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Limitations of the Villalta scale in diagnosing post-thrombotic syndrome

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ABSTRACT

Introduction: The Villalta scale is currently the recommended tool for diagnosing post-thrombotic syndrome (PTS) in clinical studies, but there is concern that the sensitivity and specificity of the scale might be low. We aimed to evaluate the diagnostic accuracy of the Villata scale using criteria in line with clinical practice as a reference.

Material and methods: We invited patients with a history of proximal DVT during 2006–09 to participate in a cross-sectional follow-up study of long-term complications after DVT. PTS was diagnosed by the Villalta scale, and by the following four mandatory and predefined clinical criteria used as a reference for PTS: 1. Objectively verified DVT; 2. chronic complaints (> 1 month) in the DVT leg; 3. complaints appeared after the DVT; and 4. an alternative diagnosis was unlikely.

Results: We included 88 of 170 eligible patients (52%). With our clinical criteria as a reference the sensitivity and specificity of the Villalta scale for diagnosing PTS were 75% (95% CI 60–87%) and 66% (95% CI 50–80%), respectively. Fifteen patients were diagnosed with PTS by the Villalta scale only. These patients more often experienced pain or had comorbidity that could explain their leg symptoms and signs. Eleven patients diagnosed with PTS by the clinical criteria only, had more fluctuating heaviness and edema.

Conclusions: Our findings indicate that the diagnostic accuracy of the Villalta scale has limitations. Incorporating chronicity, whether the leg problems appeared following the DVT, fluctuations of heaviness and edema, and comorbidity in PTS assessment may improve the diagnostic accuracy.

1. Introduction

Approximately 50% of patients will develop chronic leg problems known as the post-thrombotic syndrome (PTS) following an acute proximal deep vein thrombosis (DVT) [1]. Manifestations of PTS include pain, hereunder pain on exercise or venous claudication, swelling, heaviness, skin changes, and in severe cases, venous ulcers [2]. Symptoms can be intermittent or persistent and are typically aggravated by standing or walking, and relieved by resting and leg elevation [3]. A number of clinical tools have been used for PTS assessment; however, the correlations between them are poor [4–6]. To standardize the assessment of PTS for research purposes, the International Society on Thrombosis and Haemostasis (ISTH) has recommended the use of the Villalta scale (Table 1), which was developed for the diagnosing, grading, prediction, and follow-up of PTS [7–9].

In the absence of a gold standard objective diagnostic test, the Villalta scale has been validated in terms of correlation to validated health related quality of life (QoL) instruments and correlations between the Villalta summary score and known anatomic and physiologic abnormalities associated with chronic venous disease [11]. The Villalta scale is now widely accepted and used in cohort studies and in recent multicenter randomized trials evaluating functional end-points [6,12,13]. However, the scale does not reflect the duration of the symptoms and signs or whether they appeared or worsened following the DVT. The various symptoms and signs included in the Villalta scale can be seen also in other conditions, e.g., primary venous insufficiency, trauma, central venous hypertension, and arthrosis [3,14–17]. Previous studies have shown that Villalta scores in the ipsilateral and

Abbreviations: PTS, post-thrombotic syndrome; DVT, deep venous thrombosis; CaVenT, catheter-directed venous thrombolysis; ISTH, International Society on Thrombosis and Haemostasis; QoL, quality of life; Q-5D-3 L, EuroQoL-5D-three level version; VEINES, Venous Insufficiency Epidemiological and Economic Study; SPSS, Statistical Package for Social Sciences; CDT, catheter-directed thrombolysis; CI, confidence interval

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Table 1
Diagnostic tools developed for post-thrombotic syndrome.

PTS instrument	Criteria
Villalta scale [8][a]	5 symptoms (scored by the patient) • Pain • Cramps • Heaviness • Paresthesia • Pruritus 6 clinical signs (scored by nurse/physician) • Edema • Skin induration • Hyperpigmentation • Redness • Venous ectasia • Pain on calf compression
Ginsberg measure [10][b]	Pain and swelling (made worse by standing/walking and relieved by rest/elevation of the leg) of ≥1 month duration and ≥6 months after DVT

[a] The symptoms and clinical signs in the Villalta scale are scored from 0 (=absent) to 3 (=severe) and are summed for total score (range 0–33). Presence/absence of venous ulcer (open or healed) is registered. A total score < 5 indicates no PTS. ≥5 points corresponds to any grade of PTS; 5–9 points indicate mild PTS, 10–14 points moderate PTS, and ≥15 points or the presence of a venous ulcer is classified as severe PTS [8].

[b] The Ginsberg measure does not grade PTS.

contralateral legs are strongly correlated indicating that cases considered as PTS may reflect pre-existing chronic venous disease [18,19].

In our experience, some patients with leg problems that obviously relate to the DVT, i.e., they appeared after a DVT in the same leg with no other obvious causes, may not qualify as PTS by the Villalta scale. This is typical for patients suffering from venous claudication, which can develop from persistent iliofemoral post-thrombotic obstruction and is a condition of limiting pain and tightness in the thigh or calf during exercise which subsides with rest [20]. Some of these patients only report symptoms related to activity and without any other PTS symptoms or signs. The Villata scale addresses “pain”, “heaviness”, and “pain on calf compression”, but does not relate symptoms or sign to activity or to fluctuation during activity or time of day. In contrast to the Villalta scale, the Ginsberg measure includes assessment of leg symptoms and signs with activity and diurnal changes (Table 1) [10]. In studies were PTS has been assessed by both clinical tools; the Villalta scale has diagnosed nearly 5 times more patients with PTS than the Ginsberg measure [6,21]. Moreover, the correlation between the two tools was poor, and patients diagnosed by the Ginsberg measure reported poorer quality of life (QoL) [6,21].

Accordingly, the sensitivity and specificity of the Villalta scale seems to have important limitations, and there is an urgent need for improving the assessment of PTS in clinical trials. In clinical practice, PTS should not be diagnosed earlier than 3–6 months post-DVT when characteristic chronic symptoms without any other obvious reason develop in the DVT leg [3,8]. The present study aimed to examine the accuracy of the Villalta scale using four predefined clinical criteria in line with clinical practice as a reference standard in patients with a history of upper femoral and/or iliac DVT.

2. Materials and methods

2.1. Study design and population

In 2017 we invited the 170 patients still alive who were included in 2006–09 for a randomized clinical study that compared additional catheter-directed thrombolysis (CDT) for high proximal DVT to conventional anticoagulant treatment, the catheter-directed venous thrombolysis (CaVenT)study [12,22,23] to participate in a one time visit, cross-sectional follow-up study. The southeastern Norway Regional Committee for Medical and Health Research Ethics (REK) approved the study (no. 2015/1567), and written informed consent was obtained from all participants.

Table 2
Four mandatory and predefined clinical criteria for PTS.

1. Previous objectively verified DVT
2. Development of chronic complaints in the DVT leg
3. The complaints appeared or worsened following the DVT
4. An alternative diagnosis to the patient's complaints is not likely

2.2. Variables and instruments

We extracted data from baseline and five years follow-up of the CaVenT study, including PTS assessment and comorbidities. At the study visit both lower limbs were clinically examined, PTS was assessed by the Villalta scale using the Villalta visual guide [3,19]and by the Ginsberg measure [10], in addition to four mandatory and predefined clinical criteria (Table 2). Characteristics of the patients' leg symptoms and signs and various leg comorbidities, including varicose veins, previous surgery, fractures, and musculoskeletal disorders were registered during the study visit. If comorbidity was present, the chronology of the affected limb, i.e. index DVT, and the leg symptoms and signs as well as the chronicity of the patient's complaints, were further explored. QoL was assessed by the generic QoL questionnaire EQ-5D-3L [24,25], and the disease-specific QoL questionnaire VEINES QoL/Sym [26,27].

2.3. Statistical analyses

Normally distributed continuous variables were presented as means and standard deviations, and when compared between groups a two-sample *t*-test was used. Non-normally distributed continuous variables were presented as medians and interquartile ranges, and a non-parametric test (Mann–Whitney) was used for comparison between groups. All statistical tests were two-sided, and p-values < 0.05 were considered statistically significant. Sensitivity and specificity of the Villalta scale and the Ginsberg measure were calculated with four mandatory and predefined clinical criteria as a reference (Table 2). The EQ-5D-3L summary index was calculated based on values from a Danish population [28]. The VEINES-QoL and VEINES-Sym scores were computed using standard scoring algorithms obtained from the authors [27]. Statistical Package for Social Sciences (SPSS) version 25 was used for all analyses (SPSS Inc., Chicago, Illinois, USA).

3. Results

From October 2017 to June 2018, 88 (52%) of still eligible patients from the CaVenT study [12,23] accepted to participate and presented for a study visit. The mean age was 60.7 (SD 15.4) years, and 31 (35%) participants were female (Table 3). Based on the baseline, and five years follow-up data of these patients, the characteristics of participants and non-participants in the present study were comparable except for comorbidity of the index leg which was present in 32 (36%) of non-participants compared to 11 (12.5%) of participants (p < 0.001) (Supplementary table).

PTS was diagnosed in 44 patients (50%) by the predefined clinical criteria, in 48 patients (54.5%) by the Villalta scale, and in 23 patients (26.1%) by the Ginsberg measure (Table 4). With the clinical criteria as a reference, the sensitivity and specificity of the Villalta scale were 75% (95% CI, 60–87%) and 66% (95% CI, 50–80%), respectively, and of the Ginsberg measure 52% (95% CI, 37–68%) and 100%, (95% CI, 92–100%) respectively.

In subgroups analysis, there was statistically no significant difference of PTS diagnosed by the predefined clinical criteria in the participants receiving additional CDT versus conventional anticoagulant

Table 3
Demographic and clinical characteristics of study participants.

	Total N = 88	Additional CDT[a,b] N = 43	Conventional anticoagulant treatment[a] N = 45
Age (years)	60.7 (15.4)	63.4 (14.6)	58 (15.8)
Women	31 (35)	12 (27.9)	19 (42.2)
Weight women (kg)	77.1 (21.3)	74.4 (17)	78.7 (24)
Weight men (kg)	89.9 (13.7)	91.2 (14.6)	88.4 (12.7)
Time since index DVT (years)[c]	9.5 (1.2)	9.5 (1.2)	9.6 (1.3)
Localization of index DVT[c,d]			
Isolated pelvic	3 (3.4)	2 (4.7)	1 (2.2)
Iliofemoral	40 (45.5)	18 (41.9)	22 (48.9)
Upper femoral	42 (47.7)	23 (53.5)	19 (42.2)
Recurrent ipsilateral DVT[e]	4 (4.5)	1 (2.3)	3 (6.7)
Venous leg ulcer, healed	5 (5.7)	3 (7)	2 (4.4)
Venous leg ulcer, open	1 (1.1)	–	1 (2.2)
Occupational status			
Full-time work	28 (32)	11 (25)	17 (38)
Retired	45 (51)	24 (56)	21 (47)
Part time work/on sick leave	15 (17)	8 (19)	7 (15)
Continued anticoagulation	45 (51)	25 (58)	20 (44)
Continued regular use of elastic compression stockings	59 (67)	26 (61)	33 (73)
For symptom relief	29 (49.2)	13 (30.2)	16 (35.6)
On physician's recommendations	30 (50.8)	14 (32.6)	16 (35.6)

Data are mean (SD) or n (%).
[a] Treatment groups in the catheter-directed venous thrombolysis (CaVenT) study [29].
[b] CDT; catheter-directed thrombolysis.
[c] Baseline data from the CaVenT study.
[d] Data missing on three study participants.
[e] Five years follow-up data from the CaVenT study.

Table 4
PTS by the four clinical criteria, the Villalta scale, and the Ginsberg measure.

	PTS by clinical criteria		
	Yes	No	Total
PTS by Villalta scale			
Yes	33 (37.5)	15 (17.0)	48 (54.5)
No	11(12.5)	29 (33.0)	40 (45.5)
PTS by Ginsberg measure			
Yes	23 (26.1)	0	23 (26.1)
No	21 (29.9)	44 (50.0)	65 (73.9)
Total	44 (50.0)	44 (50.0)	88 (100)

Data are n (%).

treatment, i.e., 19 (44.2%) versus 25 (55.6%), respectively (p = 0.286).

Overall, seventy-three of the 88 patients (83%) reported chronic symptoms and signs in the index leg, and the majority of these (53%) could be explained by various comorbidities. Post DVT symptoms consistent with venous claudication were reported in eight (9%) patients. Nine patients (10.2%) reported chronic leg symptoms and signs present before the index DVT. Forty-three (48.8%) also had chronic symptoms and signs in the contralateral leg, and 38 of these (88.3%) could relate this to a specified comorbidity. Twenty-two (25%) had a history of DVT also in the contralateral leg, and 11 (50%) of these reported contralateral chronic post-thrombotic leg symptoms and signs.

The diagnostic evaluation by the Villalta scale and by the predefined clinical criteria was non-consistent in 26 patients (Table 4). Thirteen of the 15 patients diagnosed with PTS by the Villalta scale, but not by our clinical criteria, reported leg comorbidities that were likely to explain their leg symptoms and signs. Five of these 15 patients had varicose veins, one had sequelae from fractures, one had sequelae from trauma and stroke, six reported symptoms consistent with arthrosis, and one had psoriasis arthritis. The remaining two reported leg symptoms and signs associated with the use of elastic compression stockings, e.g., pain, pruritus, and redness. Two of the 11 patients diagnosed with PTS by our clinical criteria only, reported leg comorbidities in addition to possible PTS.

Of the 15 patients diagnosed with PTS by the Villalta scale only, 10 reported having the same chronic leg symptoms and signs in both the index leg and in the contralateral limb, as opposed to two of the 11 patients diagnosed by our clinical criteria only. Correspondingly, three (29%) vs. two (18%) reported a history of DVT in the contralateral limb, while none had a history of venous leg ulcers.

Of the 15 patients diagnosed with PTS by the Villalta scale only, 11 reported pain compared to three of 11 patients diagnosed with PTS by our clinical criteria only. The 11 patients diagnosed by our clinical criteria only, more frequently reported heaviness (8 vs. 5), edema (11 vs. 6), and fluctuation (11 vs. 5).

Post DVT symptoms consistent with venous claudication were reported in one patient diagnosed with PTS by the Villalta scale only, and in one patient diagnosed by our clinical criteria only. None of the 15 patients with PTS by the Villalta scale only, had PTS according to the Ginsberg measure while two of the 11 diagnosed by our clinical criteria only were also diagnosed with PTS by the Ginsberg measure.

3.1. Quality of life

Regardless of method for PTS assessment, the median EQ-5D index value, VEINES-QoL, and VEINES-Sym scores were lower, i.e., indicating poorer HRQoL, in patients with PTS compared to patients without PTS. The patients diagnosed with PTS by the Ginsberg measure tended to have the lowest scores (Table 5).

Table 5
Generic and disease-specific quality of life and symptom severity according to diagnostic criteria of PTS assessment.

Quality of life, N = 88						
	EQ-5D index value	p value[a]	VEINES-QOL	p value[a]	VEINES-Sym	p value[a]
Our predefined clinical criteria						
PTS	0.82 (0.7–1.0)	0.024	47.7 (41.6–55.2)	< 0.001	46.5 (39.8–53.8)	< 0.001
No PTS	1.0 (0.8–1.0)		56.1 (53.3–58.4)		56.6 (51.0–60.0)	
Villalta scale						
PTS	0.82 (0.8–1.0)	0.002	48.2 (40.8–54.7)	< 0.001	46.3 (40.0–53.8)	< 0.001
No PTS	1.0 (0.8–1.0)		56.8 (54.1–58.2)		56.9 (52.8–60.0)	
Ginsberg measure						
PTS	0.77 (0.7–0.8)	< 0.001	44.2 (33.2–48.4)	< 0.001	42.2 (34.0–47.0)	< 0.001
No PTS	1.0 (0.8–1.0)		55.5 (52.3–57.9)		55.8 (49.6–58.8)	

Data are median values (interquartile range).
[a] Mann Whitney *U* test.

4. Discussion

Compared to predefined clinical criteria based on clinical practice we found that the Villalta scale had limitations in specificity and sensitivity for diagnosing PTS. Patients diagnosed with PTS by the Villalta scale only, more often reported leg comorbidities and pain than those diagnosed with PTS by the clinical criteria only. Among patients diagnosed with PTS by the clinical criteria only, fluctuating heaviness and edema were more frequent.

The results add to the evidence that the diagnostic accuracy of the Villalta scale has limitations, and that patients can be diagnosed with PTS despite leg problems of non-thrombotic etiology. We found that limitations in specificity were mainly due to co-existing leg comorbidity. In line with our findings, Galanaud et al. found a strong correlation between the Villalta scale in the ipsi- and contralateral limbs (40% of the 116 patients) suggesting that many patients diagnosed with PTS by the Villalta scale could have a preexisting chronic venous disease and not PTS [18]. In another study, 27 of 92 (29.3%) PTS patients had a Villalta score of four or higher in the contralateral limb not previously affected by DVT [19].

The Villalta scale does not reflect fluctuation of edema and heaviness of the leg, and our findings indicate that this may contribute to its limitations in diagnostic sensitivity. The typical fluctuation of chronic venous leg symptoms and signs has been reported by others [3,30,31], and in one study this was what best distinguished chronic venous disease from other diseases of the lower limb [16]. In contrast to the Villalta scale, the Ginsberg measure includes fluctuation of swelling made worse by standing/walking and relieved by rest/elevation of the leg. This might explain the superior specificity of the Ginsberg measure indicated in our findings.

In line with other studies, both generic QoL and disease-specific QoL were poorer in patients with PTS compared to patients without PTS [32,33]. This was regardless of clinical PTS tool. Additionally, both generic QoL and disease-specific QoL tended to be lower among patients diagnosed with PTS by the Ginsberg measure indicating that this tool captures more severe PTS and may be more specific. Previous studies have reported poorer QoL in patients assessed with PTS by the Ginsberg measure than patients diagnosed with PTS by the Villalta scale [21,33,34]. Others have shared our concerns regarding the limitations of the Villalta scale, and it has been postulated that an incorporation of a disease-specific QoL questionnaire in addition to the Villalta scale could be superior to the Villalta scale alone [31,33].

The Villalta scale does not necessarily reflect physical limitations, e.g., venous claudication as a manifestation of the PTS [31], and this is likely to contribute to the limited sensitivity of the scale. However, there were no differences in physical limitations among the patients where the diagnostic evaluations were non-consistent. This may relate to lack of statistical power due to the small number of participants in this study and the low frequency of isolated iliac DVT [35].

PTS is associated with increased health care costs and reduced QoL, and there is no curative treatment for PTS [32,36–38]. Hence there is need for more research as patients with clinically relevant PTS are in need of better treatment options. However, the various clinical tools that have been used to diagnose PTS limit the possibility to compare results across studies on how to prevent and treat PTS [4,5]. The Villalta scale does not capture all important symptoms of PTS. Moreover, PTS assessment must relate to a previously verified DVT and be performed following the acute phase, i.e., no < 3 months following the DVT diagnosis to reflect the true chronicity of the syndrome. We believe that PTS assessment with stricter clinical criteria will increase the accuracy and facilitate more robust PTS research in the future. Until we have a better diagnostic tool for PTS, results from existing studies reporting on PTS prevalence, risk factors, prophylaxis, and treatment should be interpreted with caution [4–6,21,39].

This exploratory analysis is based on a small number of patients, and not from a formal derivation study for a new diagnostic tool for PTS. Another major limitation is the lack of a gold standard diagnostic test for PTS assessment. The four mandatory predefined clinical criteria used as a reference method has previously not been validated. Additionally, one study investigator performed the assessments of PTS by all three diagnostic instruments. The participants were asked not to wear compression stockings on the examination day, however this was often forgotten, and as a result this may have masked symptoms and signs of PTS at the clinical visit. The inclusion of 52% of eligible patients may indicate a selection bias that can have influenced our results. However, the characteristics of participants and non-participants were comparable except for leg comorbidity, which was less frequent among those who participated. Our findings indicate that leg comorbidity is the main contributing parameter for the limited specificity of the Villalta scale. Accordingly, the specificity of the scale may be even lower than our findings indicate. The value of CDT in PTS prevention is still debatable [12,23,40]. Despite an equal distribution between participants previously treated with additional CDT versus conventional treatment an effect on the long-term symptoms and signs in the CDT group cannot be excluded. Finally, the generalizability of our findings may be limited as our study population with a high proximal DVT is likely to be at higher risk for developing PTS compared to less proximal DVT.

We conclude that both specificity and sensitivity of the Villalta scale are limited when compared to predefined clinical criteria. Accordingly, improvements in the sensitivity and specificity of a diagnostic tool seem warranted. Based on our findings we suggest further research to incorporate chronicity, the chronology of DVT and the leg symptoms and signs, fluctuations of heaviness and edema, and possible comorbidity in the development of future diagnostic criteria for PTS.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.10.018.

Addendum

T. Enden, H. S. Wik, and P.M. Sandset conceived the research study design. M. Engeseth performed the interviews and the clinical examinations. M. Engeseth and H. S. Wik performed the analysis and interpreted the data. M. Engeseth drafted the manuscript, and all authors critically revised the manuscript.

Declaration of competing interest

The authors state that they have no conflict of interest.

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