

Effect of Postthrombotic Syndrome on Health-Related Quality of Life After Deep Venous Thrombosis

Susan R. Kahn, MD, MSc; Andrew Hirsch, MD; Ian Shrier, MD, PhD

Background: Postthrombotic syndrome (PTS) is a frequent chronic complication of deep venous thrombosis, yet its impact on health-related quality of life has not been well characterized. We compared generic and venous disease-specific quality of life in patients with and without PTS, and assessed whether quality of life correlated with severity of PTS.

Methods: Subjects with previous deep venous thrombosis were participants in a study of the effects of exercise after deep venous thrombosis. We ascertained PTS and its severity using a validated clinical scale. Subjects completed generic (the 36-Item Short-Form Health Survey) and disease-specific (Venous Insufficiency Epidemiologic and Economic Study quality-of-life questionnaire [VEINES-QOL] and its validated subscale of 10 items on venous symptoms [VEINES-Sym]) quality-of-life measures. Age- and sex-adjusted mean quality-of-life scores were compared in patients with and without PTS, and by severity of PTS.

Results: Of the 41 subjects (mean age, 51.2 years), 19 (46%) had PTS. Subjects with PTS had significantly worse disease-specific quality-of-life scores than those without PTS (mean \pm SD VEINES-QOL score, 44.5 ± 11.6 vs 54.8 ± 5.4 , respectively [$P < .001$]; mean \pm SD VEINES-Sym score, 45.6 ± 11.4 vs 54.1 ± 6.7 , respectively [$P = .003$]), which worsened significantly with increasing severity of PTS. We found no differences in generic quality-of-life scores between subject groups.

Conclusions: Postthrombotic syndrome has a significant impact on disease-specific quality of life that may not be captured by generic quality-of-life measures. Patient-based quality-of-life measures correlated well with physician-assessed PTS. Further research is indicated to assess the value of including quality of life as a routine measure of outcome in clinical studies of patients with deep venous thrombosis and PTS.

Arch Intern Med. 2002;162:1144-1148

POSTTHROMBOTIC syndrome (PTS), a chronic condition consisting of leg pain, edema, venous ectasia, and skin induration and ulceration, is estimated to occur in 20% to 50% of patients after an episode of deep venous thrombosis (DVT) and usually becomes established within the first 2 years after the acute thrombotic episode.¹⁻³ Deep venous thrombosis affects adults of all age groups, and the incidence of associated PTS is high; hence, the population prevalence of PTS is considerable.

Little doubt remains among the clinicians caring for patients with DVT and among the patients that PTS adversely affects several aspects of quality of life, including limitations in daily activity, interference with work and social activities, psychological distress, and change in health perceptions.^{4,5} However, despite its high prevalence and associated morbidity, the impact of PTS on the quality of life of these patients has not been adequately quantified.³ For chronic conditions such as PTS, assess-

ment of quality of life may provide important information on burden of illness that is not adequately captured by traditional measures of morbidity and mortality.^{4,6}

In the course of performing the recently completed cohort study, the Venous Insufficiency Epidemiologic and Economic Study (VEINES),⁷ the VEINES quality-of-life questionnaire (VEINES-QOL),⁸ a venous disease-specific measure of quality of life that is intended for use in quantifying outcomes of interventions in patients with chronic venous disease, was developed and validated. The objectives of the present study were to compare generic and venous disease-specific quality of life in patients with and without PTS after DVT, and to examine whether quality of life correlates with severity of PTS.

RESULTS

STUDY POPULATION

Forty-three patients were recruited for the study during a 1-year period (September 1, 1999, through November 30,

From the Department of Medicine (Drs Kahn and Hirsch) and the Center for Clinical Epidemiology and Community Studies (Drs Kahn and Shrier), Sir Mortimer B. Davis Jewish General Hospital, Montreal, Quebec.

SUBJECTS AND METHODS

SUBJECTS

Study subjects were recruited from the Thrombosis Clinic of the Sir Mortimer B. Davis Jewish General Hospital, Montreal, Quebec, where all patients with a diagnosis of venous thromboembolism are seen and followed up (about 350 cases per year). Sequential patients with a first diagnosis of unilateral DVT established by means of objective testing at least 1 year before were approached for participation in a study on the impact of treadmill exercise on the affected limb after DVT,⁹ for which a sample size of 17 subjects with and 17 without PTS was required. Subjects who participated in the exercise study served as the convenience sample for the quality-of-life portion of the study, presented herein. Subjects were excluded if they had bilateral or recurrent DVT, symptomatic pulmonary embolism with the DVT episode, or a medical condition(s) that precluded treadmill exercise (eg, cardiorespiratory disease and arthritis of the lower extremity), if they were incapable of self-administering a questionnaire in French or English, or if they were unable or refused to provide informed consent. Before its initiation, the hospital's Research Ethics Committee approved the study.

STUDY PROCEDURES

Only those procedures that pertain to the quality-of-life portion of the study are described herein.

One of 2 research assistants collected data from the subjects' hospital records on age, sex, objective test used to diagnose DVT, and side and site of DVT. The physician supervising the exercise experiment (one of the 3 coauthors), who was unaware of data from the hospital record, ascertained the diagnosis and the severity of PTS in the affected leg at baseline. We used the Villalta Scale,¹⁰ a clinical PTS scale based on physician-assessed symptoms and signs that assigns a general severity score (ie, with no time frame specified) from 0 (not present or minimal) to 3 (severe) for 5 symptoms (pain, cramps, heaviness, pruritus, and paresthesia) and 6 signs (edema, skin induration, hyperpigmentation, venous ectasia, redness, and pain during calf compression). The points are summed, and an overall score of 4 or less indicates absence of PTS; 5 to 14, mild/moderate PTS; and 15 or more, or the presence of a venous ulcer, severe PTS. The Villalta Scale has been shown to have high interobserver agreement and high sensitivity and specificity for discriminating mild/moderate vs severe PTS.⁹

Generic quality of life was measured using the 36-Item Short-Form Health Survey (SF-36).¹¹ Standard

algorithms were used to calculate scores for the Mental Component Scale, a summary score that reflects scores on the vitality, social functioning, mental health, and emotional role scales, and the Physical Component Scale, a summary score that reflects scores on the physical functioning, physical role, bodily pain, and general health perceptions scales.¹²

Venous disease-specific quality of life was measured using the 25-item VEINES-QOL questionnaire, which was previously shown to be acceptable, valid, reliable, and responsive in 1531 patients with a wide spectrum of chronic venous disorders,⁸ 10% of whom had physician-reported previous DVT. The VEINES-QOL contains 10 items on venous symptoms (9 items on frequency of each of the following leg symptoms: heavy feeling, aching, swelling, night cramps, heat or burning sensation, restless legs, throbbing, itching, and tingling, and 1 item on intensity of leg pain during the past 4 weeks), 9 items on limitation in daily activities due to chronic venous disease, 5 items on the psychological impact of the leg problem, and 1 item on the change in the leg problem during the past year. We also assessed the specific impact of symptoms on quality of life associated with PTS using a validated subscale of the VEINES-QOL,⁸ which contains only the 10 items on venous symptoms described in this paragraph (VEINES-Sym). As for the SF-36 questionnaire, scores for individual items on the VEINES-QOL and VEINES-Sym are combined to create a raw summary score, which is then transformed to T scores based on a mean of 50 and an SD of 10 to give an easily understood range of scores.¹³ For all quality-of-life measures, lower scores indicate worse quality of life.

STATISTICAL ANALYSIS AND SAMPLE SIZE

We compared mean quality-of-life scores, adjusted for age and sex, in subjects with and without PTS and by severity of PTS using analysis of covariance. In subjects with PTS as defined by the Villalta Scale, we also calculated mean PTS scores according to most proximal venous segment affected by the index DVT, which are presented descriptively. Unless otherwise indicated, results are reported as mean \pm SD. We assessed the correlation between quality-of-life scores and the Villalta Scale PTS score expressed as a continuous variable using the Pearson coefficient of correlation. For all statistical tests, a *P* value of .05 or less was considered significant. The sample size achieved for the exercise study provided a power of 82% to detect a 6-point difference and 67% power to detect a 5-point difference in mean quality-of-life scores. Differences of as low as this order of magnitude are considered to be clinically meaningful.^{11,12}

2000). Two patients were excluded (one had a history of bilateral DVT and the other was not capable of following the research assistant's instructions), leaving a study population of 41 subjects. Postthrombotic syndrome was present in 19 subjects (46%), and was categorized as mild/moderate in 17 and severe in 2. No differences were found in mean age or number of years since DVT diagnosis in patients with PTS compared with those without PTS (**Table**). Although higher proportions of subjects with PTS were women and had

proximal (vs distal) DVT compared with those without PTS, these differences were not statistically significant. Among subjects with proximal DVT (*n*=29), the most proximal venous segment affected was the iliac vein in 3 subjects, the common femoral vein in 8, the superficial femoral vein in 4, and the popliteal vein in 14. Fifteen subjects with proximal DVT (52%) had PTS (mild/moderate in 13 and severe in 2) compared with 4 (33%) of the 12 subjects with distal DVT (mild/moderate in all 4).

Characteristics of Study Subjects*

	PTS (n = 19)	No PTS (n = 22)
Female, No. (%)	10 (53)	7 (32)
Age, mean (SD), y	51.8 (12.0)	50.5 (15.0)
Years since previous DVT, mean (SD)	2.4 (1.4)	2.0 (1.4)
Proximal-distal DVT, No.	15:4	14:8
PTS severity, No.		
Mild/moderate	17	...
Severe	2	...

*PTS indicates postthrombotic syndrome; DVT, deep venous thrombosis.

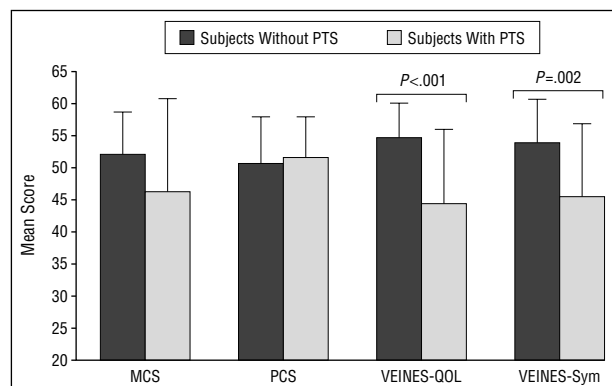


Figure 1. Generic and disease-specific quality-of-life scores in subjects with and without postthrombotic syndrome (PTS). Analyses are adjusted for age and sex. Error bars represent SDs. Comparisons are between subjects with and without PTS. MCS indicates Mental Component Scale; PCS, Physical Component Scale; VEINES-QOL, Venous Insufficiency Epidemiologic and Economic Study quality-of-life measure; and VEINES-Sym, a validated subscale of the VEINES-QOL that contains only the 10 items on venous symptoms.

QUALITY-OF-LIFE SCORES

Missing Data

There were no missing data for any items on the quality-of-life questionnaires.

Generic Quality of Life

Mean Mental Component Scale score was 46.3 ± 14.5 in subjects with PTS and 52.2 ± 6.5 in subjects without PTS ($P = .10$) (**Figure 1**). For the Physical Component Scale, mean scores in subjects with PTS were 51.7 ± 6.3 vs 50.8 ± 7.1 in subjects without PTS ($P = .69$). The Mental Component Scale and Physical Component Scale scores were similar whether PTS was absent, mild/moderate, or severe (data not shown).

Disease-Specific Quality of Life

Subjects with PTS had significantly worse scores on the VEINES-QOL questionnaire and VEINES-Sym subscale compared with subjects without PTS (**Figure 1**). Furthermore, the VEINES-QOL and VEINES-Sym scores worsened significantly with increasing categories of severity of PTS (**Figure 2**) and were inversely correlated with the Villalta Scale score expressed as a continuous

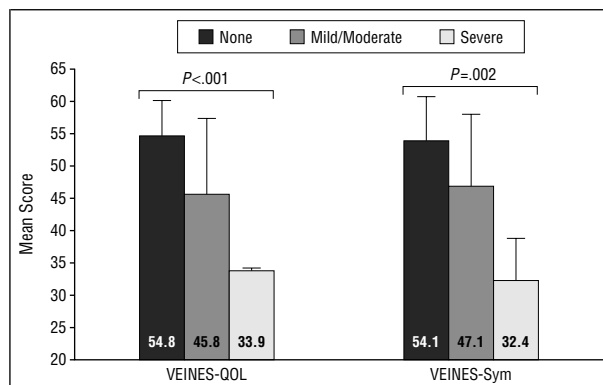


Figure 2. Disease-specific quality of life according to severity of postthrombotic syndrome (PTS). Analyses are adjusted for age and sex. Error bars represent SDs. Comparisons are between subjects with none, mild/moderate, and severe PTS. Abbreviations are described in the legend to **Figure 1**. Ratings of severity of PTS are described in the "Study Procedures" subsection of the "Subjects and Methods" section.

measure (VEINES-QOL, $r = -0.63$ [$P < .001$]; VEINES-Sym, $r = -0.61$ [$P < .001$]) (**Figure 3**). These r values represent moderate to good correlation.¹⁴ The 2 clear outliers on both figures were the same 2 subjects, one aged 39 years and the other, 29 years, both of whom had severe PTS (Villalta Scale score of 19 each). Exclusion of these outliers did not appreciably change the above-noted correlations.

COMMENT

In a population of relatively young and healthy patients with previous DVT, we found that the presence of PTS, as defined by means of the Villalta Scale, had a significant impact on disease-specific quality of life, as measured by means of the VEINES-QOL questionnaire and its symptom subscale, the VEINES-Sym. Furthermore, patients with severe PTS had significantly worse quality of life than did those with mild to moderate PTS. To our knowledge, this is the first study to show that PTS and its clinical severity result in a measurable, graded, adverse effect on health-related quality of life in patients with DVT.

In contrast, we found no demonstrable effect of PTS on generic quality of life in our study patients. Moreover, the overall mean scores for the Mental Component Scale and Physical Component Scale in our study population were similar to the population-based normative scores for a community-dwelling Canadian population of similar age and sex distribution to our study subjects,¹⁵ suggesting that DVT at least 1 year before, on average, does not affect generic quality of life. However, because of the limited power afforded by our sample size, further study of the potential usefulness of a generic quality-of-life tool in discriminating between DVT patients with and without PTS is indicated.

For chronic conditions such as PTS, assessment of quality of life may provide important information on burden of illness that is not adequately captured by traditional clinical measures of morbidity and mortality.⁴ Comprehensive measurement of quality of life requires generic and disease-specific measures.^{4,6} Generic measures al-

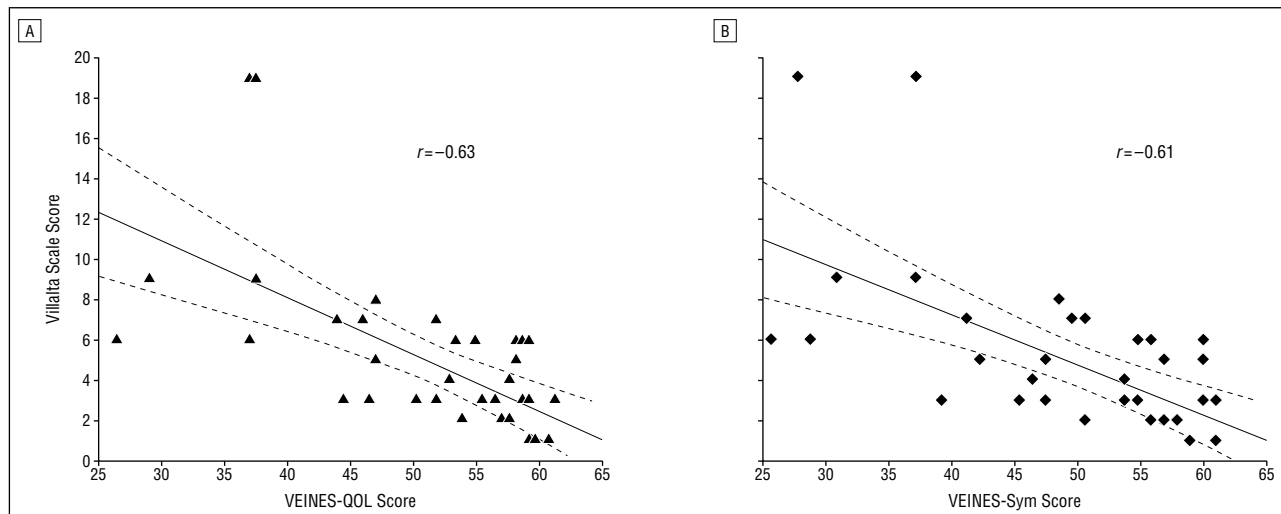


Figure 3. Correlation between Villalta Scale postthrombotic syndrome (PTS) score and VEINES-QOL (A) and VEINES-Sym (B) scores. Outer curves represent 95% confidence limits. Higher Villalta Scale scores indicate worse PTS; lower VEINES-QOL and VEINES-Sym scores, worse quality of life. Abbreviations are described in the legend to Figure 1.

low comparison of findings with those of patients with different diseases, whereas disease-specific measures may be more responsive to change in a particular condition because of their greater specificity and relevance to a given patient group.⁶

Few published studies exist on quality of life after DVT. Beyth and coworkers¹⁶ interviewed 52 surviving patients from a cohort of 124 patients who had DVT 6 to 8 years earlier. They found that patients who reported symptoms of PTS had poorer perceptions of their health, lower levels of physical functioning, and more severe role limitations due to physical health, as measured by the SF-36 generic quality-of-life instrument. However, the mean age of their population was about 10 years older than ours; many of their patients had severe comorbid conditions that could have independently affected quality of life, not all of which were adjusted for; and PTS was not assessed using a validated scale. Although quality of life was not measured using a standardized instrument, an earlier study of the long-term effects of iliofemoral DVT¹⁷ showed that among 21 patients followed up for 10 years or longer, 11 of the 12 men were disabled and unable to maintain a steady job because of their leg symptoms, and 7 of the 9 women were unable to perform household duties and required a housekeeper.

An important limitation in the field of PTS research to date has been the lack of comparability of studies due to differing definitions of PTS. Also, overall, poor correlation exists between objective measures of deep venous dysfunction such as reflux and venous hypertension and patient-based measures such as symptoms and signs.³ Our finding that the impact on quality of life as measured by means of the VEINES-QOL and VEINES-Sym varied directly with clinically diagnosed PTS and its severity suggests that these disease-specific quality-of-life instruments are useful measures of the burden of PTS as perceived by the patient. Furthermore, there may be a role for the use of these instruments as standardized, patient-based measures of outcome in clinical studies of patients with deep venous thrombosis and PTS.

Our study has several limitations. First, there is no single objective, criterion standard test to diagnose PTS.³ However, we used a validated clinical scale that has been used in prospective studies of long-term outcome after DVT^{1,2} to diagnose and establish the severity of PTS. Nevertheless, it is possible that misclassification of diagnosis or severity of PTS may have occurred for some subjects. Second, our study population was a convenience sample of patients attending our Thrombosis Clinic who volunteered to participate in an exercise study; hence, we may have selected less severely affected patients, since those with more severe symptoms at baseline or with symptoms that worsen with exercise might have declined participation. However, this might have decreased the likelihood of finding a measurable difference in quality of life between groups. Third, subjects who had medical conditions that precluded exercise testing (eg, cardiorespiratory illness and arthritis of the lower limbs) were ineligible for the study. Although this exclusion likely helped to avoid confounding by comorbid conditions that could independently affect quality of life, it could limit the quantitative generalizability of our findings to patients with PTS with a broader spectrum of severity than that of our subjects. However, it is unlikely to affect the qualitative conclusions.

CONCLUSIONS

We have shown that patients with DVT in whom PTS develops have a worse disease-specific quality of life than those without PTS, and that quality of life worsens with severity of PTS. Further prospective studies on larger and more diverse populations of patients with DVT are required to determine the value of using disease-specific quality-of-life measures to assess outcome in studies examining therapies to prevent or treat DVT and PTS. The use of such patient-based outcome measures may allow the effectiveness of treatment to be assessed in more relevant terms, for the patient, than those of traditional clinical measures. Also, further evaluation of the impact of

DVT and PTS on generic quality of life would help to determine whether use of generic quality-of-life tools provides additional information to that provided by disease-specific quality-of-life measures in this patient population.

Accepted for publication September 26, 2001.

Drs Kahn and Shrier are Chercheurs Boursier Clinicien (Clinical Research Scholars) supported by the Fonds de Recherche en Santé du Québec, Montreal. This study was supported by an unrestricted grant-in-aid from the Beiersdorf-Jobst Research Program of the American College of Phlebology, Oakland, Calif.

This study was presented in part as a poster at the 42nd Annual Meeting of the American Society of Hematology, San Francisco, Calif, December 3, 2000.

We thank our research assistants, Laurent Azoulay and Michael Haber, and our recruiting nurse, Carla Strulovitch, RN, for their help.

Corresponding author: Susan R. Kahn, MD, MSc, Center for Clinical Epidemiology and Community Studies, Sir Mortimer B. Davis Jewish General Hospital, 3755 Cote Ste, Catherine Room A-114, Montreal, Quebec, Canada H3T 1E2 (e-mail: susan.kahn@mcgill.ca).

REFERENCES

1. Brandjes DPM, Buller HR, Heijboer H, et al. Randomized trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet*. 1997;349:759-762.
2. Prandoni P, Lensing AWA, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med*. 1996;125:1-7.
3. Kahn SR, Solymoss S, Lamping DL, Abenhaim L. Long-term outcomes after deep vein thrombosis: postphlebotic syndrome and quality of life. *J Gen Intern Med*. 2000;15:425-429.
4. Lamping DL. Measuring health-related quality of life in venous disease: practical and scientific considerations. *Angiology*. 1997;48:51-57.
5. Krasner D. Painful venous ulcers: themes and stories about their impact on quality of life. *Ostomy Wound Manage*. 1998;44:38-42, 44, 46 passim.
6. Patrick DL, Deyo RA. Generic and disease-specific measures in assessing health status and quality of life. *Med Care*. 1989;27(suppl 3):S217-S232.
7. Abenhaim L, Kurz X, for the VEINES Group. The VEINES Study (Venous Insufficiency Epidemiologic and Economic Study): an international cohort study on chronic venous disorders of the leg. *Angiology*. 1997;48:59-66.
8. Lamping DL, Abenhaim LA, Kurz X, Schroter S, Kahn SR, and the VEINES Group. Measuring quality of life and symptoms in chronic venous disorders of the leg: development and psychometric evaluation of the VEINES-QOL/VEINES-Sym Questionnaire. *Qual Life Res*. 1998;7:621-622.
9. Kahn SR, Shrier I, Azoulay L, Haber M, Hirsch A. Exercise function after deep vein thrombosis in patients with and without post-thrombotic syndrome [abstract]. *Blood*. 2000;96(suppl):438a. Abstract 2793.
10. Villalta S, Bagatella P, Piccioli A, Lensing AWA, Prins MH, Prandoni P. Assessment of validity and reproducibility of a clinical scale for the post-thrombotic syndrome [abstract]. *Hemostasis*. 1994;24:158A.
11. Ware JE Jr, Snow KK, Kosinski MA, Gandek B. *SF-36 Health Survey: Manual and Interpretation Guide*. Boston, Mass: Health Institute, New England Medical Center; 1993.
12. Ware JE Jr, Kosinski MA, Keller SD. *SF-36 Physical and Mental Summary Measures: A User's Manual*. Boston, Mass: Health Institute, New England Medical Center; 1994.
13. Colton T. *Statistics in Medicine*. Boston, Mass: Little Brown & Co Inc; 1974:210-211.
14. Streiner DL, Norman GR. *Health Measurement Scales: A Practical Guide to Their Development and Use*. New York, NY: Oxford University Press Inc; 1989.
15. Hopman WM, Towheed T, Anastassiades T, et al, and the Canadian Multicentre Osteoporosis Study Research Group. Canadian normative data for the SF-36 Health Survey. *CMAJ*. 2000;163:265-271.
16. Beyth RJ, Cohen AM, Landefeld CS. Long-term outcomes of deep-vein thrombosis. *Arch Intern Med*. 1995;155:1031-1037.
17. O'Donnell TF Jr, Browse NL, Burnand KG, Thomas ML. The socioeconomic effects of an iliofemoral venous thrombosis. *J Surg Res*. 1977;22:483-488.