7] Clinically, it can be recognized by the development of dilated vessels, cutaneous changes, local edema, localized pain and reduced function, and, in the more severe cases, venous ulcers.[5,6] In children, PTS generally occurs at the lower end of the severity spectrum seen in adult patients.[8,9]

Previous studies in children who experience thrombosis after cardiac surgery found a 17% prevalence of PTS at 6 years after surgery.[4] In a meta-analysis of the pediatric literature, the reported prevalence of PTS ranged between 3.1% and 70%, where the prevalence of PTS differed according to study design (eg, retrospective vs prospective) or specific scale that had been used to diagnose PTS within the given study (eg, structured vs unstructured). The diagnosis of PTS is based on clinical scales that require assessors to rate the presence and severity of subjective and objective clinical findings.[5,10] The International Society on Thrombosis and Hemostasis has sanctioned the Villalta Scale as a tool for diagnosing PTS in adult patients.[11,12] The Society's Pediatric and Neonatal Subcommittee has endorsed 2 scales for clinical use in children, the modified Villalta Scale (MVS)[13] and the Manco-Johnson Scale,[14] despite the recognized limitations of these instruments.[15] Matters are further complicated in children with congenital heart disease (CHD), who often have multiple comorbidities and in whom many of the clinical features

ASQ	Ages & Stages Questionnaires
CHD	Congenital heart disease
DVT	Deep vein thrombosis
MVS	Modified Villalta Scale
PedsQL	Pediatric Quality of Life Inventory
PTS	Post-thrombotic syndrome

From the [1]Labatt Family Heart Centre, University of Toronto, The Hospital for Sick Children; and [2]Division of Haematology/Oncology, Department of Pediatrics, University of Toronto, The Hospital for Sick Children, Toronto, ON, Canada

Supported by the Labatt Family Heart Centre Innovation Funds and the Canadian Institutes of Health Research. The authors declare no conflicts of interest.

Portions of this study were presented at the American Heart Association Scientific Sessions, Orlando, Florida, November 12-14, 2011, and at the XXIII Congress of the International Society on Thrombosis and Haemostasis, Kyoto, Japan, July 23-28, 2011.

https://doi.org10.1016/j.jpeds.2018.10.064

associated with PTS can be explained by other clinical problems common in this population. PTS characterization has not previously been performed in children with heart disease. We sought to assess the MVS's feasibility, reliability, and correlation with clinical history in children with CHD, and also to assess the functional consequences for neurodevelopment and health-related quality of life in these patients.

Methods

This cross-sectional study included 101 children aged >2 years selected from 3 populations: children with repaired heart disease complicated by an objectively confirmed postoperative upper or lower extremity DVT, children with repaired heart disease without thrombosis (positive controls), and siblings with an unremarkable medical history (negative controls). Patients were selected at random from the overall CHD patient population and contacted by phone/mail to solicit participation in the study. Oversampling of patients followed at our hospital's pediatric thrombosis clinic was performed to ensure inclusion of a sufficient number of patients at increased risk for post-thrombotic syndrome. Parents of children with CHD who agreed to participate in the study were invited to bring siblings along on the testing day to be included as negative controls. All patients were seen at least 6 months after their last cardiac intervention. The local Research Ethics Board approved the study protocol. Parental written informed consent and appropriate assent were obtained for all participants.

Physical examination, performed by 4 medical students previously trained to apply the MVS under supervision, included assessments of all 4 limbs for classic PTS clinical signs: change in skin color, hyperpigmentation, presence of dilated superficial collateral vessels, ulceration, pitting edema, and tenderness on palpation.[10,13] Bilateral limb circumference was measured in a standardized manner. For the upper extremities, the midpoint of the upper arm, defined as the mid-length of the humerus in a fully extended relaxed limb, was used to measure arm circumference. For the lower extremities, the midpoint of the upper thigh, defined as the halfway point between the anterior superior iliac spine and the tibial tuberosity in a fully extended relaxed limb, was used to measure thigh circumference. Absolute differences with the contralateral limb circumference were included in the assessment of PTS (discordance established with a difference of >1.0 cm for arms and >1.5 cm for legs). A random subset of patients underwent inter-rater reliability assessment for limb circumference measurements. Assessors were completely blinded to patient medical history including history of thrombosis. When families with >1 child were tested (cases + sibling[s]), the children were instructed by a coinvestigator not involved in the physical testing to not reveal their medical history to the assessor, thus preserving the assessor's blinding.

All patients underwent physical function assessment focused mainly on pain with use in all 4 limbs. Patients were asked to describe pain in all 4 limbs when inactive, when a little active (eg, during daily routine tasks, such as walking to school, shopping with family, participating in birthday parties, doing chores), and when very active (eg, during sports, playing on playground, running, swimming). Older children responded using a 6-point generic Likert Scale, and younger participants used the Wong-Baker Pain Scale. All participants used the Pediatric Quality of Life Inventory (PedsQL) pain report (patient or parent report, depending on the child's capacity) to complement the physical function assessment.

Neurodevelopment and/or health-related quality of life were assessed for all participants through the Ages & Stages Questionnaires (ASQs), which have been used to screen for neurodevelopmental delays in academic studies.[16] Families with children aged ≤6 years completed the parent-reported PedsQL and the age-appropriate ASQ. The ASQs are parent-reported questionnaires eliciting information on age-expected completion of tasks by their child. Multiple versions of the questionnaire are used corresponding to 6- to 12-month age increments. Children are assessed on 5 neurodevelopmental dimensions: communication, gross motor skills, fine motor skills, problem-solving, and personal-social. For each dimension, children receive a score for each task to be accomplished and are then classified as normal development, surveillance required, or below-normal development. A parent/guardian of children age >6 years completed the age-appropriate PedsQL. The PedsQL is a questionnaire-based assessment in which respondents indicate their level of agreement with various statements on a scale of 1-6. Responses are then converted to a 100-point scale across 4 functional dimensions: physical, emotional, social, and school. All questionnaires were coded and scored according to validated algorithms.[17,18]

For each participating child, a complete clinical history, including any previous history of thrombosis, was collected from the medical record and reviewed with the parent/guardian at the time of assessment. All children with at least 1 positive diagnostic criteria on the MVS were referred for specialized assessment in the thrombosis clinic by a thrombosis expert and for further ultrasound investigation to confirm the presence of persistent thrombosis (unless a clinical ultrasound was performed within the past 6 months, in which case the clinical study was used). Patients followed in the pediatric thrombosis clinic for PTS (either followed previously or a new referral) were considered to have a confirmed clinical diagnosis of PTS.

Data are presented as mean with SD, median and IQR, or frequency as appropriate. Comparisons between children with CHD with and without a history of previous thrombosis and comparisons between those with and without PTS were performed using the Fisher exact test and Student *t* test, assuming unequal variance between groups. All comparisons among the 3 study groups were performed in regression models (logistic for binary outcomes, linear for continuous outcomes) using control subjects as the reference category. The Wald χ^2 test was used to obtain *P* values for difference across the 3 study groups. A contingency table was used to compare MVS results with clinical diagnosis of PTS and derive diagnostic metrics. Inter-rater and intrarater agreement on the presence or absence of PTS were evaluated using the Cohen κ statistic. Pearson correlation was used to determine the correlation between

separate measurements performed on a limb. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina).

Results

A total of 101 patients were enrolled in this study, including 33 with CHD and a previous history of objectively documented extremity DVT, 37 with CHD without a previous history of thrombosis, and 31 controls. On examination, 1 control subject reported chronic, generalized pain of >3 months' duration, thus PTS assessment was not appropriate and this patient was subsequently excluded from our analysis. Relevant medical history data for the patients with CHD are presented in **Table I**.

Patients with limb DVT had a higher prevalence of hypoplastic left heart syndrome, more previous operations, and higher rates of previous surgery with circulatory arrest or ever needing extracorporeal life support and/or heart transplantation. Subjective assessment findings, including functional health status and self-reported clinical and functional signs of PTS, are reported in **Table II**. Overall, abnormal findings were infrequent and universally mild in severity, but children with a previous history of limb DVT had a higher prevalence of pain and abnormal findings in the lower limbs. Physical examination findings are reported in **Table III**. Abnormal findings were also generally mild but were more frequent than seen in the subjective assessment, with slightly more abnormal findings in patients with a previous history of thrombosis. No patient had any physical findings indicative of severe PTS.

Based on the subjective and objective assessments, using the MVS, 21 patients screened positive for PTS, including 14 of 33 (42%) in the CHD with previous limb DVT group, 5 of 37 (14%) in the CHD without previous DVT group, and 2 of 30 (7%) controls ($P = .001$) (**Figure**). All patients with a positive screen had mild clinical findings, except for 1 patient with moderate PTS. On comprehensive clinical assessment for PTS, 7 of the 8 patients who screened positive for PTS did not have a previous history of thrombosis (false-positive), and 1 patient with a previous diagnosis of PTS screened negative. Overall, the MVS had an accuracy of 91% for diagnosing PTS, with a sensitivity of 93%, specificity of 91%, positive predictive value of 62%, and negative predictive value of 99%. In the patients with CHD, the MVS had an accuracy of 94%, sensitivity of 93%, specificity of 95%, positive predictive value of 93%, and negative predictive value of 95%.

Table I. Medical history of the patients with CHD with or without previous thrombosis

Variables	Previous thrombosis (N = 33)	No previous thrombosis (N = 37)	*P* value
Cardiac diagnosis, n (%)			
Aortic or mitral valve disease (including HLHS)	11 (33)	2 (5)	.004
Aortic arch abnormalities (including coarctation)	3 (9)	3 (8)	1.00
DORV/TGA	9 (27)	6 (16)	.25
Tetralogy of Fallot, pulmonary or tricuspid atresia	5 (15)	12 (32)	.38
Septal defects	3 (9)	9 (24)	.06
Other	2 (6)	5 (14)	.71
Age at last surgery, y, median (IQR)	0.6 (0.2-3.2)	0.6 (0.1-2.5)	.73
Interval between last surgery and study, y, median (IQR)	2.8 (1.9-4.3)	4.0 (3.1-4.8)	.59
Number of previous surgeries, n (%)			.10
1	17 (52)	28 (76)	
2	7 (21)	3 (8)	
>2	9 (27)	6 (16)	
Underwent surgery with circulatory arrest, n (%)	6 (18)	1 (3)	.05
Previous history of ECLS/heart transplantation, n (%)	6 (18)	2 (5)	.14
Previous thrombosis history, n (%)			
Upper limb venous thrombi			
0	19 (57)		
1	6 (18)		
2	3 (9)		
>2	5 (15)		
Lower limb venous thrombi			
0	11 (33)		
1	8 (24)		
2	7 (21)		
>2	7 (21)		
Arterial thrombosis	15 (45)		
Documented unresolved venous occlusion, n (%)	17 (52)		
Treatment with unfractionated heparin, n (%)	23 (70)		
Duration of treatment, d, median (IQR)	4 (2-7)		
Daily dose, U/kg/d, mean ± SD	675 ± 133		
Treatment with enoxaparin, n (%)	26 (79)		
Duration of treatment, d, mean ± SD	86 ± 56		
Daily dose, mg/kg/d, mean ± SD	3.3 ± 0.8		

DORV, double-outlet right ventricle; *ECLS*, extracorporeal life support; *HLHS*, hypoplastic left heart syndrome; *TGA*, transposition of the great arteries.

Table II. Physical function and subjective assessment

	Previous thrombosis		No previous thrombosis		Controls		
Variables	**N**	**Value**	**N**	**Value**	**N**	**Value**	***P* value**
Male sex, n (%)	33	20 (61)	37	18 (49)	30	18 (60)	.52
Age at assessment, y mean ± SD	33	5.6 ± 3.8	37	5.7 ± 3.1	30	7.7 ± 3.4	.03
<5 y, n (%)		20 (61)		20 (54)		8 (27)	
5-10 y, n (%)		9 (27)		14 (38)		15 (50)	
>10 y, n (%)		4 (12)		3 (8)		7 (23)	
Dominant side, n (%)	33		37		30		.02
Left		8 (24)		8 (22)		3 (10)	
Right		21 (64)		29 (78)		27 (90)	
Undetermined		4 (12)		0 (0)		0 (0)	
Functional assessment, n (%)	33		37		30		.08
No pain reported		29 (88)		37 (100)		28 (94)	
Localized pain		3 (9)		0 (0)		1 (3)	
Pain in >1 location		1 (3)		0 (0)		1 (3)	
Severity of current pain (10 cm VAS), median (IQR)	14	0.1 (0.0-0.6)	18	0.2 (0.1-0.5)	23	0.2 (0.0-1.2)	.30
Severity of worst pain this week (10 cm VAS), median (IQR)	14	0.3 (0.0-3.6)	18	0.3 (0.0-2.1)	23	0.3 (0.1-2.3)	.87
Subjective assessment, upper body, n (%)							
Spontaneous pain in upper arm	33	0 (0)	37	0 (0)	30	0 (0)	
Spontaneous pain in lower arm	33	0 (0)	37	0 (0)	30	0 (0)	
Pain in upper arm with use	33	0 (0)	37	0 (0)	30	0 (0)	
Pain in lower arm with use	33	1 (3)	37	0 (0)	30	0 (0)	
Swelling of upper arm	33	0 (0)	37	1 (3)	30	0 (0)	
Swelling of lower arm	33	0 (0)	37	0 (0)	30	0 (0)	
Discoloration of upper arm	33	1 (3)	37	0 (0)	30	0 (0)	
Discoloration of lower arm	33	0 (0)	37	0 (0)	30	0 (0)	
Heaviness of arm	33	0 (0)	37	1 (3)	30	0 (0)	
At least 1 positive finding, upper body, n (%)	33	2 (6)	37	2 (5)	30	0 (0)	.55
Subjective assessment, lower body, n (%)							
Spontaneous pain in calf	33	0 (0)	37	0 (0)	30	0 (0)	
Spontaneous pain in thigh	33	0 (0)	37	0 (0)	30	0 (0)	
Pain in calf with use	33	2 (6)	37	0 (0)	30	0 (0)	
Pain in thigh with use	33	3 (8)	37	0 (0)	30	0 (0)	
Swelling of foot/calf	33	0 (0)	37	0 (0)	30	0 (0)	
Swelling of thigh	33	0 (0)	37	0 (0)	30	0 (0)	
Discoloration of calf	33	1 (3)	37	0 (0)	30	0 (0)	
Discoloration of thigh	33	1 (3)	37	0 (0)	30	0 (0)	
Heaviness of leg	33	0 (0)	37	0 (0)	30	0 (0)	
At least 1 positive finding, lower body, n (%)	33	4 (12)	37	0 (0)	30	0 (0)	.02

VAS, visual analog scale.

There was moderate inter-rater agreement for the MVS results (positive or negative PTS screen), with a κ value of 0.64 (95% CI, 0.18-0.81; $P = .002$; raw agreement, 85%) and excellent intrarater agreement, with a κ of 0.79 (95% CI, 0.28-0.79; $P < .001$; raw agreement, 93%). There were high intrarater ($R^2 = 0.83$-0.98) and inter-rater ($R^2 = 0.89$-0.97) correlations between circumference measurements on the same limb. The average inter-rater difference in circumference was 0.81 cm at the thigh and 0.38 cm at the upper arm, and the average intrarater difference in circumference was 0.73 cm at the thigh and 0.32 cm at the upper arm.

Results from the health-related quality of life and neurodevelopmental testing are reported in **Table IV** for the children with CHD, stratified by the presence or absence of clinically- confirmed PTS. Health-related quality of life was similar in the children with PTS and those without PTS, but the children with PTS had higher rates of neurodevelopmental delays on the gross motor skill and problem-solving indicators.

Discussion

In this study, we have shown that screening for PTS using the MVS is feasible and reliable in children with repaired CHD. The MVS performed reasonably well as a screening tool but showed limitations as a diagnostic tool. Although children with clinically confirmed PTS had delayed achievement of some developmental milestones, given that most PTS findings were mild and of unclear clinical relevance, a detrimental effect of PTS on long-term outcomes in children with repaired CHD remains to be proven. One possible explanation for the delays in achieving developmental milestones in patients with PTS is the higher rate of extracorporeal support and circulatory arrest in children with thrombosis after cardiac surgery. It also should be noted that the group of patients with thrombosis included an overrepresentation of children with hypoplastic left heart syndrome, who are known to be at high risk for developmental delays, which may partly explain the observed association

Table III. Physical assessment findings

Variables	Previous thrombosis (N = 33)	No previous thrombosis (N = 37)	Controls (N = 30)	*P* value
Upper body				
Discoloration, upper arm, n (%)	3 (8)	0 (0)	0 (0)	
Discoloration, lower arm, n (%)	0 (0)	0 (0)	0 (0)	
Hyperpigmentation, upper arm, n (%)	1 (3)	0 (0)	0 (0)	
Hyperpigmentation, lower arm, n (%)	0 (0)	0 (0)	0 (0)	
Dilated superficial collaterals, n (%)	4 (12)	4 (12)	2 (6)	
Upper arm circumference, left, cm, mean ± SD	16.1 ± 3.2	18.5 ± 4.6	19.9 ± 3.8	
Upper arm circumference, right, cm, mean ± SD	16.0 ± 3.3	18.5 ± 4.4	20.0 ± 3.9	
Difference in upper arm circumference				
Absolute difference, cm, mean ± SD	0.29 ± 0.33	0.36 ± 0.44	0.29 ± 0.34	
≥1.0 cm, n (%)	3 (9)	3 (8)	3 (10)	
Relative difference, %, mean ± SD	2.1 ± 2.6	1.9 ± 1.9	1.5 ± 1.7	
>3%, n (%)	7 (21)	3 (8)	3 (10)	
At least 1 positive finding, upper body, n (%)	7 (21)	4 (11)	2 (6)	.23
Lower body				
Discoloration, thigh, n (%)	0 (0)	0 (0)	0 (0)	
Discoloration, calf, n (%)	0 (0)	0 (0)	0 (0)	
Hyperpigmentation, thigh, n (%)	2 (6)	0 (0)	0 (0)	
Hyperpigmentation, calf, n (%)	1 (3)	0 (0)	0 (0)	
Dilated superficial collaterals, n (%)	3 (9)	4 (11)	1 (3)	
Thigh circumference, left, cm, mean ± SD	29.0 ± 4.6	32.9 ± 8.3	36.0 ± 7.3	
Thigh circumference, right, cm, mean ± SD	29.2 ± 4.8	32.9 ± 8.3	35.9 ± 7.5	
Difference in thigh circumference				
Absolute difference, cm, mean ± SD	0.68 ± 0.68	0.54 ± 0.46	0.52 ± 0.50	
≥1.5 cm, n (%)	6 (18)	3 (8)	3 (10)	
Relative difference, %, mean ± SD	2.4 ± 2.3	1.7 ± 1.5	1.4 ± 1.4	
>3%, n (%)	10 (30)	3 (8)	3 (10)	
At least 1 positive finding, lower body, n (%)	5 (15)	4 (11)	1 (3)	.28

between PTS and delayed neurodevelopment.[19,20] However, even after adjustment for these factors in regression models, the observed difference remained statistically significant, so this explanation can only partially account for the difference observed in this study. An association between PTS and impaired activity/participation in children has been reported recently.[21] Thus, it can be hypothesized that the children with cardiac defects with potential brain injury (ie, problem-solving delay on the ASQ) had their baseline motor impairment (ie, motor skills delay) potentiated by the presence of PTS, given that PTS is also associated with functional limitations irrespective of the underlying condition, working as a "second hit." Our findings are hypothesis-generating only, and as such, our data should be interpreted with caution.

An important challenge in diagnosing PTS is the lack of a diagnostic gold standard. Currently, the diagnosis is based on the presence of physical findings that are often subtle and of only mild severity. An important additional challenge in children is difficulty recognizing functional pain, further complicating the diagnosis. This challenge was particularly noticeable when we attempted to use the Manco-Johnson Instrument, which includes many more subjective elements. Given those limitations, we chose to focus solely on the MVS in this study and recommend using the MVS in young children with CHD.

	PTS positive screen	PTS negative screen
PTS positive diagnosis	CHD with thrombosis: 13/33 (39%) CHD no thrombosis: 0/37 (0%) Control subjects: 0/30 (0%)	CHD with thrombosis: 1/33 (3%) CHD no thrombosis: 0/37 (0%) Control subjects: 0/30 (0%)
PTS negative diagnosis	CHD with thrombosis: 1/33 (3%) CHD no thrombosis: 5/37 (14%) Control subjects: 2/30 (7%)	CHD with thrombosis: 18/33 (55%) CHD no thrombosis: 32/37 (86%) Control subjects: 28/30 (93%)

Figure. Comparison of results from PTS screening with MVS and clinical diagnosis of PTS stratified by patient category.

Table IV. Age-specific neurodevelopment and health-related quality of life assessment findings

Variables	PTS N	PTS Value	No PTS N	No PTS Value	*P* value	OR/EST (95% CI)	Adjusted *P* value*
PedsQL, mean ± SD							
Physical function	14	83 ± 16	56	84 ± 19	.90	–1.7 (–12.0 to 8.6)	.74
Emotional function	14	78 ± 19	56	74 ± 20	.51	–3.3 (–14.5 to 7.9)	.56
Social function	14	83 ± 17	56	82 ± 19	.84	–2.9 (–12.9 to 8.7)	.70
School function	9	78 ± 23	46	74 ± 21	.57	–4.9 (–19.4 to 12.0)	.65
ASQ, n (%)†	10		34				
Communication		6 (60)		11 (26)	.15	1.9 (0.3-10.6)	.49
Gross motor skills		7 (70)		8 (24)	.02	18.9 (2.3-155)	.006
Fine motor skills		5 (50)		10 (29)	.27	1.8 (0.3-9.6)	.51
Problem-solving		6 (60)		5 (15)	.008	6.2 (1.1-37)	.04
Personal-social		4 (40)		8 (24)	.42	1.2 (0.2-7.5)	.81

EST, parameter estimates.
*Adjusted in linear (PedsQL) and logistic (ASQ) regression models for hypoplastic left heart syndrome/left heart disease, use of extracorporeal life support, and operations performed with circulatory arrest.
†Proportion of patients in the delayed development or surveillance categories.

In children with CHD, many of the physical signs and symptoms often attributed to PTS can have other causes, including congenital conditions and sequelae of other complications. Given the range of signs and symptoms of PTS, it is difficult to know whether PTS is overdiagnosed when nonspecific clinical signs mimicking PTS are present or underdiagnosed, given the lack of a more objective test.

Our finding that most of the children with PTS in our cohort had only mild disease and nonspecific findings raises the question about the clinical relevance of mild PTS in children. Most previous studies have reported similar findings, with the majority of pediatric patients labeled with "PTS" having only mild and asymptomatic disease; in contrast, adult studies have shown important impacts from PTS. A few severe cases have been previously reported in the pediatric literature. The long-term effects on vascular function, functional status and quality of life remain to be determined, but in previous studies, negative impacts seem to have been limited to children with moderate or severe PTS.[22]

Another challenge to be considered is that the original Villalta Scale for adults focuses mostly on the lower limbs, whereas in children, approximately one-half of DVTs occur in the upper extremities. Although the MVS incorporates additional elements in an effort to account for this factor, a difference in accuracy between the upper and lower limbs remains. To address this, more recent studies have elected to increase the threshold for diagnosing PTS in children (≥2 clinical manifestations),[8,9] and new child-specific scales have been developed.[23]

This study must be viewed in light of some limitations. First, our cohort is not an inception cohort, and thus the proportion of patients with signs and symptoms of thrombosis or PTS cannot be taken as an estimate of PTS prevalence in pediatric patients after cardiac surgery. In addition, given the lack of a gold standard for diagnosing PTS, we had to use clinical history to confirm the diagnosis. Even if the clinical diagnosis of PTS were based on long-term evaluation of the limb affected by DVT in specialized clinics, using the clinical diagnosis of PTS might have artificially increased the diagnostic performance of the MVS, because the same clinical features are used by the thrombosis clinic. Furthermore, the application of the MVS by students (ie, non-content experts) may have contributed to overinterpretation of pain related to limb activity despite supervision provided by a local content expert. However, we believe that this limitation mimics the application of pediatric PTS scales outside of thrombosis clinic settings, reinforcing the importance of educational material to better orient healthcare providers on how to appropriately apply them.

The tools used for assessing quality of life were generic, pediatric-specific tools rather than disease-specific; PTS-specific tools for the assessment of quality of life in children are expected in the near future but are not currently available.[24] Finally, although we have shown delayed achievement of neurodevelopmental milestones in children with PTS, the number of patients assessed in this study was limited, and we were not able to adjust for the many other clinical factors known to be associated with neurodevelopment in children with CHD.[24]

Given that the majority of patients had mild disease, nonspecific clinical signs, and limited effects on functional status and quality of life, the clinical relevance of a PTS diagnosis in these children remains to be determined. Recent studies describing a new pediatric scale have attempted to overcome the issue of overcalling PTS.[23] Moreover, additional research elucidating the pathophysiology of PTS in children with the aim of improving diagnosis and case definition are also needed. ■

We acknowledge the invaluable contribution of Darlene Castle, RN, senior registered nurse in the Thrombosis Clinic at The Hospital for Sick Children, who evaluated children with positive clinical findings; Arvin Abadilla, MD, Stefan Kegel, MD, and Sameer Masood, MD for their help with the physical assessments; and Carly Imai-Compton, BAS, Janet McMullen, MD, and Katie Patterson for help with the pain assessment, neurodevelopment assessment, and health-related quality of life assessment.

Submitted for publication Jun 18, 2018; last revision received Sep 21, 2018; accepted Oct 26, 2018

Reprint requests: Cedric Manlhiot, PhD, 555 University Ave, Toronto, Canada M5G1X8. E-mail: cedric.manlhiot@sickkids.ca.

References

1. Raffini L, Huang YS, Witmer C, Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. Pediatrics 2009;124:1001-8.
2. Manlhiot C, Brandão LR, Kwok J, Kegel S, Menjak IB, Carew CL, et al. Thrombotic complications and thromboprophylaxis across all three stages of single ventricle heart palliation. J Pediatr 2012;161:513-9.e3.
3. Manlhiot C, Menjak IB, Brandão LR, Gruenwald CE, Schwartz SM, Sivarajan VB, et al. Risk, clinical features, and outcomes of thrombosis associated with pediatric cardiac surgery. Circulation 2011;124:1511-9.
4. Manlhiot C, Brandão LR, Schwartz SM, Sivarajan VB, Williams S, Collins TH, et al. Management and outcomes of patients with occlusive thrombosis after pediatric cardiac surgery. J Pediatr 2016;169:146-53.
5. Goldenberg NA, Donadini MP, Kahn SR, Crowther M, Kenet G, Nowak-Göttl U, et al. Post-thrombotic syndrome in children: a systematic review of frequency of occurrence, validity of outcome measures, and prognostic factors. Haematologica 2010;95:1952-9.
6. Kahn SR, Ginsberg JS. The post-thrombotic syndrome: current knowledge, controversies, and directions for future research. Blood Rev 2002;16:155-65.
7. Bergan JJ, Schmid-Schönbein GW, Smith PD, Nicolaides AN, Boisseau MR, Eklof B. Chronic venous disease. N Engl J Med 2006;355:488-98.
8. Avila ML, Duan L, Cipolla A, Kim A, Kahr WH, Williams S, et al. Postthrombotic syndrome following upper extremity deep vein thrombosis in children. Blood 2014;124:1166-73.
9. Avila ML, Pullenayegum E, Williams S, Yue N, Krol P, Brandão LR. Postthrombotic syndrome and other outcomes of lower extremity deep vein thrombosis in children. Blood 2016;128:1862-9.
10. Boulden BM, Crary SE, Buchanan GR, Journeycake JM. Determination of pediatric norms for assessment of upper venous system post-thrombotic syndrome. J Thromb Haemost 2007;5:1077-9.
11. Goldenberg NA, Brandão L, Journeycake J, Kahn S, Monagle P, Revel-vilk S, et al. Definition of post-thrombotic syndrome following lower extremity deep venous thrombosis and standardization of outcome measurement in pediatric clinical investigations. J Thromb Haemost 2012;10:477-80.
12. Kahn SR, Partsch H, Vedantham S, Prandoni P, Kearon C. Definition of post-thrombotic syndrome of the leg for use in clinical investigations: a recommendation for standardization. J Thromb Haemost 2009;7:879-83.
13. Kuhle S, Koloshuk B, Marzinotto V, Bauman M, Massicotte P, Andrew M, et al. A cross-sectional study evaluating post-thrombotic syndrome in children. Thromb Res 2003;111:227-33.
14. Goldenberg NA, Durham JD, Knapp-Clevenger R, Manco-Johnson MJ. A thrombolytic regimen for high-risk deep venous thrombosis may substantially reduce the risk of postthrombotic syndrome in children. Blood 2007;110:45-53.
15. Revel-Vilk S, Brandão LR, Journeycake J, Goldenberg NA, Monagle P, Sharathkumar A, et al. Standardization of post-thrombotic syndrome definition and outcome assessment following upper venous system thrombosis in pediatric practice. J Thromb Haemost 2012;10:2182-5.
16. Marks K, Hix-Small H, Clark K, Newman J. Lowering developmental screening thresholds and raising quality improvement for preterm children. Pediatrics 2009;123:1516-23.
17. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care 2001;39:800-12.
18. Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. Med Care 1999;37:126-39.
19. Goldberg CS, Mussatto K, Licht D, Wernovsky G. Neurodevelopment and quality of life for children with hypoplastic left heart syndrome: current knowns and unknowns. Cardiol Young 2011;21(Suppl 2):88-92.
20. Sananes R, Manlhiot C, Kelly E, Hornberger LK, Williams WG, MacGregor D, et al. Neurodevelopmental outcomes after open heart operations before 3 months of age. Ann Thorac Surg 2012;93:1577-83.
21. Avila ML, Brandão LR, Williams S, Ward LC, Montoya MI, Stinson J, et al. Pediatric post-thrombotic syndrome in children: toward the development of a new diagnostic and evaluative measurement tool. Thromb Res 2016;144:184-91.
22. Kumar R, Rodriguez V, Matsumoto JM, Khan SP, Weaver AL, McBane RD, et al. Health-related quality of life in children and young adults with post-thrombotic syndrome: results from a cross-sectional study. Pediatr Blood Cancer 2014;61:546-51.
23. Avila ML, Brandão LR, Williams S, Montoya MI, Stinson J, Kiss A, et al. Development of CAPTSure™ —a new index for the assessment of pediatric postthrombotic syndrome. J Thromb Haemost 2016;14:2376-85.
24. Smith J, Thornhill D, Goldenberg NA, Brandão LR, Sung L, Kahn S, et al. Validation of outcome instruments for venous thrombosis in children. Blood 2017;130:1101.