Measuring functional limitations after venous thromboembolism: Optimization of the Post-VTE Functional Status (PVFS) Scale

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Abstract: INTRODUCTION We recently proposed a scale for assessment of patient-relevant functional limitations following an episode of venous thromboembolism (VTE). Further development of this post-VTE functional status (PVFS) scale is still needed. METHODS Guided by the input of VTE experts and patients, we refined the PVFS scale and its accompanying manual, and attempted to acquire broad consensus on its use. RESULTS A Delphi analysis was performed involving 53 international VTE experts with diverse scientific and clinical backgrounds. In this process, the number of scale grades of the originally proposed PVFS scale was reduced and descriptions of the grades were improved. After these changes, a consensus was reached on the number/definitions of the grades, and method/timing of the scale assessment. The relevance and potential impact of the scale was confirmed in three focus groups totaling 18 VTE patients, who suggested additional changes to the manual, but not to the scale itself. Using the improved manual, the -statistics between PVFS scale self-reporting and its assessment via the structured interview was 0.75 (95%CI 0.58-1.0), and 1.0 (95%CI 0.83-1.0) between independent raters of the recorded interview of 16 focus groups members. CONCLUSION We improved the PVFS scale and demonstrated broad consensus on its relevance, optimal grades, and methods of assessing among international VTE experts and patients. The interobserver agreement of scale grade assignment was shown to be good-to-excellent. The PVFS scale may become an important outcome measure of functional impairment for quality of patient care and in future VTE trials.

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ABSTRACT

Introduction: We recently proposed a scale for assessment of patient-relevant functional limitations following an episode of venous thromboembolism (VTE). Further development of this post-VTE functional status (PVFS) scale is still needed.

Methods: Guided by the input of VTE experts and patients, we refined the PVFS scale and its accompanying manual, and attempted to acquire broad consensus on its use.

Results: A Delphi analysis was performed involving 53 international VTE experts with diverse scientific and clinical backgrounds. In this process, the number of scale grades of the originally proposed PVFS scale was reduced and descriptions of the grades were improved. After these changes, a consensus was reached on the number/definitions of the grades, and method/timing of the scale assessment. The relevance and potential impact of the scale was confirmed in three focus groups totaling 18 VTE patients, who suggested additional changes to the manual, but not to the scale itself. Using the improved manual, the k-statistics between PVFS scale self-reporting and its assessment via the structured interview was 0.75 (95%CI 0.58–1.0), and 1.0 (95%CI 0.83–1.0) between independent raters of the recorded interview of 16 focus groups members.

Conclusion: We improved the PVFS scale and demonstrated broad consensus on its relevance, optimal grades, and methods of assessing among international VTE experts and patients. The interobserver agreement of scale grade assignment was shown to be good-to-excellent. The PVFS scale may become an important outcome measure of functional impairment for quality of patient care and in future VTE trials.

1. Introduction

Along with recurrent venous thromboembolism (VTE), bleeding and mortality, both quality of life and functional limitations are important outcome measures that matter greatly to VTE patients [1–7]. These two issues are mostly determined by the presence and severity of leg or chest pain, dyspnea, anxiety, post thrombotic panic syndrome, and depression, all of which are important determinants of recovery after VTE [4–6,8–21]. Persistent functional limitations and/or decreased quality of life after an episode of VTE are framed within the concepts of...
the post-thrombotic syndrome (PTS) and post-pulmonary embolism (PE) syndrome [2,22]. PTS manifests as chronic venous insufficiency in a limb affected by deep vein thrombosis (DVT) caused by venous obstruction and/or venous reflux [22,23]. The post-PE syndrome includes chronic thromboembolic pulmonary hypertension (CTEPH), chronic thromboembolic pulmonary vascular disease (CTED), and persistent right ventricular dysfunction, but also otherwise unexplained new or progressive exercise intolerance after PE [2,24–26].

While there are validated questionnaires for the assessment of pain, dyspnea, anxiety, and depression, these were mostly not designed to rank patients into meaningful categories and do not target functional outcomes per se. The same holds true for measures of quality of life [5,14,23,24,27,28]. Therefore, quality of life outcomes between treatment strategies are difficult to put into a comprehensive perspective and may not always serve their purpose when used as a main outcome measure in the setting of an experimental study. Given these gaps, we recently proposed the first version of the post-VTE functional status (PVFS) scale, which is meant to be used as a comprehensive measure to quantify the consequences of VTE on functional status. It covers the full spectrum of functional outcomes, ranging from no symptoms to death, and focuses on both limitations in usual duties/activities and changes in lifestyle (Appendix A) [11]. The scale, required further development (Table 1).

In the current study, we sought to refine the scale and acquire broad consensus on the methods of assigning a PVFS scale grade at a certain time point, guided by the expertise of VTE specialists as well as by patient focus groups. Moreover, we aimed to establish the reproducibility of PVFS scale assessment.

2. Methods

2.1. Study design

The Delphi method was used to assess expert consensus among a panel of VTE specialists with scientific and clinical expertise in measuring and managing long-term outcomes of VTE across different patient subgroups. A Delphi analysis is a widely used structured process to achieve consensus through opinions and feedback from a group of informed experts [29–31]. The process is anonymous and focuses on a predefined dilemma, usually lacking empirical evidence. The expert panel is consulted via questionnaires. Responses are analyzed and used to guide the next round of new questions. In the subsequent rounds of questions, experts are provided with the overall results of the previous round of the Delphi study. The optimal level of consensus is usually achieved after two or more rounds [32].

A patient focus group represents a qualitative research method in which a small group of participants discuss a topic chaired by a moderator [33]. It is an appropriate and suitable method to involve patients in the development of scales and other medical instruments for various medical conditions. Following a number of semi-structured questions to help focus the group’s discussion, participants can explore issues of concern, propose changes and identify strategies for further exploration of the topic at hand.

In both stages of the study, we aimed to achieve consensus and explore the experts’ and patients’ view on six issues: 1) the relevance of measuring functional limitations after VTE both in clinical trials and in clinical practice, 2) whether current available tools are sufficiently reliable to assess functional limitations after VTE, 3) the appropriateness of the PVFS scale for measuring functional limitations after VTE, 4) whether the PVFS scale has sensible and representative scale categories, 5) whether the PVFS scale captures both PTS and post-PE syndrome, and 6) how and when the scale should be measured.

2.2. Selection of experts and patients

Experts were selected based on the following criteria: 1) leaders in the VTE field, as demonstrated by a strong publication track record and leading roles in scientific societies; or 2) clinical experience in treating patients with post-VTE complications. The panel of physicians and epidemiologists was selected to represent a wide geographic area, to include both sexes, and to cover broad medical specialties, including (pediatric) hematology, cardiology, pulmonology, vascular medicine and vascular surgery. The experts completed the questionnaires anonymously and were unaware of the identity of the other experts involved. Patients were invited to participate in the focus groups via mailings from the Netherlands Thrombosis Foundation (patient association). As with the panel, we aimed to include patients who do or did experience functional limitations after their VTE diagnosis, rather than to represent the whole of VTE patients. Therefore, we did not apply any selection criteria except for consenting to participation, accepting that selection bias would occur.

2.3. Delphi and focus group processes

A multinational steering committee of four members was established to oversee the process (DB, SB, BS and FK). A first version of the Delphi questionnaire was drafted by two members (DB and FK). All members of the steering committee provided feedback on the questionnaire and approved its final version. The first round of our Delphi study consisted of a total of 10 multiple choice questions/statements (Appendix B). Each question included a free text box for further elaboration. Additionally, a final open question was included, which allowed the experts to provide any input about the PVFS scale, including its design, and how it may be used. Subsequent rounds were planned until consensus was reached, which had been predefined as a minimum level of agreement of 70%, in line with previous Delphi reports [34–37]. The Delphi questionnaire was distributed by using an online

### Table 1

| Proposed steps of development of performance outcome instruments, and current status of development of the post-VTE functional status scale. |
|---|
| **Steps of development** | **Status of the PVFS scale** |
| 1. Review of evidence for functional scales and tools assessing functional status in patients with VTE ([first publication]) | ✓ |
| 2. Identification of the key characteristics of the modified Rankin Scale for patients with stroke in order to draft measure and item specifications, and fields of applicability which may be relevant for patients with venous thromboembolisms ([first publication]) | ✓ |
| 3. Assemble a dedicated multidisciplinary work group (including patients, and physicians, nurses, and representatives of major societies) to achieve consensus on the instrument ([current manuscript]) | ✓ |
| 4. Formal rounds of review of the proposed categories of the ordinal scale from the dedicated multidisciplinary work group ([current manuscript]) | ✓ |
| 5. Formal assessment of reliability and validity of the scale ([current manuscript]) | ✓ |
| 6. Next research topics: | Ongoing |
| - Formal assessment of reliability and feasibility (e.g. logistics and costs) of the scale in clinical trials | ✓ |
| - Formal evaluations of assessment methods; blinded versus non-blinded raters, and structured interview versus self-report | ✓ |
| - Assessment of interrater agreement of structured interviews after translation into other languages | ✓ |
| - Assessment of variability in time of the PVFS scale grades following the intended time points for assessing functional status | ✓ |
| - Relating quality of life and utilities to functional status, with focus on cultural differences | ✓ |
| 7. Dissemination and implementation in both research protocols and clinical practice for routinely collected data analyses (quality indicator) | Ongoing |
survey tool (Google Forms). Responses were filed at the experts’ discretion until a given deadline date, a total of two reminders were sent before reaching this date.

For the focus groups, semistructured interview questions were developed by the steering committee. The questions were divided into three parts, namely engagement questions, exploration questions, and exit questions (Table 2). The two-hour meetings were conducted in Dutch and chaired by two members of the steering committee. All participants agreed to a voice-recording of the meeting. Extraction of all relevant suggestions and remarks that needed to be implemented in the PVFS scale or its manual was done by the steering committee.

2.4. Interrater agreement

Interobserver variability was determined by comparing the self-reported PVFS scale grade to the scale grade identified via the structured interview. One member of the steering committee interviewed the patients from the focus groups in a standardized way according to the updated manual for the structured interview (Appendix C). These interviews were recorded on tape. Before the interview was conducted, patients were given the self-report flowchart and corresponding table and were given instructions on how to determine their PVFS scale grade (Appendix C). Upon completion of the interview, the interviewer noted the identified PVFS scale grade, independently and blinded to the scoring determined by the patient. Two additional raters independently from the interviewer and patient and blinded to both of their ratings reevaluated the recording and assigned the patients to a scale grade in accordance with the manual for the structured interview.

2.5. Analysis

Descriptive statistics and interobserver variability were calculated using SPSS version 25.0.0 (SPSS, IBM). The interobserver agreement of PVFS scale grade assessment between the patients and the rater as well as between the raters themselves was assessed by calculating the k-statistic. The k-statistic was interpreted as follows: poor (<0.20), fair (0.21–0.40), moderate (0.41–0.60), good (0.61–0.80) or excellent (0.81–1.00) [38].

3. Results

3.1. Delphi analysis

In April 2019, the first round of the Delphi questionnaire was distributed among 70 international VTE experts. Of those, 53 (76%) consented to participate and completed the questionnaire. The expert panel included VTE specialists practicing in 15 different countries. A total of 48 out of 53 participants completed the full Delphi procedure. Among them, 17 were women. Several specialties were represented, including (pediatric) hematology (n = 21), vascular medicine/surgery (n = 13), pneumology (n = 10), cardiology (n = 3), radiology (n = 1), psychologists (n = 2) and clinical epidemiology (n = 3).

Following compilation of the first Delphi round, immediate consensus was reached on 5 of 10 questions/statements. The vast majority agreed that measuring functional outcomes after VTE was relevant for both research purposes (98%) and clinical practice (96%). Also, the panel considered current tools (among others Villalta Score, Venous Clinical Severity Score, New York Heart Association Classification, Modified Medical Research Council Dyspnea Scale, 6-minute walk distance, pulmonary function test and quality of life measures) unsatisfactory reliable for both research purposes (73%) and clinical practice (83%). They agreed that the PVFS scale would be a potentially helpful tool for these purposes (79% and 71%, respectively). Further, the experts considered the design of the PVFS scale to be optimal (84%) and its manual to be clear and complete (78%).

The Delphi panel, however, clearly indicated that the originally proposed 7-level ordinal scale needed to be improved in regards to two main points: 1) the score should better reflect functional impairment related to PTS and 2) the categories needed to be more distinctive. Moreover, the impact of anxiety and depression needed to be addressed more explicitly. All comments were discussed within the steering committee, which led to modifications to the scale and manual. Specifically, the following adjustments were made (in addition to linguistic tweaking): 1) the scale was adjusted to be more sensitive to DVT-associated functional limitations by replacing ‘symptoms/discomfort’ to ‘symptoms, pain, or anxiety’ in the grade description (in this way, psychological aspects of physical functioning were incorporated as well); 2) specific symptoms/signs (such as dyspnea at rest or venous ulceration) were removed to avoid measuring symptoms rather than their functional impact; 3) one scale grade was removed (“moderately-severe functional limitations”) to facilitate distinctive grades in the middle spectrum of severity, and 4) ‘death’ was considered as a ‘D’ class instead of ‘grade 6’ to make it more visually distinctive.

The updated scale and manual were sent out for a second Delphi questionnaire round; the same respondents were able to see which of the multiple-choice options of the first round achieved the highest level of consensus, and how and why adjustments had been made. The second questionnaire consisted of four statements, all of which achieved consensus (Fig. 1): 89% of 48 respondents agreed that the adjusted scale had additional value to quality of life questionnaires and exercise tests to measure functional outcome after VTE; 94% agreed that the adjusted scale reflected functional limitations after both DVT and PE; 92% agreed that the adjusted scale comprised sensible, clear and distinctive scale grades, and 83% agreed that the scale could best be assessed at the time of VTE diagnosis and after 90 days, leaving explicit room for longer follow-up depending on the clinical setting or objective of a clinical trial. The respondents advised to mention the possibility of measuring the pre-VTE functional status, which was then incorporated as an optional item in order to obtain a true picture of change in functional status after the VTE event.

Table 2

Semi-structured interview questions for the patients focus groups.

| Engagement questions | Explorative questions | Exit question |
|----------------------|----------------------|--------------|
| Can you tell about yourself and your experience with VTE? | Do you consider assessment of functional limitations after VTE to be relevant? Was this assessed in your case, and how? | Is there anything else that you would like to say about the PVFS scale? |
| How did the VTE influence your physical and mental condition? | What do you think of the PVFS scale and how can it be used? | |
| How did the VTE influence your working, family, and social life? | Are the scale categories straightforward and rational? Are any important aspects of functional outcomes after VTE missing? | |
| Have you been/are you functionally impaired by the VTE? | Is the wording of the scale categories adequate and comprehensible? | |

Fig. 1: 89% of 48 respondents agreed that the adjusted scale comprised sensible, clear and distinctive scale grades, and 83% agreed that the scale could best be assessed at the time of VTE diagnosis and after 90 days.
3.2. Patient focus groups

A total of 18 patients responded to the invitation and participated in one of three patient focus group sessions. Their ages ranged between 21 and 70 years, and two were men. Their background was diverse: the group included physicians, nurses, teachers, journalists and house-cleaners. Several patients had administrative jobs, and one was retired at the time of the VTE diagnosis. Most had been diagnosed with both DVT and acute PE (n = 9), and 11 had recurrent VTE. None of the patients were known with CTEPH or severe PTS with leg ulcers. The mean time since last VTE event varied from 6 to 108 months, with most patients were known with CTEPH or severe PTS with leg ulcers. The background was diverse: the group included physicians, nurses, teachers, journalists and house-cleaners. Several patients had administrative jobs, and one was retired at the time of the VTE diagnosis. Most had been diagnosed with both DVT and acute PE (n = 9), and 11 had recurrent VTE. None of the patients were known with CTEPH or severe PTS with leg ulcers. The mean time since last VTE event varied from 6 to 108 months, with most patients were known with CTEPH or severe PTS with leg ulcers. The mean time since last VTE event varied from 6 to 108 months, with most patients (67%) between 0 and 2 years after their event.

All participants highlighted their appreciation of focused attention to functional limitations after VTE. All 18 considered it a relevant topic as they had (and most of them still) suffered greatly from the long-term impact of their VTE in regards to their professional and personal life. Several had lost their jobs or had to reduce the intensity of their work. Furthermore, several marriages and relations were broken, and most of them considered the VTE a traumatic experience. The quote "I had a different life before than after the VTE diagnosis" by one of the focus group participants was heartedly endorsed by the other participants. Many still faced anxiety due to the possibility of recurrent events. In general, they recognized the lack of attention from their treating physician to aspects of their recovery other than management of the anticoagulant treatment. The lack of a status scale such as the PVFS scale was considered to be a significant deficiency in clinical practice. The scale (after adjustments suggested and approved by the Delphi panel) was considered to be adequate, and no further changes were suggested or incorporated by the patients. The final scale is shown in Table 3; the final patient self-report flowchart and corresponding table are shown in Fig. 2 and Table 4.

3.3. Interrater agreement

Structured interviews were conducted and recorded for 16 focus group participants. There was full agreement between the patient self-reported scale grade and the grade assigned by the interviewer in 14/16 patients (88%) for a kappa statistic of 0.75 (95%CI 0.58–1.0). The two discrepancies were in patients who rated themselves a grade 2 while the interviewer categorized them as grade 3. Two independent raters blinded to the grading by the patient and the interviewer evaluated the recorded interview post-hoc, were both in full agreement with each other and with the interviewer, for a kappa statistic of 1.0 (95%CI 0.83–1.0).

4. Discussion

The concept of the PVFS scale was endorsed by a large panel of international VTE experts as well as by VTE patients of diverse ages and backgrounds. The results of our Delphi consensus indicate that the PVFS...
scale may help to address an unmet clinical need. Moreover, we were able to improve the original proposed scale, refine the optimal assessment method, and establish good-to-excellent interobserver agreement between different medical professionals as well as between the structured interview and the patient self-report. The development of the scale is in an advanced stage, and it can be now used in clinical practice and implemented in clinical trials (Table 1).

In the field of stroke research, the modified Rankin Scale (mRS) - by which the authors were inspired when proposing and developing the PVFS scale - has achieved a key position as an important, and often primary, outcome of seminal trials that have subsequently shaped the current standard of care [39, 40]. With the introduction of the PVFS scale, VTE trials can now start to include an overall outcome measure that captures the broad range of physical and psychological long-term complications of VTE and its treatment, expressed in meaningful categories that are linked to quality of life with both social and economic impact (e.g. healthcare costs and societal costs). This scale could be used to identify patients with slower than expected recovery after VTE. In such cases, the culprit symptom can be identified and targeted, although this latter is beyond the scope of the scale itself. Another example of how the score may be used is to establish the optimal duration of treatment in unprovoked VTE, in which the balance between the impact of relatively frequent recurrences of VTE and less frequent but more impactful occurrences of bleeding complications is still a matter of debate and research [41–44]. A third example where the PVFS scale may help to determine conclusively the optimal treatment strategy is the dilemma of the benefit of early pharmacomechanical catheter-directed thrombolysis in iliofemoral DVT, which has been associated with better quality of life in some studies, but not with less PTS [45, 46]. Based on our results presented here, the PVFS scale has been included as a secondary outcome in four clinical trials scheduled to start on short notice: PEITHO-3 (PHRCN_16-0580), SAFE-SSPE (NCT04263038), L-TRRiP (ZonMw 848017007) and ARIVA (NCT04128956). We will learn more about the value of the PVFS scale by analysing the results of the PVFS scale assessments within those and other clinical trials on correlation between PVFS scale grades and health-related quality of life or health-care costs. The development of the PVFS scale is described in Table 3.

Table 3

| PVFS scale grade | Description |
|------------------|-------------|
| 0                | No functional limitations |
| 1                | Negligible functional limitations |
| 2                | Slight functional limitations |
| 3                | Moderate functional limitations |
| 4                | Severe functional limitations |
| D                | Death |

| PVFS scale grade | Description |
|------------------|-------------|
| 0                | All usual duties/activities at home or at work can be carried out at the same level of intensity. Symptoms, pain and anxiety are absent. |
| 1                | All usual duties/activities at home or at work can be carried out at the same level of intensity, despite some symptoms, pain, or anxiety. |
| 2                | Some usual duties/activities at home or at work are carried out at a lower level of intensity or are occasionally avoided due to symptoms, pain, or anxiety. |
| 3                | Usual duties/activities at home or at work have been structurally modified (reduced) due to symptoms, pain, or anxiety. |
| 4                | Assistance needed in activities of daily living due to symptoms, pain, or anxiety: nursing care and attention are required. |
| D                | Death occurred before the scheduled assessment. |

Fig. 2. Flowchart for patient self-report of the post-VTE functional status scale (full manual for structured interview and patient self-report provided in Appendix C).
more specific components of PTS and the post-PE syndrome (e.g. pain or dyspnea). In the clinical setting, the PVFS scale may help health care providers to monitor the recovery of individual patients, may better identify complications such as CTEPH at an early stage and help explaining the impact of persistent symptoms to the treating physician and relatives.

The main strength of this study is the broad consensus reached among a large sample of international experts from various backgrounds, as well as the clear endorsement of the PVFS scale by the patient focus groups. The scale and its manual were refined to a point with good-to-excellent interrater agreement, either self-reported or assessed via a structured interview, underlining its validity when used as an outcome of clinical trials. Although patient self-reporting is probably the most practical approach for collecting PVFS scale outcome data, the structured interview is the preferred mode of assessment from a scientific point of view until the value of self-reported data has been established by future research.

This study is limited by an obvious selection bias in the patient focus groups: only patients with moderate to severe presentations of PTS and/or post-PE syndrome responded to our call, leading to a probable overestimation of the relevance for VTE patients as a whole group. Of note, this bias is inherent to any outcome measure since generally the majority of patients would never meet a given endpoint. Another potential limitation lies in using focus groups to obtain qualitative data. There is a risk of data bias if more forthright participants dominate the discussions. This risk was ameliorated by using an experienced and unprejudiced researcher to facilitate discussions and ensure all participants were involved. Also, while we involved a broad international panel of VTE experts and developed the first versions of the scale in the English language, only Dutch patients participated in the focus groups and the interobserver assessment was only tested in the Dutch language. Hence, the scale and its manual for the structured interview and patient self-report need to be evaluated in other countries and languages. Still, because of the simplicity of the PVFS scale, we do not expect much different scale performance or interobserver agreement when translated into other languages.

In conclusion, we demonstrated broad consensus on the relevance and methods of assessment of the PVFS scale among international VTE experts and patients. Based on their comments and suggestions, the scale and its manual were improved after which the interobserver agreement of scale assessment in our study was good-to-excellent. These findings suggest that the PVFS scale can be integrated as a relevant outcome measure in future clinical trials as well as in daily clinical practice to monitor patient recovery.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2020.03.020.

Declaration of competing interest

All authors declare to have no relevant conflict of interests related to this work.

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VTE experts that participated in the Delphi analysis

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