Received: 17 October 2017 | Accepted: 12 January 2018
DOI: 10.1002/rth2.12082

BRIEF REPORT

Assessment of limb edema in pediatric post-thrombotic syndrome

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Funding information
Physicians' Services Incorporated Foundation

Abstract

Background: Pediatric tools for diagnosis of post-thrombotic syndrome (PTS) include the assessment of limb edema as a symptom (patient/proxy-reported) and as a sign. However, it is unclear whether these two approaches refer to the same clinical aspect of PTS. This could result in overestimation of disease severity. We sought to evaluate the correlation among different techniques to assess limb edema as a sign and as a symptom in children who sustained upper extremity (UE) or lower extremity (LE) deep vein thrombosis (DVT) and were, therefore, at risk of PTS.

Methods: Limb edema was cross-sectionally measured as a symptom (ie, patient- or proxy-reported) and as a sign (ie, clinician-assessed limb circumference difference, limb volume ratio, bioimpedance spectroscopy ratio (BIS), and durometry ratio) in 140 children at risk of PTS (n = 70 UE-DVT, n = 70 LE-DVT). Item-item correlations were estimated using Pearson or Spearman correlation coefficients, as appropriate, and separately for the UE and LE groups.

Results: In the UE-DVT group, proxy-reported swelling correlated weakly to moderately with circumference difference and with volume ratio, but not with BIS ratio. In the LE-DVT group, proxy-reported swelling correlated moderately with thigh circumference difference and volume ratio, and patient-reported swelling correlated moderately with BIS ratio.

Conclusion: Our findings suggest that patient/proxy-reported and clinician-assessed limb edema measure slightly different aspects of PTS, justifying their inclusion in pediatric PTS tools. In addition, proxy-reported swelling was in closer agreement with clinician-assessed total limb size (ie, observed edema), and patient-reported swelling in the LE seemed to reflect limb fluid content (ie, perceived edema).

KEYWORDS
child, deep vein thrombosis, lower extremity, signs and symptoms, upper extremity

Essentials

- It is unclear if limb edema as a symptom and as a sign refers to the same clinical aspect of PTS.
- Limb edema was measured as a symptom and as a sign in 140 children at risk of PTS.
- Proxy-reported edema correlated weakly-moderately with circumference difference and volume ratio.
- Patient-reported edema correlated with bioimpedance ratio in the lower extremities only.
- Limb edema measured as a sign and as a symptom refers to slightly different aspects of PTS.

1 | BACKGROUND

Limb edema is a clinical feature common to all diagnostic classification schemes used in post-thrombotic syndrome (PTS) for children and adults,[1–5] and is one of the most frequent findings in children with upper extremity (UE)[6] and lower extremity (LE) PTS.[7]

The development of limb edema in the context of PTS is a consequence of the inflammatory response that accompanies thrombotic events. The inflammatory response opens gaps between endothelial cells, enhancing transcapillary filtration and extravasation of plasma proteins.[8] Limb edema develops when filtration exceeds lymphatic drainage, lymphatic drainage being the "safety valve" that prevents interstitial edema.[9]

Two of the instruments available for the diagnosis and severity rating of pediatric PTS, the Modified Villalta Scale[2] and the index for the Clinical Assessment of Post-Thrombotic Syndrome in children (CAPTSure™),[10,11] assess limb edema as a sign and as a symptom. The Modified Villalta Scale includes the symptom *swelling*, and the signs *increase in limb circumference*, and *pitting edema*, whereas CAPTSure™ assesses *patient/proxy-reported limb swelling* (symptom) and *limb circumference difference* (sign). In contrast, a third pediatric tool for PTS diagnosis, the Manco-Johnson Instrument,[1] only assesses the symptom *swelling with/without pitting edema*.

The inclusion in these instruments of more than one item assessing a single aspect of PTS, such as limb edema, can be of concern since this aspect may be overly weighted, potentially overestimating the severity of the disease. Moreover, according to theory, items included in a clinical index are expected to define different aspects of a complex clinical phenomenon or construct, and are therefore expected to be heterogeneous. According to Feinstein, if certain items are so closely related to each other that one can be substituted for the other, one of these items can be eliminated because it does not make a distinctive contribution to a clinical index.[12]

The present work aimed to investigate the item-item correlations between different techniques and approaches used to assess limb edema, including the items that are part of CAPTSure™. We focused on the relationship between edema as a symptom (patient- or proxy-reported) and as a sign (clinician-assessed limb edema as determined using different methods). The main goal was to investigate the degree to which the items that measure limb edema in CAPTSure™ overlap and measure the same aspect of PTS. This is relevant, since the potential overestimation of disease severity can have consequences not only in clinical practice (eg, treatment decisions), but also in research (eg, the identification of patients who might benefit from early interventions in order to prevent PTS).

2 | METHODS

The present study was part of a cross-sectional investigation on the diagnostic performance of a pool of signs and symptoms of pediatric UE and LE-PTS. PTS signs and symptoms were measured in 140 consecutive patients, aged 1-21 years, diagnosed with unilateral UE (n = 70) or LE-DVT (n = 70)[10,11] who were at risk of PTS, and who agreed to participate in the study. All patients were assessed at least 6 months post-DVT. The sample size of the original study was based on 95% confidence interval widths for sample correlations.[11]

The assessment of segmental edema included the following:

1. Limb edema as a symptom: Patient- or proxy-reported limb swelling was recorded using a standardized questionnaire, part of CAPTSure™, that inquired about frequency of limb edema in the past 4 weeks. Proxy report was sought in children aged ≤9 years and patient report was inquired in older children. Responses ranged from "never" to "every day", based on the questionnaire of the Edinburgh Vein Study (courtesy of Prof. FGR Fowkes, with permission).
2. Limb edema as a sign (clinician-assessed edema):
   a. Measurement of limb circumference: Circumferences of DVT-affected and unaffected limbs were measured using a tension-controlled measuring tape (Gulick II, Country Technology Inc.). In children with UE-DVT, the circumference of the mid-arm was assessed at the mid-distance between the acromium and olecranon process. In children with LE-DVT, the circumference of the mid-calf was measured at the mid-distance between the medial malleolus and the tibial tuberosity; mid-thigh circumference was measured at the mid-distance between the anterior superior iliac spine and the tibial tuberosity. The absolute difference between the DVT-affected and unaffected extremities was then estimated. Measurement of limb circumference was the method selected by experts to assess limb edema in CAPTSure™.[10]
   b. Measurement of limb volume: The volume of a series of truncated cones was estimated and volumes were then added up to determine the UE and LE volume, as previously described.[13] The upper and lower radius of each cone was calculated from the circumferences taken at six landmarks using the tension-controlled tape; the height (distance between the landmarks) of each truncated cone was measured using digital calipers. The volume of the DVT-affected limb was normalized by comparison to the unaffected limb and expressed as a ratio.

c. Bioimpedance Spectroscopy (BIS): The technique involves estimating the fluid content of a limb as the inverse of the impedance or resistance of the tissues to the passage of imperceptible electrical current[14]; impedance at low frequency reflects extracellular limb fluid content. UE and LE extracellular fluid content was estimated with a BIS SFB7 device (ImpediMed, Inc.). The protocol to assess segmental fluid content using BIS in children has been described elsewhere.[11,15] The obtained data were processed using the Bioimped Software to estimate the extracellular (R0) resistance value for each of the limbs; results were normalized by comparing the R0 value of the DVT-affected and unaffected the extremities and were expressed as a ratio (unaffected/affected limb resistance ratio or R0/R0 ratio).[16]
d. Pitting edema was measured using a 1- to 4-point clinical scale,[17] which assesses the depth of the indentation left after pressing firmly against the skin for five-seconds.
e. Skin resistance to indentation (durometry), which has been used to assess limb edema,[18,19] was measured using a hand held digital force gauge (initially Mecmesin Basic Force gauge, Mecmesin, and later Chatillon, Ametek Test & Calibration Instruments). Since the use of the device required patients to stay still for a few seconds, measurements were only performed in patients able to fulfill this requirement. Skin resistance to indentation was measured three times at one anatomic location in the UE or LE. Results, expressed in Newtons, were averaged to calculate the affected to unaffected limb skin resistance ratio.

Statistical analysis: Pearson and Spearman correlation coefficients were used to assess item-item correlations, as appropriate. This type of analysis is a central feature of index and scale development that helps explore the dimensionality of the data, and is a key determinant of scale reliability and quality under classical test theory.[20] In fact, the pattern of item-item correlation is one of the aspects that differentiates formative from reflective measurement models, the two main models used for tool development.[21] Analysis was stratified for UE and LE-DVT, given that the clinical manifestations of PTS were expected to differ when comparing these venous territories. Statistical analysis was performed using R (R Foundation for Statistical Computing, Vienna, Austria).

The study was approved by the Research Ethics Boards at The Hospital for Sick Children and the University of Toronto. Informed consent and assent, when applicable, were obtained.

3 | RESULTS AND DISCUSSION

The median age (25-75th percentile) of the patients at the time of study participation was 7 years (3-11 years) for children in the UE-DVT group, and 8.3 years (4-12 years) for patients in the LE-DVT group. The male to female ratio was 1.6 in both groups.

Limb edema was reported as a symptom in 9% (6/70) of cases in the UE-DVT group and 24% (17/70) of cases in the LE-DVT group. In terms of signs of PTS, clinician assessment of limb circumference difference showed that 21% (15/70), 50% (35/70), and 29% (20/70) of patients had an arm, thigh, and calf circumference difference larger than 1 cm, respectively. In addition, 26% (18/70) of children with UE-DVT and 49% (34/70) of those with LE-DVT had a BIS R0/R0 ratio above the 97th percentile for their age.[15] The median (25-75th percentile) volume ratio was 1.02 (1.00-1.07) for UE-DVT, and 1.06 (1.02-1.09) for LE-DVT. The median (25-75th percentile) durometry ratio was 1.06 (1.00-1.10) for UE-DVT and 0.98 (0.87-1.09) for LE-DVT. Pitting edema was not observed.

Item-item correlations corresponding to the UE-DVT and LE-DVT groups are shown in Tables 1 and 2. *Proxy-reported* frequency of swelling correlated weakly to moderately with items assessing total limb volume (limb circumference difference and volume ratio), but did not correlate with BIS R0/R0 ratio in the UE and LE-DVT group. In contrast, *patient-reported* frequency of swelling correlated significantly with BIS R0/R0 ratio in the LE-DVT group.

Two conclusions can be drawn from the results:

First, the overall weak to moderate correlations found between *proxy-reported* limb edema and limb circumference difference as well as the lack of correlation between *patient-reported* limb edema

TABLE 1 Correlations between items assessing upper extremity limb edema in children with deep vein thrombosis

	Circ. difference n = 70	BIS ratio n = 70	Limb volume ratio n = 70	Durometry n = 11
Swelling, patient-reported (≥10 years of age) n = 27	0.11 (−0.02 to 0.26; *P* = .57)	0.25 (0.17 to 0.50; *P* = .19)	0.05 (−0.10 to 0.21; *P* = .80)	−0.54 (−0.88 to −0.49; *P* = 0.13)
Swelling, proxy- reported (≤9 years of age) n = 43	**0.36 (0.14 to 0.53; *P* = .02)**	0.21 (−0.03 to 0.46; *P* = .18)	**0.42 (0.26 to 0.56; *P* = .005)**	–
Circ.difference n = 70	–	**0.48 (0.27 to 0.64; *P* < .001)**[a]	**0.57 (0.38 to 0.71; *P* < .001)**[a]	−0.004 (−0.77 to 0.67; *P* = .99)
BIS ratio n = 70	–	–	**0.25 (0.01 to 0.45; *P* = .04)**[a]	−0.27 (−0.74 to 0.81; *P* = 0.42)
Limb volume ratio n = 70	–	–	–	−0.09 (−0.8 to 0.67; *P* = 0.79)

Statistically significant correlations are shown in bold text. BIS, Bioimpedance Spectroscopy.
[a]Pearson correlation coefficient (other correlations: Spearman correlation coefficient).

TABLE 2 Correlations between items assessing lower extremity limb edema in children with deep vein thrombosis

	Circ. difference thigh n = 70	Circ. difference calf n = 70	BIS ratio n = 70	Limb volume ratio n = 70	Durometry n = 11
Swelling, patient-reported (≥10 years of age) n = 26	0.10 (−0.28 to 0.54; *P* = .61)	−0.09 (−0.45 to 0.23; *P* = .68)	**0.42 (0.17 to 0.66; *P* = .03)**	0.01 (−0.33 to 0.41; *P* = .94)	0.59 (0.22 to 0.87; *P* = .09)
Swelling, proxy- reported (≤9 years of age) n = 44	**0.49 (0.27 to 0.65; *P* < .001)**	0.05 (−0.16 to 0.26; *P* = .74)	0.15 (−0.14 to 0.34; *P* = .34)	**0.40 (0.24 to 0.59; *P* = .006)**	–
Circ. difference thigh n = 70	–	**0.50 (0.30 to 0.66; *P* < .001)**[a]	**0.45 (0.24 to 0.62; *P* < .001)**[a]	**0.68 (0.53 to 0.79; *P* < .001)**[a]	0.27 (−0.49 to 0.95; *P* = .42)
Circ. difference calf n = 70	–	–	**0.36 (0.14 to 0.55; *P* = 0.002)**[a]	**0.61 (0.44 to 0.74; *P* < .001)**[a]	0.47 (−0.49 to 0.97; *P* = .14)
BIS ratio n = 70	–	–	–	**0.39 (0.17 to 0.57; *P* < .001)**[a]	0.34 (−0.60 to 0.81; *P* = .30)
Limb volume ratio n = 70	–	–	–	–	0.46 (−0.34 to 0.92; *P* = .15)

Statistically significant correlations are shown in bold text. BIS, Bioimpedance Spectroscopy.
[a]Pearson correlation coefficient (other correlations: Spearman correlation coefficient).

and limb circumference difference suggest that the items included in CAPTSure™ for the assessment of limb edema measure different aspects of PTS, thus not overcalling PTS severity. It also suggests the value of measuring limb edema as a sign and as a symptom in older pediatric patients in particular.

Second, there was an interesting correlation pattern between some of the items. The statistically significant correlations found between *proxy-reported* limb swelling and *circumference difference* and *volume ratio* in the UE and LE-DVT group could be explained by the fact that they all reflect observable change in limb size (ie, *observed swelling*). In contrast, *patient-reported* swelling only correlated significantly with *BIS R0/R0 ratio* in the LE-DVT group, which suggests that the perception of swelling in the LE might correspond to a distinct aspect of limb edema, different from the observable edema that is assessed using a measuring tape. A study involving 108 adult patients following inguinal lymphatic surgery measured limb edema using patient report, clinical exam, and an image 3D method to estimate limb volume.[22] The researchers found that post-surgical patients who reported swelling and had clinically observed swelling had a mean volume increase of 477 mL in the operated leg as compared to the contralateral limb; patients who reported swelling that was not clinically observed had a mean 150 ml increase in limb volume, and patients without reported or clinical observed swelling had a mean 71 mL increase. Hence, whereas very small amounts of fluid accumulation in a limb are neither seen by the clinician nor perceived by the patient, large volume changes would be perceived and seen. An average 150 mL retention of limb fluid corresponds to the threshold for the perception of swelling, even when the swelling may not be clinically detectable, lending support to the difference between *perceived* and *observed* limb edema. Moreover, our findings suggest that BIS may play a role in detecting early signs of PTS as it has been shown to play in the early detection of lymphedema in adult patients.[23] Indeed, BIS is regarded the method of choice for early detection of lymphedema in adults.[24]

Whereas the existing pediatric PTS tools assess limb edema by measuring limb circumference, measurement of limb volume has been the standard method to determine the presence of edema associated with other diseases characterized by localized fluid accumulation, such as lymphedema, in adult patients.[24] Three main methods to measure limb volume are used in clinical practice: geometric volume assessment, water displacement, and perometry. However, these methods only provide a measurement of the total volume of the extremity, which is then inferred to reflect edema. In contrast, BIS allows obtaining specific information on the fluid content of an extremity, since it overcomes the bias that fat and muscle tissues can introduce.[24] The difference between assessing limb volume and limb fluid content may explain the correlation patterns found in our study.

No statistically significant correlations were found between durometry and the remaining items.

Our study needs to be interpreted in the light of a potential limitation. The number of patients overall, and specifically the ones undergoing durometry testing was small. The latter precludes drawing definitive conclusions regarding the role of durometry in the assessment of limb edema.

To conclude, we found that the assessment of edema as a sign and as a symptom likely captures different aspects of PTS and the inclusion of these two items is unlikely to lead to overestimation of disease severity. Moreover, the assessment of edema as a sign and as a symptom is particularly relevant in older patients, since patient-reported swelling measured an aspect of edema that resembled BIS-measured limb fluid content (perceived swelling), rather than clinician-assessed total limb size (observed swelling), at least in the LE. The role of BIS in the clinical assessment of PTS, particularly in the early detection of limb edema, remains to be further explored.

ACKNOWLEDGMENTS

The study was funded by a Health Research Grant from the Physicians' Services Incorporated Foundation.

RELATIONSHIP DISCLOSURES

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

LA/LB/BF designed the study. LA/LB/SW/MM performed measurements. LW assisted with BIS use and interpretation. CL/JV/MM assisted with study management. LA performed statistical analysis and wrote the manuscript. LB/LW/MM/ILC/AK/JS/CL/BF critically reviewed the manuscript.

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How to cite this article: Avila ML, Feldman BM, Williams S, et al. Assessment of limb edema in pediatric post-thrombotic syndrome. *Res Pract Thromb Haemost*. 2018;2:591–595. https://doi.org/10.1002/rth2.12082