



Full Length Article

Pediatric post-thrombotic syndrome in children: Toward the development of a new diagnostic and evaluative measurement tool



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ABSTRACT

Objective: Our goal was to conduct the item generation and piloting phases of a new discriminative and evaluative tool for pediatric post-thrombotic syndrome.

Methods: We followed a formative model for the development of the tool, focusing on the signs/symptoms (items) that define post-thrombotic syndrome. For item generation, pediatric thrombosis experts and subjects diagnosed with extremity post-thrombotic syndrome during childhood nominated items. In the piloting phase, items were cross-sectionally measured in children with limb deep vein thrombosis to examine item performance.

Result: Twenty-three experts and 16 subjects listed 34 items, which were then measured in 140 subjects with previous diagnosis of limb deep vein thrombosis (70 upper extremity and 70 lower extremity). The items with strongest correlation with post-thrombotic syndrome severity and largest area under the curve were pain (in older children), paresthesia, and swollen limb for the upper extremity group, and pain (in older children), tired limb, heaviness, tightness and paresthesia for the lower extremity group.

Conclusion: The diagnostic properties of the items and their correlations with post-thrombotic syndrome severity varied according to the assessed venous territory. The information gathered in this study will help experts decide which item should be considered for inclusion in the new tool.

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1. Introduction

Venous thromboembolic events are increasingly being reported in children [1]. This is in part due to the increased use of invasive diagnostic and therapeutic procedures, and the improvement of the detection methods for thrombotic events in modern medicine. As a consequence, venous thromboembolic events have become “the new epidemic” of hospitalized children [2], affecting approximately 1 in 250 hospitalized patients [3].

Post-thrombotic syndrome (PTS) is the most frequent long-term complication of deep venous thrombosis (DVT) affecting the upper and lower extremities in children and adults [4–6]. PTS is estimated to occur in 15 to 50% of adults affected by lower extremity (LE) deep vein thrombosis [7], and 7 to 46% of adult patients after sustaining

upper extremity (UE) deep vein thrombosis [8]. A systematic review of PTS in the pediatric population reported an overall frequency of 26% [95% Confidence Interval (CI): 23–28] and a frequency of 17% [95% CI: 14–20] among prospective studies [9], including both UE and LE venous territories.

It is well-established that PTS can lead to significant disability and poor quality of life in adult patients, particularly when complicated by skin ulcers [10]. The negative repercussion of PTS is largely due to its difficult, costly, and frustrating treatment [11,12].

The significance of PTS requires specific considerations in the pediatric population, since it is expected that the medical consequences of this syndrome will be disproportionately higher in younger patients [13], who are anticipated to endure the sequelae of PTS for a longer period of time [14]. Nonetheless, the proper diagnosis and monitoring of PTS remains a difficult challenge in this young population.

A systematic review identified two outcome-assessment tools that are commonly used in pediatric patients: the Modified Villalta Scale and the Manco-Johnson Instrument [9]. Both were derived from tools

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used in adult patients and are the current reference instruments proposed by the International Society of Thrombosis and Hemostasis (ISTH) for the assessment of PTS in children [15].

The Modified Villalta Scale derives from the Villalta Scale. The Villalta Scale [16,17] was developed for the assessment of LE PTS in adults, since 96 to 99% of DVT occurring in adult patients affects the venous territory of the LE, whereas only 1 to 4% affects the UE [18]. In striking contrast, 30 to 50% of cases of DVT in children affect the UE, thus highlighting the need for a pediatric tool that can be used to assess both UE and LE. For this reason, the original Villalta Scale was modified for use in pediatric patients by incorporating items (head edema, increase in limb circumference, and collateral vessels), replacing the four-point scoring system used in the adult scale to indicate the severity of signs and symptoms with a dichotomous score (absent/present) for most items, and reducing the five symptoms measured by the Villalta Scale (pain, cramps, heaviness, paresthesia, and pruritus) to two symptoms: pain or abnormal use and swelling, to simplify its applicability in children of all ages [19].

The Manco-Johnson Instrument [20], adapted from a classification tool for chronic venous diseases in adults, the Clinical-Etiologic-Anatomic-Pathophysiologic (CEAP) classification [21], combines clinical signs (edema, collateral circulation, skin changes, and skin ulcer) and one symptom (pain). Pain is assessed with the Wong-Baker FACES Pain scale [22] and is evaluated at three different levels: rest, daily activities, and aerobic exercise [15,20].

Both the Modified Villalta Scale and Manco-Johnson Instrument have been acknowledged to have limitations, which are mainly related to their measurement properties and the information they provide. The Pediatric PTS Task Force within the Pediatric and Neonatal Hemostasis Subcommittee of the ISTH advocated for further investigation in order “to identify [their] advantages and disadvantages” [15].

One of the main shortcomings of these tools is the lack of operationalization of the items (i.e., signs and symptoms), since the tools do not clearly define all the items and do not always specify how the items should be measured.

Importantly, physicians caring for adult patients with chronic venous disorders, including PTS, have already recognized that the lack of consistent definitions of the terms used in venous diseases negatively impacts the comparison of clinical outcomes across studies and the exchange of medical information [23], and can affect the reliability of the tools. To address this issue, an international and interdisciplinary group of experts in venous disorders developed several consensus documents, including the CEAP, revised CEAP, and VEIN-TERM consensus, which provided a common language for the reporting of chronic venous diseases [21,23].

In order to address the aforementioned limitations to the instruments currently used for the evaluation of pediatric PTS, we developed a new PTS assessment tool for this population. The present study includes the steps of item generation and piloting. The latter stage served to investigate the diagnostic properties of the items obtained and their association (correlation) with PTS severity.

2. Methods

Underlying theory: The construct PTS was defined according to the literature as “chronic venous symptoms and/or signs secondary to DVT and its sequelae” [23,24]. Therefore, PTS was considered to be defined precisely by the items (signs and symptoms) that are chosen to measure it [25]. This conceptualization of the nature of the construct is one of the features of the formative model, and is consistent with the theory underlying the measurement of clinical phenomena [26]. Moreover, under the formative model, the items that define PTS are not expected to be interchangeable, but rather each item represents a different facet or aspect of PTS.

Conceptual framework: Given our focus on signs and symptoms, the construct PTS was mapped to the Body Functions and Structures

component of the International Classification of Functioning, Disability and Health, Children and Youth Version [27]. Signs were defined as “visible manifestations of venous disorders”, and symptoms as “complaints related to venous disease”, as defined in the VEIN-TERM consensus [23].

Measurement purpose: The instrument was intended to be used for discriminative and evaluative purposes (i.e., to assess and monitor pediatric PTS) [28].

2.1. First phase: item generation and operationalization

2.1.1 Source of the items: items were obtained from two different sources

a. Expert survey. Physicians involved in the care of children with PTS for at least five years were identified using the ISTH Pediatric and Neonatal Hemostasis Subcommittee directory, in combination with recent publications in pediatric PTS. We aimed to reach experts from different continents and centers, since a panel of members with different perspectives on PTS would render a high proportion of high quality responses, over and above that of a homogeneous group [29]. Experts were asked to complete a survey by listing the signs and symptoms they considered should be measured to define and monitor UE and LE-PTS in children. The survey was designed using REDCap (Research Electronic Data Capture) software. To avoid introducing bias in the study by imposing our views, we used open ended questions [30]. In view of the potential use of different terms by different respondents for items that were essentially the same and for subsequent item operationalization, the experts were asked to provide a brief description/meaning of the items and/or proposed measurement approach. The design and implementation of the survey followed the theory of social exchange to motivate participation [31]. Reminder e-mails and/or phone calls were used to enhance response rates.

b. Patient interview. We conducted semi-structured interviews with school-aged children and teenagers who had sustained UE or LE-DVT before the age of 18 years, and who were subsequently diagnosed with mild to severe PTS by a pediatric thrombosis clinician. Patients <10 years of age were interviewed using a dyad-approach, in which the parent or proxy and the patient are interviewed at the same time. This approach has been reported to improve the assessment of health status in children, as compared to parent/proxy report alone [32]. In fact, we did not seek parent/proxy report alone, as the correlation between parent and child response has been shown to be low to moderate [32,33]. Young adults no longer followed-up at our institution were interviewed over the phone. Patients with cognitive impairment or not fluent in English were not enrolled in the study.

2.1.2. Sample size

Given the well-defined area of knowledge and the limited number of experts in the field, a sample size of at least 14 experts providing complete responses to the survey was considered adequate in the context of the study [34]. Patients were enrolled until reaching saturation (i.e., no new items were obtained), which usually entails between 5 and 25 patients, based on general guidelines for the conduction of qualitative studies using the phenomenological approach [35].

2.1.3. Analysis

Clinical judgment [36] was followed to identify and group items that measure the same aspect of PTS.

2.2. Second phase: item piloting

Under the formative model, each item (sign or symptom of PTS) captures a different aspect of the construct PTS. Hence, the challenge is to select the items that are most representative of the construct. To address this issue, we piloted the items obtained in the previous phase in a cohort of children at risk of PTS, and assessed the diagnostic

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