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ORIGINAL ARTICLE

Impact of thrombosis location on walking capacity: a cohort study of patients with acute deep vein thrombosis

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Abstract

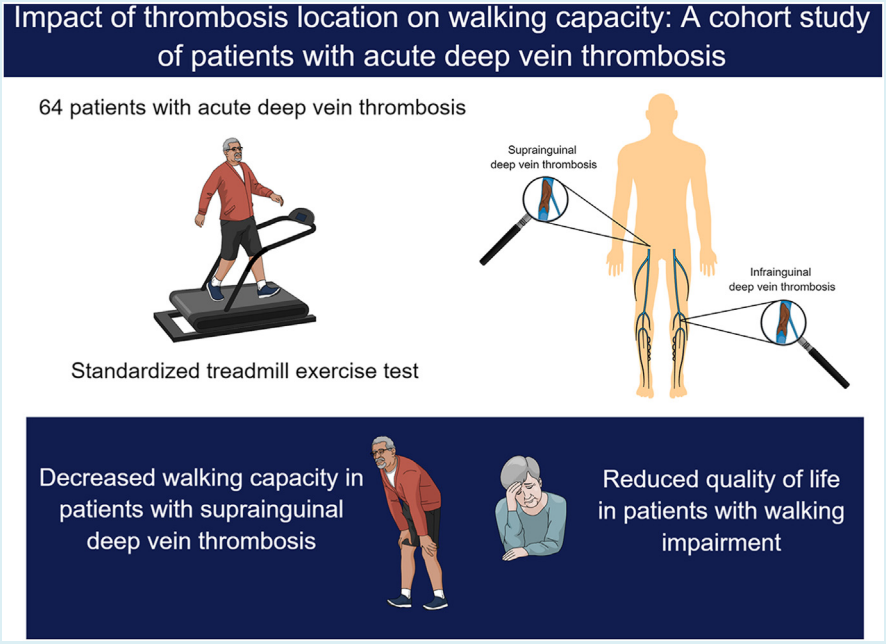
Background: Data on walking impairment during the acute phase of deep vein thrombosis (DVT) are limited.

Objectives: This study aimed to assess the degree of walking impairment in patients with acute DVT, with a particular focus on the relation to the DVT's anatomical location.

Methods: Patients with sonographically confirmed DVT were eligible for inclusion in this cohort study. Pain-free walking distance (PWD) and maximum walking distance (MWD) were determined using standardized treadmill ergometer tests and analyzed in relation to DVT location. The impact of previous DVT on walking capacity was evaluated in an exploratory analysis.

Results: The study included 64 patients (31% women; median age, 55 years). The median (IQR) time from diagnosis to exercise test was 3 (1-5) days. Patients with suprainguinal DVT demonstrated significantly shorter median (IQR) MWD than those with infrainguinal DVT (130 (61-202) m vs 565 (128-750) m; $P < .01$), while PWD did not significantly differ (PWD: 20 (0-30) m vs 40 (0-222) m; $P = .14$). The proportion of patients who had to terminate treadmill tests prematurely was higher in patients with suprainguinal DVT (91.7% vs 57.7%; $P = .04$). PWD and MWD seemed to be similar in patients with and without a history of DVT. Premature test termination and suprainguinal DVT location were associated with reduced quality of life, as measured by the EuroQoL Group 5-Dimension 5-Level questionnaire and visual analog scale.

Conclusion: Suprainguinal DVT was linked to a more pronounced walking impairment compared with infrainguinal DVT. Limited walking capacity was associated with a reduced quality of life.



KEYWORDS
deep vein thrombosis, exercise test, mobility limitation, quality of life, venous thromboembolism

Essentials

- Data on walking capacity during the acute phase of deep vein thrombosis are scarce.
- We assessed the walking capacity of 64 patients with acute deep vein thrombosis.
- Acute deep vein thrombosis impaired walking capacity depending on the location of thrombosis.
- Limited walking capacity was associated with a decreased quality of life.

1 | INTRODUCTION

Deep vein thrombosis (DVT) is a common disease, with an incidence rate of about 0.8 to 0.95 events per 1000 patient years [1–3]. Patients suffering from DVT exhibit significant morbidity due to acute symptoms, reduced quality of life, and impaired functional status [4–7]. However, data on patient-centered outcomes such as impairment in walking capacity and its relation to DVT location during the acute phase of DVT are scarce.

Improving patient quality of life after DVT through the reduction of acute symptoms and mitigation of the risk of postthrombotic syndrome (PTS) has been a topic of discussion. As such, interventional treatment of DVT as an adjuvant to anticoagulation has been proposed [8]. Previous studies have indicated the severity of acute symptoms and the location of DVT as decisive factors in predicting the potential benefits of endovascular thrombus removal [8,9]. Clinical scores, such as the Villalta score, are routinely used to grade signs and symptoms of venous diseases, including acute DVT [10]. However, these scores have originally been introduced for assessing chronic venous diseases and have not been validated in the setting of acute DVT [10,11]. Moreover, walking impairment, which potentially reduces patients' mobility and impacts daily life in the acute phase of DVT, is not adequately represented by any of the existing clinical scores.

Therefore, we aimed to investigate the extent of walking impairment in patients with acute DVT and to evaluate its association with DVT location in the setting of a prospective cohort study.

2 | METHODS

2.1 | Study design

We conducted a single-center, prospective, observational cohort study at the Medical University of Vienna, a tertiary care center in Austria, entitled "A prospective observational study to investigate predictors of Bleeding and Assess long-term outComes on Health in patients with Venous ThromboEmbolism" (BACH-VTE study). The BACH-VTE study has been described previously [12]. Shortly, consecutive patients with objectively confirmed acute pulmonary embolism and/or DVT are included within 21 days of diagnosis. Patients below 18 years of age and patients on therapeutic

anticoagulation within 3 months prior to VTE are excluded. In patients entering the study because of DVT, the diagnosis of DVT has to be confirmed by venous ultrasound as recommended by guidelines [8,13].

For the present study, all enrolled patients diagnosed with DVT were invited to participate in a standardized treadmill exercise test at study inclusion. Patients with intermediate- or high-risk pulmonary embolism, dyspnea, chest pain, active cancer, pregnancy, postpartum state, a systolic blood pressure of >200 mmHg, a diastolic blood pressure of >110 mmHg, or a heart rate of >100/min were excluded. Active cancer was defined according to the International Society on Thrombosis and Haemostasis, including a diagnosis within the previous 6 months; recurrent, regionally advanced, or metastatic disease; treatment administration within previous 6 months; or hematological cancer that is not in complete remission [14]. Furthermore, patients with a reduced exercise tolerance caused by other limitations than DVT (frailty or musculoskeletal restrictions) were excluded from treadmill tests.

All patients included in the study provided written informed consent. 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 managed using Research Electronic Data Capture (REDCap) tools [15,16].

2.2 | Clinical characteristics

Patients underwent duplex sonography of the affected limb to confirm the diagnosis of DVT and to determine the most proximal extent of thrombosis (inferior vena cava, iliac, femoral, popliteal, or infrapopliteal veins). Patients were then categorized into suprainguinal DVT, encompassing inferior vena cava and iliac veins, and infrainguinal DVT, encompassing femoral, popliteal, and infrapopliteal veins. In all patients, therapeutic anticoagulation and compression therapy (ie, compression bandages or compression stockings) were established upon diagnosis of DVT.

At study inclusion, patients' clinical and demographical characteristics, such as body mass index (BMI), smoking status, and the presence of comorbidities, were recorded. Finally, history of DVT and provoking factors of VTE were evaluated [17].

2.3 | Treadmill exercise test

Walking impairment was assessed by a standardized treadmill exercise test using a treadmill ergometer (Ergo Run Medical 8, Daum Electronic). The test was performed in a well-ventilated room with a constant room temperature, which is equipped with a recovery couch and chairs as well as emergency equipment. Blood pressure and heart rate were recorded for every patient before and after exercise testing. Compression therapy was not interrupted for the treadmill exercise test. All tests were performed by 2 trained biomedical analysts, who were blinded to the location and extent of thrombosis, under the supervision of a senior physician.

All patients were instructed to report any symptoms or discomfort, ie, pain, exhaustion, dyspnea, and others, occurring during the treadmill exercise test. Patients were informed that the test could be stopped at any time when any symptoms would force them to stop, but not when leg symptoms first occur. During exercise testing, biomedical analysts and physicians refrained from encouraging patients. The treadmill speed was set to 3.2 km/h and the slope to 12%. In the case of unsteadiness on the treadmill, a speed of 1.6 km/h was allowed. In the absence of symptoms forcing patients to stop, the test was terminated at a maximum of 750 meters (m). For every patient, pain-free walking distance (PWD; ie, distance without leg symptoms), maximum walking distance (MWD), and premature termination of the treadmill exercise test (ie, before completing 750 m) were assessed.

2.4 | Quality of life

Generic quality of life was assessed with the EuroQoL Group 5-Dimension 5-Level (EQ-5D-5L) questionnaire and visual analog scale [18]. All patients received the questionnaire and the visual analog scale from study personnel at the time of study inclusion before treadmill exercise testing, and were asked to fill them out themselves. The EQ-5D-5L questionnaire focuses on 5 dimensions (ie, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is assessed with 1 question ranging from 1 to 5 on a Likert scale, with higher values indicating more problems for the specific dimension. Taking into account all questions, an overall index is calculated based on a country-specific reference value set. In contrast to the Likert scale, higher values indicate better health for the overall index. Due to the absence of a value set for Austria, we used the value set for Germany for calculating the overall index, with values ranging from −0.661 to 1 [19]. The visual analog scale ranges from 0 to 100, with higher values indicating better health. The EQ-5D-5L questionnaire and the visual analog scale refer to the day of assessment. Missing data in quality of life assessment were not imputed.

2.5 | Statistical analysis

Categorical variables are presented as absolute numbers and frequencies, and numerical variables as median and IQR. Differences in PWD and MWD according to location of DVT were assessed with the Wilcoxon rank-sum test. Differences in numbers of patients who had to terminate the treadmill exercise test prematurely and who completed the whole distance were assessed with the chi-squared test. In the case of expected frequencies below 5, Fisher's exact test was used. In an exploratory analysis, the impact of a history of DVT on PWD, MWD, and number of patients who had to terminate the treadmill exercise test prematurely was evaluated. Correlations between PWD and MWD with quality of life were evaluated with Spearman correlation coefficients, with a coefficient of 0.10 to 0.39 considered weak, 0.40 to 0.69 considered moderate, 0.70 to 0.89 considered strong, and 0.90 to 1.00 considered very strong [20]. The

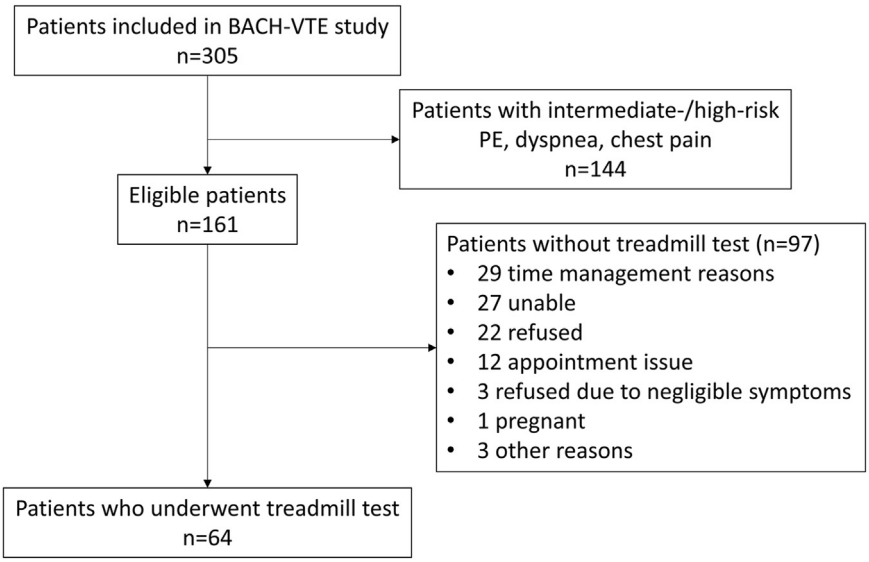


FIGURE 1 Patient flow chart. Time management reasons include time of inclusion, resulting in unavailability of treadmill exercise test, and transport issues of patients (ie, transport already waiting). Appointment issues include patients who had an urgent appointment at a different department. Other reasons include 2 patients who were not asked to participate and 1 patient who unexpectedly left the outpatient clinic waiting room.

level of significance was set at $P < .05$ in advance. All analyses were performed using R Statistical Software (v4.2.2; R Core Team 2023).

3 | RESULTS

3.1 | Demographics and patient characteristics

A total of 305 patients were included in the BACH-VTE study, of which 144 had intermediate- or high-risk pulmonary embolism, dyspnea, or chest pain and were therefore not eligible for the treadmill exercise test. Of the remaining 161 patients, 64 (39.8%) underwent exercise testing (Figure 1). Most common reasons for not performing the treadmill exercise test included time management reasons (18.0%), inability to walk due to frailty, postsurgery state or immobilization of lower extremity after trauma (16.8%), refusal to participate (13.7%), and appointment issues (7.5%; Figure 1). Clinical characteristics of patients who performed treadmill exercise tests are shown in Table 1. Their median (IQR) age was 54.6 (44.6-60.0) years and 31.3% were female.

The most common location of DVT was infrainguinal (encompassing femoral, 34.4%; popliteal, 12.5%; and infrapopliteal, 34.4%). One quarter of all patients had a history of DVT. None of the included patients had a known history of peripheral artery disease or any other comorbidity causing walking impairment. Demographics and clinical characteristics stratified by location of DVT (infrainguinal vs suprainguinal) are provided in the Supplementary material (Table S1).

3.2 | Treadmill exercise test results

Median (IQR) time from diagnosis to treadmill exercise test was 3 (1-5) days. Median (IQR) PWD and MWD were 30 (0-153) and 385 (110-750 m), respectively. Patients who had to terminate treadmill exercise test prematurely tended to be older; to be female; to have higher BMI, suprainguinal DVT, unprovoked DVT, or bilateral DVT; to be admitted to the hospital; to have comorbidities; and to be a current or former smoker compared with those who completed the whole distance (Table 2).

3.3 | Walking capacity in relation to DVT location and history of DVT

Median MWD (IQR) was significantly shorter in patients with suprainguinal DVT than in patients with infrainguinal DVT (130 (61-202 m) vs 565 (128-750 m), $P < .01$), while PWD seemed to be similar (median [IQR]: 20 [0-30 m] vs 45 [0-222 m], $P = 0.14$; Figure 2). Eleven patients (91.7%) with suprainguinal DVT and 30 (57.7%) with infrainguinal DVT had to terminate treadmill exercise tests prematurely (Fisher's exact test, $P = .04$). MWD, PWD, and number of patients who had to terminate the treadmill exercise test prematurely stratified by the most proximal location of DVT (ie, inferior vena cava, iliac, femoral, popliteal, or infrapopliteal veins) are shown in Table 3 and Figure 3.

Patients with a history of DVT appeared to have similar MWD (IQR) to patients without previous DVT (330 [IQR, 118-750 m] vs 390 [110-750 m]; $P = .91$). Similarly, PWD did not differ considerably between these groups (25 [IQR, 0-100 m] vs 40 [IQR, 0-170 m]; $P = .53$). Ten patients (62.5%) with a history of DVT terminated the treadmill exercise test prematurely compared to 31 (64.5%) of those without a history of DVT (Chi-squared test, $P = .88$).

3.4 | Quality of life

Two patients had missing data for EQ-5D-5L visual analog scale, and none had missing data for EQ-5D-5L index. The median (IQR) EQ-5D-5L index and visual analog scale values were 0.850 (0.730-0.939) and 70 (60-80), respectively. EQ-5D-5L index correlated weakly with

TABLE 1 Demographics and clinical characteristics of the study cohort.

	Total cohort (*n* = 64)
Demographics	
Age, y	54.6 (44.6-60.0)
Female sex	20 (31.3)
BMI, kg/m^2	27.7 (25.1-30.5)
White race	64 (100)
DVT characteristics	
Suprainguinal DVT	12 (18.8)
Infrainguinal DVT	52 (81.3)
Most proximal location of DVT	
Cava	4 (6.3)
Iliac	8 (12.5)
Femoral	22 (34.4)
Popliteal	8 (12.5)
Infrapopliteal	22 (34.4)
Unprovoked	43 (67.2)
Bilateral DVT	3 (4.7)
Admitted	5 (7.8)
Comorbidities	
Arterial hypertension	16 (25.0)
Cardiovascular disease	6 (9.4)
Respiratory disease	5 (7.8)
Hypothyroidism	4 (6.3)
History of cancer	2 (3.1)
Diabetes mellitus	2 (3.1)
Smoking status	
Current	19 (29.7)
Former	18 (28.1)
Never	27 (42.2)
VTE history	
DVT	16 (25.0)
PE	6 (9.4)

Values are presented as median (IQR) or number (percentage).
BMI, body mass index; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

TABLE 2 Demographics and clinical characteristics of the study cohort stratified by the outcome of treadmill exercise test (ie, premature termination or completion of whole distance [750 m]).

	Premature termination (*n* = 41)	Completion (*n* = 23)
Demographics		
Age, y	55.9 (44.7-64.2)	53.8 (43.2-56.3)
Female sex	15 (36.6)	5 (21.7)
BMI, kg/m^2	28.1 (24.8-30.7)	26.7 (25.5-29.0)
DVT characteristics		
Suprainguinal DVT	11 (26.8)	1 (4.3)
Infrainguinal DVT	30 (73.2)	22 (95.7)
Most proximal location of DVT		
Cava	4 (9.8)	0 (0)
Iliac	7 (17.1)	1 (4.3)
Femoral	13 (31.7)	9 (39.1)
Popliteal	1 (2.4)	7 (30.4)
Infrapopliteal	16 (39.0)	6 (26.1)
Unprovoked	29 (70.7)	14 (60.9)
Bilateral DVT	3 (7.3)	0 (0)
Admitted	5 (12.2)	0 (0)
Comorbidities		
Arterial hypertension	14 (34.1)	2 (8.7)
Cardiovascular disease	4 (9.8)	2 (8.7)
Respiratory disease	3 (7.3)	2 (8.7)
Hypothyroidism	3 (7.3)	1 (4.3)
History of cancer	2 (4.9)	0 (0)
Diabetes mellitus	2 (4.9)	0 (0)
Smoking status		
Current	15 (36.6)	4 (17.4)
Former	12 (29.3)	6 (26.1)
Never	14 (34.1)	13 (56.5)
VTE history		
DVT	10 (24.4)	6 (26.1)
PE	2 (4.9)	4 (17.4)

Values are presented as median (IQR) or number (percentage).
BMI, body mass index; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

MWD (ρ = 0.31, P = .01) and moderately with PWD (ρ = 0.58, P < .01). EQ-5D-5L visual analog scale correlated weakly with MWD (ρ = 0.36, P < .01) and PWD (ρ = 0.33, P < .01). Patients who had to terminate treadmill exercise prematurely reported worse quality of life compared with patients who completed the maximum distance (EQ-5D-5L index: 0.813 [0.692-0.917] vs 0.891 [0.805-0.972], P = .02; EQ-5D-5L visual analog scale: 70 [50-80] vs 80 [70-80], P = .03). When focusing on DVT location, patients with suprainguinal DVT had numerically lower EQ-5D-5L index (0.787 [0.676-0.866] vs 0.871 [0.754-0.943], P = .19) and significantly lower EQ-5D-5L visual analog scale values (63 [48-71] vs 73 [60-80], P = .02) than patients with infrainguinal DVT. EQ-5D-5L dimensions and visual analog scale values stratified by infrainguinal vs suprainguinal location of DVT are shown in Figure 4.

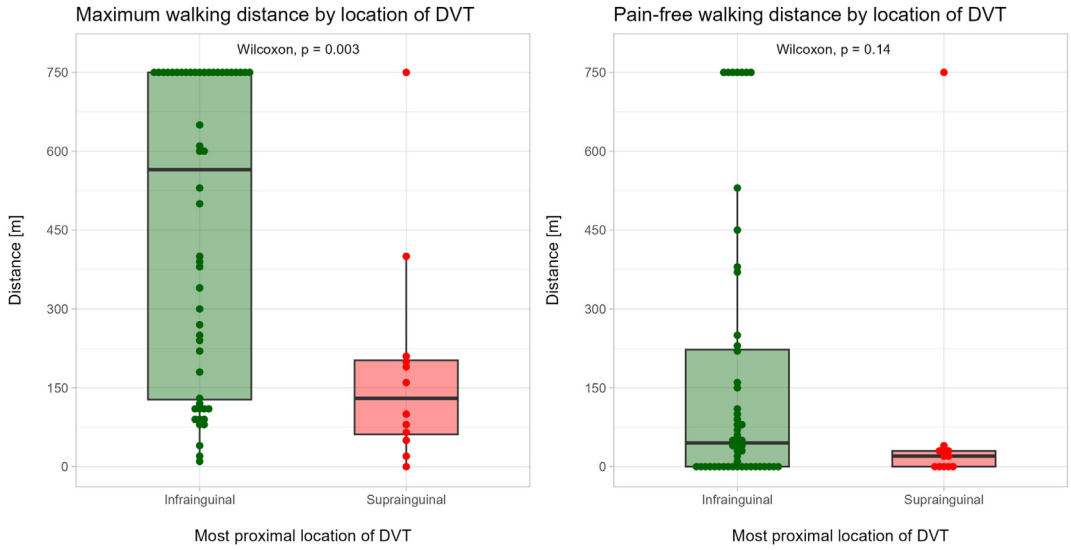


FIGURE 2 Maximum (left panel) and pain-free (right panel) walking distance stratified by infrainguinal vs suprainguinal location of DVT. Bold line represents median, upper and lower hinge represent third and first quartile, respectively, and points represent individual patients. DVT, deep vein thrombosis.

TABLE 3 PWD, MWD, and the number of patients who terminated the treadmill exercise test prematurely stratified by the most proximal location of deep vein thrombosis.

	PWD	MWD	Premature termination
Cava (*n* = 4)	10 (0-30)	105 (38-170)	4 (100.0)
Iliac (*n* = 8)	25 (0-33)	145 (76-258)	7 (87.5)
Femoral (*n* = 22)	60 (0-138)	555 (95-750)	13 (59.1)
Popliteal (*n* = 8)	170 (30-465)	750 (750-750)	1 (12.5)
Infrapopliteal (*n* = 22)	20 (0-202)	385 (228-712)	16 (72.7)

Values are presented as median (IQR) or number (percentage).
MWD, maximum walking distance; PWD, pain-free walking distance.

4 | DISCUSSION

In this study, we have demonstrated that acute DVT severely impairs walking capacity in patients who do not have other causes for walking limitations. These functional limitations were more pronounced in patients with suprainguinal location of DVT than in patients with infrainguinal DVT. Patients who were unable to complete the treadmill exercise test and patients with suprainguinal DVT reported a decreased quality of life, emphasizing the broader implications of walking impairment in this patient population.

Previous studies have used similar treadmill exercise tests to assess walking impairment in patients with a history of DVT, but not in the acute phase [21–23]. In one study, 39 patients were asked to walk at a speed of 3.5 km/h with 10% inclination for a maximum of 10 minutes [21], while in another study including 22 patients, the speed was set to 3.2 km/h and the slope to 0%, increasing by 2% every 120 seconds, for a maximum of 26 minutes [22]. The largest study so far was conducted including 84 patients, with patients walking 3.2 km/h at a slope of 10% for a maximum of 250 m [23]. Our treadmill exercise test was comparable to these studies, with a speed of 3.2 km/h, a 12% slope, and a maximum distance of 750 m.

In general, walking capacity of patients with DVT in this study was reduced compared with walking capacity of patients with a history of DVT as reported in previous studies [21,22]. One study reported a PWD of 130 m (range, 105-268 m) and, in 6 patients who had to terminate the test early, a MWD of 241 m (range: 137-298 m) [21]. Another study reported a mean PWD of 389 m (±299) and a mean MWD of 805 m (±411) [22]. In these studies, the time interval between thrombotic event and exercise test ranged up to 20 years [21–23] The difference in walking capacity between our findings and previous observations might be attributable to differences in thrombus load and venous collateralization between the acute and chronic setting of DVT. However, it needs to be acknowledged that due to the different settings of these studies, no direct conclusion can be made regarding the change of walking impairment between the acute and chronic state of DVT. To evaluate the course of walking capacity between the acute and chronic state of DVT, studies that follow acute patients with DVT from diagnosis over time are needed. Furthermore, a longitudinal follow-up of the current study might facilitate identification of acute-setting parameters associated with an increased risk for the development of the PTS.

Analyzing the impact of the location of acute DVT on the extent of walking impairment, we observed a lower MWD in patients with suprainguinal DVT than in patients with infrainguinal DVT. The difference of walking capacity between suprainguinal and infrainguinal locations of DVT becomes clear when focusing on MWD, while no significant difference between individual locations of DVT was detected when assessing PWD. This can be explained by the fact that a large proportion of patients with acute DVT reported leg symptoms

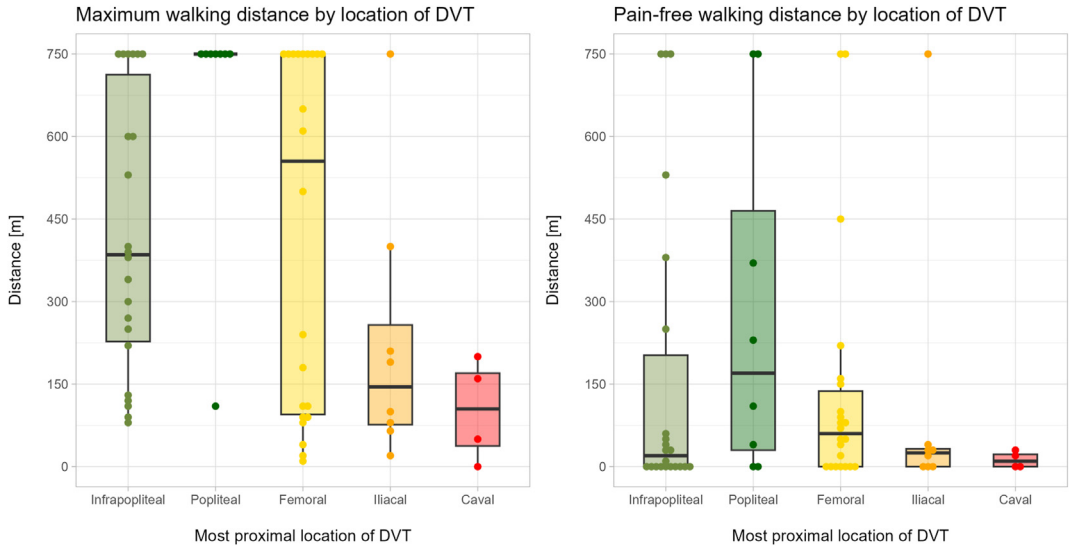


FIGURE 3 Maximum (left panel) and pain-free (right panel) walking distance stratified by most proximal location of DVT. Bold line represents median, upper and lower hinge represent third and first quartile, respectively, and points represent individual patients. DVT, deep vein thrombosis.

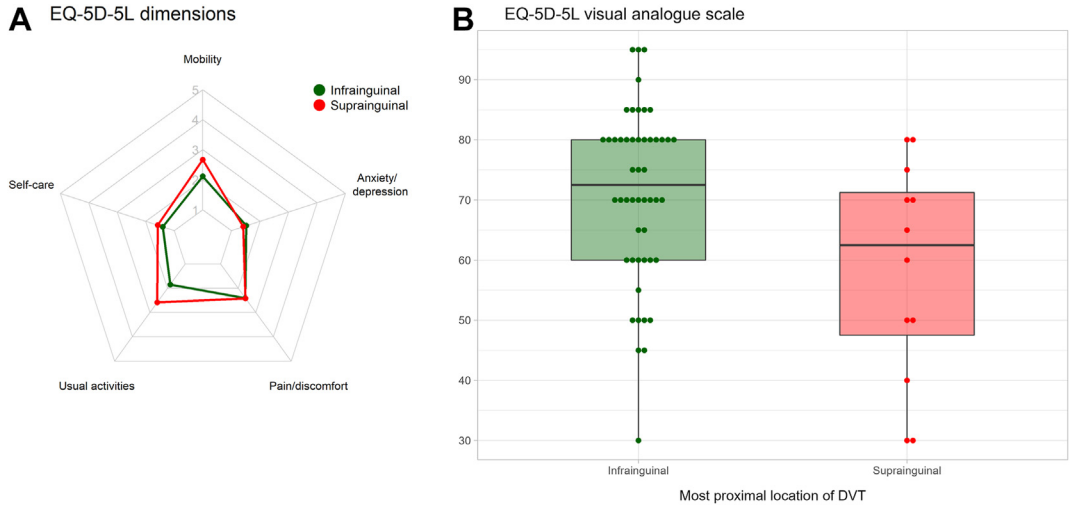


FIGURE 4 EQ-5D-5L dimensions (A) and EQ-5D-5L visual analog scale values (B) stratified by infrainguinal vs suprainguinal location of DVT. For dimension, higher values indicate more problems, and for visual analog scale, higher values indicate better health. Dimensions are presented as means, and visual analog scale values are presented as median (bold line), third and first quartile (upper and lower hinge, respectively), and individual patients (points). DVT, deep vein thrombosis; EQ-5D-5L, EuroQoL Group 5-Dimension 5-Level.

even before starting the treadmill exercise test, which makes it difficult to determine PWD. It therefore appears reasonable that MWD might be the more representative parameter for walking capacity in patients with acute DVT. Interestingly, the association between walking capacity and most proximal location of DVT seemingly showed a right-skewed shape. While patients with popliteal DVT seemed to have the least impairment, patients with infrapopliteal DVT had shorter PWD and MWD and a larger proportion had to terminate the test prematurely. The limitations of patients with infrapopliteal DVT were comparable to those of patients with femoral DVT. As previous studies have solely focused on patients with iliofemoral disease [21–23], it is unclear whether the walking impairment in patients with infrapopliteal DVT is limited to the acute phase or prevails during the chronic state. Thus, further studies are needed to unravel the disease trajectory in this potentially underrecognized patient population. When focusing on popliteal DVT and more proximal location, PWD and MWD were shorter the more proximal the DVT was located. The association between proximal location of DVT and impaired walking capacity might be attributed to hemodynamic properties: the more proximal the DVT-caused outflow obstruction is located, the more pronounced is the increase in venous pressure of the affected limb. Increased venous pressure causes venous

hypertension, which subsequently might correspond with venous claudication [22]. Nevertheless, the underlying pathophysiological changes remain to be proven by direct hemodynamic measures in affected patients. Importantly, the observed associations were not adjusted for potential confounders due to the limited sample size and might be influenced by differences in factors such as age, BMI, smoking status, or comorbidities.

PWD and MWD appeared to be similar in patients with and without a history of DVT, albeit a minor tendency toward aggravated impairment in those with a history of DVT can be discussed. This could be explained by the presence of residual chronic lesions hampering venous outflow, which potentially might be aggravated by the acute event. However, the observed differences in PWD and MWD were small and the analysis is limited by its sample size and exploratory nature.

Patients who had to terminate the treadmill test prematurely and patients with suprainguinal DVT reported reduced quality of life. Furthermore, there was a weak-to-moderate correlation of walking capacity with quality of life in our study. A previous study compared the quality of life of patients with prior iliofemoral DVT with those of healthy subjects, adjusted for age and sex [21]. Those patients reported impairments in physical functioning, physical role, general health, social function, and mental health [21]. In another study, the severity of PTS correlated moderately with disease-specific quality of life [23]. The observed relation of quality of life with walking impairment in our study confirms the importance of walking capacity in patients with DVT and the implications beyond physical functioning itself.

Our study has several strengths and limitations. First, the moderate sample size of this study needs to be mentioned. Although women were underrepresented in our study cohort, no sex-specific subgroup analyses were conducted due to this moderate sample size. Several patients with acute DVT were not able to undergo the standardized treadmill exercise test because of frailty or reduced mobility, which could potentially limit generalizability of our results. However, since we aimed at including patients in the acute phase of DVT, we anticipated a high rate of noneligible patients. Moreover, the number of participants of this study is reasonable compared with previous studies [21–23]. As our study only encompassed patients of White race, the results might not be generalizable to a more diverse population. We did not assess venous hemodynamics and intravenous pressure changes. Therefore, further studies are needed to determine the underlying hemodynamic effects. Due to the limited sample size, we were not able to account for other variables which could potentially influence walking capacity, such as age, BMI, smoking status, or comorbidities. The major strength of this study is its novelty, since this is, to the best of our knowledge, the first prospective study assessing walking impairment in patients with acute DVT in relation to the location and history of disease.

5 | CONCLUSION

In conclusion, acute DVT results in substantial limitations in walking capacity, with more pronounced impairment observed in patients with suprainguinal DVT compared with those with infrainguinal DVT. This impairment not only affects physical functioning but also significantly impinges upon the overall quality of life.

FUNDING

The authors received no funding for this study.

ETHICS STATEMENT

The study was approved by the local Ethics Committee of the Medical University of Vienna (EK 1045/2020).

AUTHOR CONTRIBUTIONS

S.N., I.P., C.A., and O.S. contributed to study concept and design. D.S., S.N., E.D., R.K., M.M., B.W., and O.S. contributed to acquisition of data. D.S. and O.S. analyzed and interpreted all data. D.S. drafted the first version of the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version for submission.

RELATIONSHIP DISCLOSURE

I.P. received personal fees for lectures and/or participation in advisory boards from Bayer, BMS, Pfizer, and Sanofi. C.A. received personal fees for lectures and/or participation in advisory boards from Bayer, BMS, Daiichi Sankyo, Pfizer, and Sanofi. O.S. received personal fees from Abbott, BARD/BD, Bayer, Biotronik, and Optimed, outside the submitted work. D.S., S.N., E.D., R.K., M.M., and B.W. have no competing interests to disclose.

DATA AVAILABILITY

Data cannot be shared because Austrian law forbids the sharing of primary patient data.

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SUPPLEMENTARY MATERIAL

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