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ORIGINAL ARTICLE

Functional limitations 3 and 12 months after venous thromboembolism: a cohort study

Daniel Steiner[1] | Stephan Nopp[1] | Georg Heinze[2] | Daniel Kraemmer[1] | Oliver Schlager[3] | Stefano Barco[4] | Frederikus A. Klok[5] | Ingrid Pabinger[1] | Benedikt Weber[6] | Cihan Ay[1]

[1]Division of Hematology and Hemostaseology, Department of Medicine I, Medical University of Vienna, Vienna, Austria

[2]Institute of Clinical Biometrics, Center for Medical Data Science, Medical University of Vienna, Vienna, Austria

[3]Division of Angiology, Department of Medicine II, Medical University of Vienna, Vienna, Austria

[4]Department of Angiology, University Hospital Zurich, Zurich, Switzerland

[5]Department of Medicine - Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, the Netherlands

[6]Department of Dermatology, Medical University of Vienna, Vienna, Austria

Correspondence
Cihan Ay, Division of Hematology and Hemostaseology, Department of Medicine I, Medical University of Vienna, 1090 Austria, Vienna.
Email: cihan.ay@meduniwien.ac.at

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Abstract

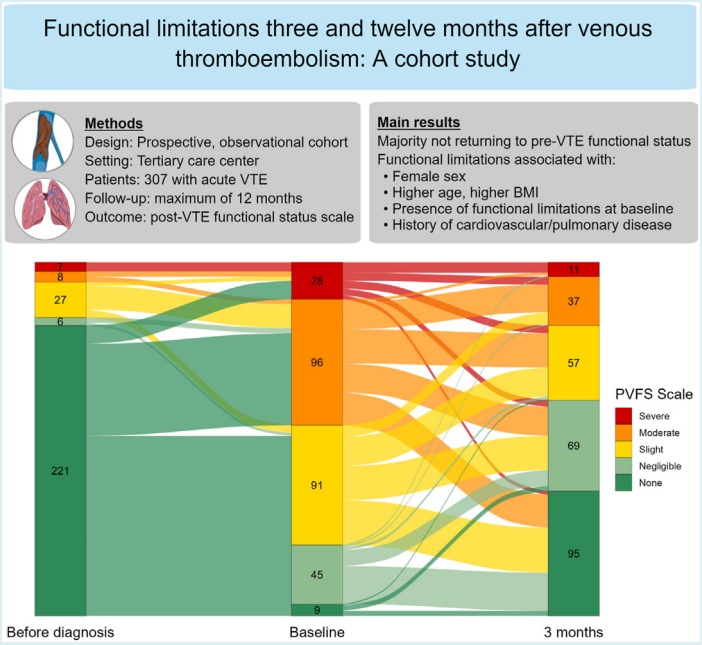
Background: Venous thromboembolism (VTE) is associated with various long-term complications.

Objectives: We aimed to investigate the association of clinical characteristics at VTE diagnosis with functional limitations 3 and 12 months afterward.

Methods: We conducted a prospective cohort study of VTE patients, excluding patients with cancer, pregnancy, and postpartum period. Functional limitations were assessed with the post-VTE functional status (PVFS) scale (range, 0-4) within 21 days of diagnosis, after 3 and 12 months (prospectively), and 1 month before diagnosis (retrospectively). Twelve-month follow-up was only performed in patients on anticoagulation. We fitted 2 proportional odds logistic regression models for the 3- and 12-month follow-ups and computed odds ratios (ORs) with 95% bootstrap percentile confidence intervals (CIs).

Results: We included 307 patients (42% female, median age 55.6 years) with a median (IQR) PVFS scale grade of 2 (2-3) at study inclusion and 0 (0-0) before diagnosis. After 3 months, PVFS scale grade in 269 patients was 1 (0-2). Female sex (OR, 2.15; 95% CI, 1.26-4.14), body mass index (OR per 1 kg/m^2 increase, 1.05; 95% CI, 1.00-1.10), functional limitations at baseline, and older age were associated with functional limitations. After 12 months, PVFS scale grade in 124 patients was 1 (0-2). Female sex (OR, 4.47; 95% CI, 2.11-16.00), history of cardiovascular/pulmonary disease (OR, 2.36; 95% CI, 1.01-6.89), and functional limitations at baseline were associated with functional limitations.

Conclusion: Functional limitations in VTE patients improved 3 and 12 months after diagnosis but did not return to pre-VTE values. We identified clinical characteristics that could help identify patients at risk of persisting functional limitations after VTE.



KEYWORDS
deep vein thrombosis, functional status, patient-reported outcomes, post-VTE functional status scale, pulmonary embolism, venous thromboembolism

Essentials

- Functional limitations after venous thromboembolism have gained increasing attention.
- We associated clinical characteristics with functional limitations after 3 and 12 months.
- Functional limitations improved compared with diagnosis but did not return to pre-venous thromboembolism values.
- Female sex, age, body mass index, comorbidities, and functional limitations at diagnosis were risk factors for functional limitations after 3 and 12 months.

1 | INTRODUCTION

Venous thromboembolism (VTE), encompassing pulmonary embolism (PE) and deep vein thrombosis (DVT), is a common disease that places a substantial burden on both patients and society [1–7]. The occurrence of a thrombotic event is associated with adverse outcomes such as VTE recurrence and bleeding complications due to anticoagulation therapy [8–10]. In addition, both DVT and PE are associated with long-term sequelae, including postthrombotic syndrome and post-PE syndrome [11–14]. Despite adequate therapy, a considerable number of patients suffer from these syndromes, exhibiting a variable degree of persisting symptoms, a decline in quality of life, and an impairment in daily physical functioning [11,15–23]. Following an acute episode of VTE, a substantial number of patients experience limitations in their physical functioning and impaired quality of life [11,24–27]. Several tools to assess generic quality of life and disease-specific quality of life have been developed for patients with DVT and PE, eg, the Venous Insufficiency Epidemiological and Economic Study Quality of Life/Symptom questionnaire and the Pulmonary Embolism Quality of Life questionnaire [28–31]. However, there has been a lack of tools to easily capture functional outcomes after an acute VTE.

Therefore, an expert group has recently proposed a new tool to measure functional limitations after VTE, the post-VTE functional status (PVFS) scale [32]. This scale is intended to cover the whole range of functional outcomes after VTE, to assess limitations in daily activities and changes in lifestyle, and to capture functional limitations in clinical trials [32]. The scale was modeled after the modified Rankin scale, representing an ordinal measurement [32,33]. It was refined with a Delphi analysis-driven optimization involving VTE experts, focus groups, and VTE patients, confirming its content validity [33,34]. Recently, we showed the construct validity and responsiveness of the scale in a prospective cohort study [35]. Due to the relevance for both patients and clinicians to assess functional limitations after VTE, an international working group of VTE experts and patients has selected the PVFS scale as one of the core instruments of the international standard set of outcome measures for VTE patients [36,37]. Ongoing

randomized trials such as the Higher-Risk Pulmonary Embolism Thrombolysis trial (NCT04790370) have included the PVFS scale as a secondary outcome. Nevertheless, little is known about the natural course of functional limitations after VTE as measured with the PVFS scale and its association with clinical parameters at the time of diagnosis.

In this study, we aimed to investigate the association between clinical parameters at the time of VTE diagnosis and functional limitations 3 and 12 months after VTE.

2 | METHODS

2.1 | Study design and patient population

This study was conducted within the framework of an ongoing cohort study called "A prospective observational study to investigate predictors of Bleeding and Assess long-term outComes on Health in patients with Venous ThromboEmbolism—the BACH-VTE study." The BACH-VTE study is a prospective, observational, single-center cohort study initiated in July 2020 at the Vienna General Hospital, which offers dedicated care to VTE patients from diagnosis up to long-term management of disease complications. The study design, inclusion criteria, and objectives of the BACH-VTE study have been described previously [35]. Briefly, patients ≥18 years of age with an objectively confirmed, symptomatic PE or DVT—restricted to deep veins of the lower limbs—are eligible for inclusion within 21 days of VTE diagnosis. Patients with therapeutic anticoagulation in the 3 months before diagnosis are excluded from the study. The primary outcome of the BACH-VTE study is a composite of major bleeding and clinically relevant non-major bleeding. One of the prespecified secondary objectives is to assess functional limitations over time. The follow-up visits are conducted after 3 to 6 months of treatment in all patients and yearly thereafter for a maximum of 5 years if the patient continues anticoagulation.

For the current analysis, we considered all patients included between July 2020 and May 2023. We excluded patients with cancer, pregnant patients, and patients in the postpartum period. At study inclusion, detailed medical history, demographic data, and VTE-specific information were collected in face-to-face interviews and checked with medical records. The first follow-up after 3 months was incorporated into routine clinical care and encompassed a face-to-face interview and review of medical records. Twelve months after the VTE diagnosis, a face-to-face interview was performed with those patients with a scheduled routine clinical visit. Patients without a scheduled visit were contacted by telephone. If a patient wished to discuss treatment, complications, or other topics with a health care professional, a routine clinical visit was scheduled, and the study follow-up was performed as described above. In all other cases, the interview was performed via telephone, and medical records were reviewed.

All patients provided written informed consent before study inclusion. The study was conducted according to the principles of the Declaration of Helsinki and approved by the local Ethics Committee of the Medical University of Vienna (EK 1045/2020). Study data were collected and managed using REDCap electronic data capture tools hosted at the Medical University of Vienna [38,39].

2.2 | Assessment of functional limitations

Functional limitations were assessed with the PVFS scale [32]. The PVFS scale ranges from grade 0 to grade 4, with grade 0 indicating no functional limitations, 1 indicating negligible functional limitations, 2 indicating slight functional limitations, 3 indicating moderate functional limitations, and 4 indicating severe functional limitations [33]. Assessment of the PVFS scale grades can be done either through a structured interview or through self-assessment by patients, with guidance from the published scale manual provided for both methods [33]. In our study, the PVFS scale was assessed at study inclusion, 3 months after diagnosis, and 12 months after diagnosis with the structured interview questions provided in the scale manual. Further, patients were asked at study inclusion to provide a pre-VTE grade as a reference value, referring to the functional status 1 month prior to the VTE diagnosis [33].

2.3 | Clinical characteristics at baseline

We assessed the association of clinical characteristics at the time of VTE diagnosis with functional limitations after 3 and 12 months. The selection of those clinical characteristics was based on previous literature on quality of life, postthrombotic syndrome, and other indicators of impaired physical functioning, as well as domain expertise [13,15,20,24,27,40]. They included the following: sex, ie, self-reported sex; age; body mass index (BMI); type of VTE, ie, PE with or without DVT, and DVT; major transient risk factor for VTE, ie, surgery with general anesthesia for more than 30 minutes, confined to bed for at least 3 days with an acute illness, or trauma with fracture during the 3 months before diagnosis [41]; history of VTE, ie, PE or DVT; history of cardiovascular or pulmonary disease, including coronary artery disease, chronic heart failure, arrhythmia, peripheral artery disease, cerebrovascular disease, and chronic pulmonary disease; smoking status, defined as current smoker, former smoker, or non-smoker; functional limitations before VTE diagnosis, as measured by the PVFS scale; and functional limitations at baseline, as measured by the PVFS scale. Smoking status was assessed in the face-to-face interview at study inclusion, with current smoker being defined as a patient reporting to smoke. As patients in the BACH-VTE study are followed for longer than 3 months only in case of continued anticoagulation, major transient risk factor was not considered as a covariate for the PVFS scale grade at 12 months.

2.4 | Statistical analysis

Categorical variables are summarized as absolute and relative frequencies, and continuous variables as median and 25th and 75th

percentiles, ie, interquartile range (IQR). Differences in PVFS scale between baseline and 3- and 12-month follow-ups were assessed with the Wilcoxon signed rank test. Two proportional odds logistic regression models, ie, cumulative logit link models, were used to describe the association between clinical characteristics at baseline and the PVFS scale grade: 1 for the 3-month and 1 for the 12-month follow-up. The described clinical characteristics were considered as covariates, with major transient risk factors included only in the model for the 3-month follow-up. Missing values in the covariates were not imputed. For every covariate, the proportional odds assumption was examined [42]. None of the covariates showed a clear violation of the proportional odds assumption. For age and BMI, a nonlinear association was modeled with restricted cubic splines with 3 degrees of freedom. The boundary knots were placed at the 5th and 95th percentile and the interior knots at the 35th and 65th percentile. The PVFS scale grades before VTE diagnosis and at baseline were modeled as continuous variables with a second-order polynomial.

After initial data analysis, it was decided not to consider PVFS functional status scale before VTE diagnosis as a covariate due to its low variability, with more than 80% of all patients having the same PVFS scale grade. Furthermore, BMI showed an approximately linear association when fitted with restricted cubic splines and was subsequently modeled linearly to increase stability of the final models. For the model considering the 12-month follow-up, age also showed an approximately linear association when fitted with restricted cubic splines, and modeling age linearly improved model fit. Therefore, age was modeled linearly for this model to increase stability.

For every categorical and linear covariate, we present odds ratios (ORs) with 95% confidence intervals (CIs), indicating the likelihood of having a higher PVFS scale grade. To account for the low number of patients in relation to the number of independent variables in the model, 95% bootstrap percentile CIs were calculated with 500 resamples. For PVFS scale grade at baseline, category 2, ie, slight functional limitations, served as the reference. The nonlinear association of age with functional limitations was visualized by partial effect plots for a specified covariate setting and described with ORs for patients at the 25th, 50th, 75th, and 90th percentile, with the 10th percentile as the reference. Performance of the model was described by a rank discrimination index, ie, the c-index, and pseudo-R-squared, ie, the Nagelkerke R^2. All analyses were done in R using the rms package [43,44].

3 | RESULTS

From July 2020 until May 2023, 307 patients were included in the BACH-VTE study. Of these patients, 25 (8.1%) were lost to follow-up (Supplementary Table S1 and Supplementary Figure). Further, 13 (4.2%) patients did not complete the 3-month follow-up, resulting in 269 (87.6%) patients with outcome data available for the 3-month follow-up (Supplementary Figure). Regarding the 12-month follow-up, 83 patients had stopped anticoagulation between 3 and 12 months after VTE, 66 have not completed their 12-month follow-up yet, 3 died, and 6 were lost to follow-up, resulting in 124 (40.4%) patients with outcome data available for the 12-month follow-up (Supplementary Figure). Baseline characteristics of the overall cohort and the patients with outcome data considered for the 3-month and 12-month follow-ups are shown in Table 1. BMI was missing in 2 patients of the full cohort and 1 patient each of those with outcome data for the 3- and 12-month follow-up. For the other covariates, no data were missing.

3.1 | Functional limitations after 3 months

Median (IQR) time between inclusion and first follow-up visit was 13.4 (12.9-16.0) weeks. The absolute and relative frequencies for the PVFS scale grades were as follows: no functional limitations were observed in 95 (35.3%) patients, negligible functional limitations in 69 (25.7%), slight functional limitations in 57 (21.2%), moderate functional limitations in 37 (13.8%), and severe functional limitations in 11 (4.1%; Figure 1). Median (IQR) PVFS scale grade 3 months after VTE diagnosis was significantly lower compared with baseline (1 [IQR, 0-2] vs 2 [IQR, 2-3]; $P < .001$). Overall, 182 (67.7%) patients improved, 67 (24.9%) remained in their PVFS scale grade, and 20 (7.4%) reported more functional limitations. When comparing the pre-VTE functional status with functional limitations 3 months after diagnosis, 115 (42.8%) patients returned to their status, 8 (3.0%) improved, and 146 (54.3%) had more functional limitations than before VTE. The trajectory of the PVFS scale grade from the time before VTE diagnosis to baseline and 3 months after VTE diagnosis is shown in Figure 1.

The association between clinical characteristics at baseline and functional limitations after 3 months is described in Table 2. Women had increased odds of having a higher PVFS scale grade (OR, 2.15; 95% CI, 1.26-4.14). Furthermore, BMI was associated with an OR of 1.05 per 1 unit increase for having a higher PVFS scale grade (95% CI, 1.00-1.10). Patients with lower PVFS scale grades at baseline showed decreased odds of having a higher PVFS scale grade after 3 months, while patients with higher grades showed increased odds (Table 2). The association between age and functional limitations is visualized in Figure 2. In general, the odds tended to show an increase with age (Table 2), although a minor drop in the log odds occurred at an age of approximately 65 years (Figure 2). The model had a c-index of 0.728 and a Nagelkerke R^2 of 0.325.

In a sensitivity analysis, we tested an interaction of age and sex that was added to the model. However, it did not improve model fit ($P = .119$). Furthermore, we performed an exploratory analysis stratified by type of VTE, ie, PE or DVT, which showed only minor differences in PVFS scale grade between these groups (Supplementary Table S2). The association between clinical characteristics at baseline and functional limitations after 3 months was similar to the main analysis, albeit with a higher degree of uncertainty of estimates due to the reduced sample size (Supplementary Tables S3 and S4).

TABLE 1 Patient demographics and clinical characteristics at baseline.

Demographics and clinical characteristics	Full cohort (*N* = 307)	Patients with outcome data for 3-mo follow-up (*n* = 269)	Patients with outcome data for 12-mo follow-up (*n* = 124)
Female	128 (41.7)	110 (40.9)	38 (30.6)
Age (y), median (IQR)	55.6 (43.7-65.7)	54.9 (43.4-63.6)	56.1 (49.2-68.6)
BMI (kg/m^2), median (IQR)[a]	27.7 (24.4-31.4)	27.7 (24.7-31.6)	27.9 (24.8-31.8)
Race			
White	303 (98.7)	267 (99.3)	123 (99.2)
Black	3 (1.0)	2 (0.7)	1 (0.8)
Asian	1 (0.3)	0 (0.0)	0 (0.0)
Type of VTE			
PE[b]	149 (48.5)	125 (46.5)	74 (59.7)
Central	51 (34.2)	39 (31.2)	28 (37.8)
Lobar	28 (18.8)	25 (20.0)	13 (17.6)
Segmental	56 (37.6)	48 (38.4)	31 (41.9)
Subsegmental	12 (8.1)	11 (8.8)	1 (1.4)
DVT	158 (51.5)	144 (53.5)	50 (40.3)
Proximal	99 (62.7)	88 (61.1)	41 (82.0)
Distal	59 (37.3)	56 (38.9)	9 (18.0)
Unprovoked VTE	191 (62.2)	166 (61.7)	92 (74.2)
Provoked VTE[c]	116 (37.8)	103 (38.3)	32 (25.8)
Major persisting risk factor	20 (17.2)	20 (19.4)	12 (37.5)
Major transient risk factor	39 (33.6)	36 (35.0)	6 (18.8)
Minor transient risk factor	71 (61.2)	60 (58.3)	14 (43.8)
History of VTE	85 (27.7)	77 (28.6)	48 (38.7)
History of cardiovascular or pulmonary disease[d]	73 (23.8)	58 (21.6)	34 (27.4)
Smoking			
Current	82 (26.7)	68 (25.3)	29 (23.4)
Former	67 (21.8)	56 (20.8)	32 (25.8)
Never	158 (51.5)	145 (53.9)	63 (50.8)
PVFS scale grade before VTE, median (IQR)	0 (0-0)	0 (0-0)	0 (0-0)
PVFS scale grade at baseline, median (IQR)	2 (2-3)	2 (2-3)	2 (2-3)

Values are presented as *n* (%) unless otherwise stated.

BMI, body mass index; DVT, deep vein thrombosis; PE, pulmonary embolism; PVFS, post-venous thromboembolism functional status; VTE, venous thromboembolism.

[a]Data are missing for 2 patients of the full cohort and 1 patient each of those with outcome data for the 3- and 12-month follow-up.

[b]Including 56 patients with objectively confirmed DVT. Data on PE extent are missing for 2 patients of the full cohort, 2 with outcome data for the 3-month follow-up, and 1 with outcome data for the 12-month follow-up.

[c]Some patients had more than 1 risk factor. Risk factors were defined according to Kearon et al. [41].

[d]Including coronary artery disease, chronic heart failure, arrhythmia, peripheral artery disease, cerebrovascular disease, and chronic pulmonary disease.

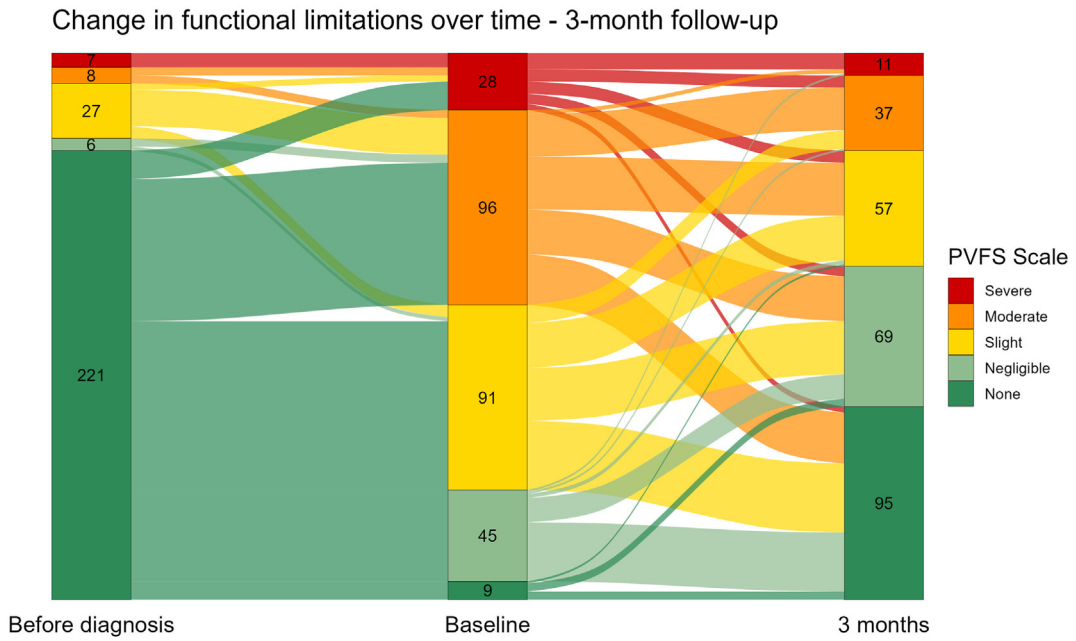


FIGURE 1 Change in functional limitations from 1 month before venous thromboembolism diagnosis over the time of diagnosis to 3 months after the diagnosis. Alluvial plot showing absolute number of patients per category of functional limitations.

3.2 | Functional limitations after 12 months

Median (IQR) time between inclusion and second follow-up visit was 55.9 (53.1-62.6) weeks. The absolute and relative frequencies for the PVFS scale grades were as follows: no functional limitations were observed in 43 (34.7%) patients, negligible functional limitations in 36 (29.0%), slight functional limitations in 27 (21.8%), moderate functional limitations in 10 (8.1%), and severe functional limitations in 8 (6.5%; Figure 3). Median (IQR) PVFS scale grade 12 months after VTE diagnosis again was significantly lower compared with baseline (1 [IQR, 0.2] vs 2 [IQR, 2-3]; $P < .001$). Overall, 89 (71.8%) patients improved, 25 (20.2%) remained in their PVFS scale grade, and 10 (8.1%) reported more functional limitations. When comparing the pre-VTE functional status with functional limitations 12 months after diagnosis, 51 (41.1%) patients returned to their status, 5 (4.0%) improved, and 68 (54.8%) had more functional limitations than before. The trajectory of the PVFS scale grade from the time before VTE diagnosis to baseline and 12 months after VTE diagnosis is shown in Figure 3.

The association between clinical characteristics at baseline and functional limitations after 12 months is shown in Table 3. Similar to the 3-month follow-up, women had increased odds of being in a higher PVFS scale grade (OR, 4.47; 95% CI, 2.11-16.00). Furthermore, history of cardiovascular or pulmonary disease was associated with an OR of 2.36 for being in a higher PVFS scale grade (95% CI, 1.01-6.89). While patients with more functional limitations at baseline showed increased odds of having a higher PVFS scale grade after 12 months, CIs for the individual grade levels were wide and less conclusive (Table 3). The model had a c-index of 0.749 and a Nagelkerke R^2 of 0.334.

4 | DISCUSSION

In this prospective cohort study, functional status of VTE survivors improved over time from a median PVFS scale grade of 2 (slight limitations) at baseline to a median of 1 (negligible limitations) at both 3 and 12 months. Female sex and functional limitations at the time of diagnosis were associated with more functional limitations both 3 and 12 months after VTE. Age showed a nonlinear association with functional limitations at 3 months, suggesting a general tendency toward more functional limitations at older age but with a slight drop in log odds at the age of approximately 65 years. Furthermore, higher BMI was associated with more functional limitations 3 months after VTE diagnosis, and history of cardiovascular or pulmonary disease was associated with more functional limitations 12 months after VTE diagnosis.

Importantly, more than half of all patients had some degree of functional limitations, ie, a PVFS scale grade of 1 or higher, both 3 months and 12 months after diagnosis. While the functional status improved from diagnosis over time, it did not return to pre-VTE levels in more than 50% of all patients despite anticoagulation therapy. This underlines the long-term clinical implications of VTE and is in line with previous data showing that survivors of VTE had their odds for frailty and poor performance on functional tests increase by a factor of 3 compared with those without VTE [45]. Similarly, an analysis of the Nurses' Health Study and the Nurses' Health Study II showed an acute decline in physical function, as measured by the Medical Outcomes Short Form-36 physical function scale, after VTE, which was estimated to be equivalent to about 5 years of aging [46]. While our study was not designed to compare functional limitations at 3 months with those at 12 months, we observed similar relative frequencies of all PVFS

TABLE 2 Odds ratios and 95% bootstrap percentile CIs for functional limitations after 3 months (n = 268).

Clinical characteristics	OR	95% CI[a]
Sex	-	-
Male (ref.)	1.00	-
Female	2.15	1.26-4.14
Age, y (percentile)[b]	-	-
31.6 (10th; ref.)	1.00	-
43.4 (25th)	2.83	1.61-6.03
54.9 (50th)	2.34	1.27-4.92
63.6 (75th)	1.79	0.84-3.80
76.3 (90th)	3.22	1.57-7.86
BMI (per 1 kg/m^2 increase)[c]	1.05	1.00-1.10
Type of VTE	-	-
DVT (ref.)	1.00	-
PE	0.95	0.56-1.52
Major transient risk factor	0.89	0.37-2.11
History of VTE	1.39	0.85-2.40
History of cardiovascular or pulmonary disease	1.29	0.64-2.68
Smoking status	-	-
Nonsmoker (ref.)	1.00	-
Current smoker	0.64	0.36-1.20
Former smoker	0.92	0.46-1.65
PVFS scale grade at baseline	-	-
2 (ref.)	1.00	-
0	0.41	0.10-1.15
1	0.53	0.32-0.74
3	2.81	2.21-4.09
4	11.64	5.43-31.26

The reported ORs and CIs are based on a multivariable proportional odds logistic regression model, with the prespecified clinical characteristics as independent variables and the PVFS scale grade after 3 months as the dependent variable.

BMI, body mass index; CI, confidence interval; DVT, deep vein thrombosis; OR, odds ratio; PE, pulmonary embolism; PVFS, post-VTE functional status; ref., reference; VTE, venous thromboembolism.

[a]95% bootstrap percentile CIs were calculated with 500 resamples.

[b]Age was modeled as a continuous variable using restricted cubic splines with 4 knots at the 5th, 35th, 65th, and 95th percentile. ORs for age are presented for the 25th, 50th, 75th, and 95th percentile, with the 10th percentile as a reference.

[c]Data are missing for 1 patient, resulting in 268 patients included in the model.

scale grades at these time points. This suggests that patients have arrived at a steady state of functional limitations after 3 months of anticoagulation therapy without significant improvement from there onwards.

Previous studies have evaluated the association of PE or DVT with a variety of different indicators of functional limitations. In a prospective cohort study of 323 patients with PE, which included patients from 4 high-volume centers of the Follow-up after Acute Pulmonary Embolism study, an abnormal 6-minute walking distance—compared with reference equations—3 or 12 months after diagnosis was associated with younger age, higher BMI, smoking, intermediate- to high-risk PE, and higher modified Medical Research Council grading [40,47]. Another analysis of the Follow-up after Acute Pulmonary Embolism study evaluated patients who had undergone cardiopulmonary exercise testing [47,48]. Three months after VTE, more than half of all patients had cardiopulmonary limitations and deconditioning. These limitations and their severity were associated with older age, history of chronic lung disease, smoking status, and intermediate or high-risk acute PE [48]. Another prospective cohort study of 86 patients with PE evaluating cardiopulmonary exercise testing, the Prospective Evaluation of Long-term Outcomes After Pulmonary Embolism study, found that percent predicted peak oxygen uptake <80% during testing as an indicator for exercise limitations was associated with male sex, younger age, higher BMI, and current or previous smoking status [24]. In an additional analysis of the Prospective Evaluation of Long-term Outcomes After Pulmonary Embolism study, including 100 patients in total, reduced improvement in quality of life, dyspnea, and 6-minute walking distance 12 months after PE were associated with female sex, higher BMI, and exercise limitations at 1 month [20]. In a large study of 620 patients with PE, reduced disease-specific quality of life at 3 and 12 months was associated with female sex, cardiopulmonary disease, and higher BMI [27]. Older age and previous VTE were associated with worsening quality of life over time [27]. Similarly, the Home Treatment of Pulmonary Embolism trial, which included nearly 580 patients and evaluated quality of life after 3 weeks and 3 months, found an association of impaired disease-specific and generic quality of life with female sex and cardiopulmonary disease as well as an association of worsening quality of life with older age [49]. When focusing on DVT, surrogates for physical functioning include severity of postthrombotic syndrome as measured by the Villalta scale and quality of life assessments. In a prospective cohort study of 387 patients with acute DVT, higher Villalta scores throughout the 2-year follow-up were associated with DVT of the common femoral or iliac vein, higher BMI, previous ipsilateral venous thrombosis, older age, and female sex [13]. Another analysis of this cohort study identified an association of presence of postthrombotic syndrome, age, proximal DVT, and inpatient status with impaired quality of life 2 years after DVT diagnosis [15]. When comparing those studies with our work, differences in the assessment of physical functioning and in the study cohorts impeding a direct comparison have to be acknowledged. We assessed functional limitations with the PVFS scale, which is an easily applicable tool and has been incorporated as one of the core instruments of the international standard set of outcome measures for VTE patients [36,37]. Furthermore, our study cohort comprised patients with both PE and/or DVT, as the PVFS scale is intended for all VTE patients [32,33,35]. We identified an association of female sex and functional limitations at the time of diagnosis with functional

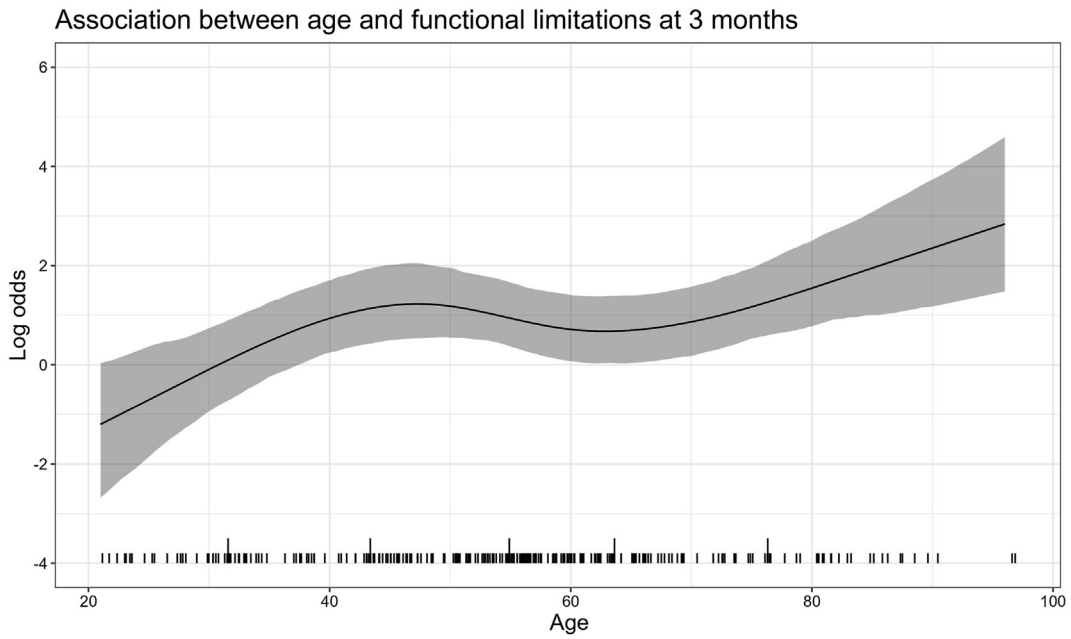


FIGURE 2 Partial effects plot of the log odds of age for having a higher post-VTE functional status (PVFS) scale grade 3 months after venous thromboembolism diagnosis. The depicted association refers to a patient of the female sex, body mass index of 28 kg/m^2, pulmonary embolism, no major transient risk factor, no history of venous thromboembolism, no history of cardiovascular or pulmonary disease, nonsmoker, and PVFS scale grade of 2 at baseline. Each line on the bottom of the graph represents an individual patient, and longer lines represent 10th, 25th, 50th, 75th, and 90th percentile of age.

limitations 3 and 12 months after diagnosis. Age and higher BMI were associated with more functional limitations after 3 months, and a history of cardiovascular or pulmonary disease with more functional limitations after 12 months. This is in line with some, but not all, previous studies, as those showed marked variability depending on type of outcome, time of assessment, and patient selection. The differences within the 2 time points might reflect that 2 different patient cohorts were analyzed, ie, unselected VTE patients for the 3-month follow-up and patients with a clinical decision for long-term anticoagulation for the 1-year follow-up. Interestingly, type of VTE, ie, PE or DVT, was not associated with functional limitations in our study. In an exploratory analysis stratified by type of VTE, there were only minor differences

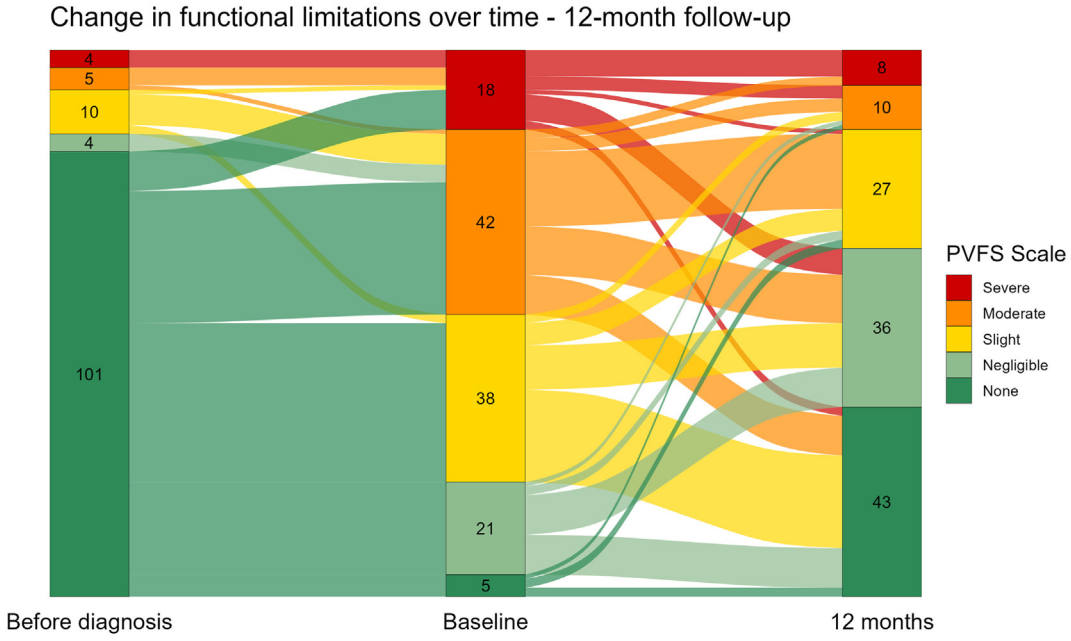


FIGURE 3 Change in functional limitations from 1 month before venous thromboembolism diagnosis over the time of diagnosis to 12 months after the diagnosis. Alluvial plot showing absolute number of patients per category of functional limitations.

TABLE 3 Odds ratios and 95% bootstrap percentile CIs for functional limitations after 12 months (n = 123).

Clinical characteristics	OR	95% CI[a]
Sex	-	-
Male (ref.)	1.00	-
Female	4.47	2.11-16.00
Age (per 10 y increase)	1.13	0.87-1.56
BMI (per 1 kg/m^2 increase)[b]	1.05	0.97-1.15
Type of VTE	-	-
DVT (ref.)	1.00	-
PE	0.64	0.25-1.62
History of VTE	0.50	0.17-1.23
History of cardiovascular or pulmonary disease	2.36	1.01-6.89
Smoking status	-	-
Nonsmoker (ref.)	1.00	-
Current smoker	0.57	0.15-1.53
Former smoker	0.60	0.18-1.76
PVFS scale grade at baseline	-	-
2 (ref.)	1.00	-
0	3.15	0.55-24.24
1	1.14	0.60-2.15
3	2.13	1.33-3.80
4	11.03	2.92-72.05

The reported ORs and CIs are based on a multivariable proportional odds logistic regression model, with the prespecified clinical characteristics as independent variables and the PVFS scale grade after 12 months as the dependent variable.

BMI, body mass index; CI, confidence interval; DVT, deep vein thrombosis; OR, odds ratio; PE, pulmonary embolism; PVFS, post-VTE functional status; ref., reference; VTE, venous thromboembolism.

[a]95% bootstrap percentile CIs were calculated with 500 resamples.

[b]Data are missing for 1 patient, resulting in 123 patients included in the model.

between patients with DVT and PE, and the association of clinical characteristics with functional limitations after 3 months was generally similar to the main analysis. This might imply a comparable effect of PE and DVT on overall physical functioning, albeit through different mechanisms and symptoms, limiting specific activities of daily living. The performance of both statistical models was moderate, with c-indices of 0.728 and 0.749 and pseudo-R-squared values of 0.325 and 0.334 of the 3-month and 12-month models, respectively. This suggests unexplained variability in the data, which could be caused by clinical characteristics we have not considered, time-varying influences during follow-up, or an unknown cellular process induced by VTE causing functional limitations.

We present the first study investigating the natural course of functional limitations as measured by the PVFS scale in a large cohort of VTE patients with a considerable follow-up time. However, our study has several limitations. Due to study design, the sample size particularly for the 1-year follow-up was limited, which increases uncertainty of the estimates. Further, the monocentric nature of the study and the selection of patients at the 1-year follow-up based on receipt of anticoagulation limit generalizability. As the PVFS scale is not intended to solely assess VTE-associated functional limitations, it is expected that a general non-VTE population would exhibit some degree of functional limitations as well [33]. However, our study did not include a control population and therefore we cannot draw conclusions about the trajectory of functional limitations in patients with VTE compared with those without VTE. While we considered a range of baseline clinical characteristics for the association with functional limitations, the analysis must be considered descriptive and does not represent a predictive model for functional limitations. Unfortunately, we were not able to consider physical activity before VTE diagnosis and changes in physical activity over time, which could influence the trajectory of functional limitations. While the results of an exploratory analysis stratified by type of VTE showed only minor differences between these groups and were generally similar to the main analysis, they need to be interpreted with caution due to the limited sample size resulting in a high degree of uncertainty of estimates. Furthermore, we could not consider individual clinical parameters, such as the severity spectrum of PE and the anatomical extent of DVT, due to limited sample size. Importantly, the functional status prior to VTE was assessed retrospectively at the time of diagnosis and is therefore prone to recall bias. Nevertheless, the magnitude of difference compared with functional limitations after 3 and 12 months implies that many patients have not returned to their pre-VTE status despite adequate treatment.

In conclusion, patients with VTE showed an improvement in functional limitations 3 and 12 months after diagnosis but did not return to their pre-VTE functional status. We identified clinical characteristics associated with functional limitations, which could help to identify patients who have a higher risk of persisting functional limitations after VTE.

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ETHICS STATEMENT

The study was approved by the local Ethics Committee of the Medical University of Vienna (EK 1045/2020). All patients provided written informed consent before study inclusion.

AUTHOR CONTRIBUTIONS

S.N., I.P., and C.A. contributed to conception and design of the study. D.S., S.N., O.S., B.W., and C.A. contributed to acquisition of data. D.S., G.H., and D.K. contributed to statistical analysis of data. All authors contributed to interpretation of data. D.S. drafted the first version of the manuscript. All authors revised the manuscript critically for

important intellectual content and approved the final version to be submitted.

RELATIONSHIP DISCLOSURE

S.B. reports institutional grants or contracts from Bayer, INARI, Boston Scientific, Medtronic, Bard, Sanofi, and Concept Medical; payment or honoraria from INARI, Boston Scientific, Penumbra, and Concept Medical; and support for attending meetings and/or travel from Bayer and Sanofi. F.A.K. received research support from Bayer, BMS, BSCI, MSD, Leo Pharma, Actelion, the Netherlands Organization for Health Research and Development, The Dutch Thrombosis Association, The Dutch Heart Foundation, and the Horizon Europe Program, all paid to his institution and outside the current work. I.P. received honoraria for lectures or advisory board meetings from CSL Behring, Bayer, BMS/Pfizer, Roche, Sobi, Sanofi, and Takeda outside the current work. C.A. reports honoraria for lectures from Bayer, Daiichi Sankyo, BMS/Pfizer, and Sanofi and participation in advisory boards for Bayer, Boehringer Ingelheim, Daiichi Sankyo, and BMS/Pfizer outside the current work. D.S., S.N., G.H., D.K., O.S., I.P., and B.W. have no conflicts of interest to declare with regard to the present study.

DATA AVAILABILITY

Data will be shared upon reasonable request to the corresponding author.

ORCID

Daniel Steiner https://orcid.org/0000-0002-4170-603X
Cihan Ay https://orcid.org/0000-0003-2607-9717

X, FORMERLY KNOWN AS TWITTER

Georg Heinze @Georg__Heinze
Oliver Schlager @SchlagerOliver
Frederikus A. Klok @Erik_Klok_MD
Cihan Ay @Cihan_Ay_MD

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SUPPLEMENTARY MATERIAL

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