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ORIGINAL ARTICLE

Health-related quality of life after first venous thromboembolism in individuals aged 70 years and older

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Abstract

Background: There is limited information on short- and long-term effects of venous thromboembolism (VTE) on health-related quality of life (HRQoL) in the elderly.

Objectives: To assess change in generic HRQoL and disease-specific HRQoL in patients 1 year after the VTE.

Methods: The Age and Thrombosis, Acquired and Genetic risk factors in the elderly (AT-AGE) study is a 2-center case-control study performed in Leiden, the Netherlands, and Vermont, United States, among individuals aged ≥70 years. We measured generic HRQoL using the 36-item Short Form Health Survey (SF-36) and disease-specific HRQoL using the Venous Insufficiency Epidemiological and Economic Study-Quality of Life/Symptoms Questionnaire (VEINES-QoL/Sym) and the Pulmonary Embolism–Specific Quality of Life Questionnaire (PEmb-QoL). All patients completed these questionnaires shortly after their VTE and 1 year later, while controls completed the 36-item Short Form Health Survey questionnaire once. Linear regression for change in quality of life scores was performed and adjusted for potential confounders.

Results: For the current analysis, we included patients who were visited twice (n = 316) and controls (n = 427) with HRQoL information. Mean age of patients and controls was similar (78.8 vs 75.5 years). In patients who survived at least 1 year after the VTE, generic HRQoL improved for both summary scores, but it did not reach the level of the age-matched controls: physical and mental summary scores increased by 5.6 and 5.5 points, respectively, but compared with controls, remained 8.2 and 6.4 points lower. For disease-specific HRQoL, the Pulmonary Embolism–Specific Quality of Life Questionnaire overall score decreased from 21.7% to 15.2%, indicating improved HRQoL. Venous Insufficiency Epidemiological and Economic Study-Quality of Life/Symptoms Questionnaire scores did not change over time.

Conclusion: Overall, the quality of life of patients with VTE was worse than that of controls after 1 year, indicating a long-term impact of VTE diagnosis in the elderly.

KEYWORDS
aged, quality of life, surveys and questionnaires, time, venous thromboembolism

Essentials

- Less is known of health-related quality of life (HRQoL) after venous thromboembolism.
- We studied change in HRQoL over 1 year after venous thromboembolism in patients aged ≥70 years.
- Generic and pulmonary embolism–specific HRQoL improved, but deep vein thrombosis–related HRQoL did not.
- Results suggest that clinicians should assess HRQoL to target potential interventions.

1 | INTRODUCTION

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE; with or without DVT), is a multicausal disease [1]. The incidence of VTE is approximately 1 to 2 per 1000 persons per year and increases exponentially with age up to approximately 1 per 100 persons per year in older people [2]. VTE may lead to short- and long-term effects, such as postthrombotic syndrome (PTS), which may affect health-related quality of life (HRQoL). Several questionnaires aimed at assessing HRQoL have been developed [3–5].

Previous studies on generic HRQoL in VTE focused mainly on young and middle-aged people [6–20], with very limited information on older individuals. To our knowledge, only 1 study investigated generic HRQoL in VTE specifically in older individuals [21], finding that older patients with VTE reported worse generic HRQoL (by the 36-item Short Form Health Survey [SF-36]) 18 months after VTE than that in the general population in Spain of the same age, with mainly physical function affected. Notably, this study did not use disease-specific HRQoL instruments. In young and middle-aged populations, studies reporting effects of VTE on generic HRQoL were inconsistent. Some reported that HRQoL was impaired after VTE [6,8–11,15,19,20], while other studies showed no effect of VTE on HRQoL [7,10,18].

With regard to disease-specific HRQoL, several studies were conducted to assess the effect of VTE in adult patients of all ages, but these studies did not evaluate older people separately [9–11,13,15–20]. van Es et al. [19] reported that, compared with the general Dutch population, patients with an acute PE had worse disease-specific HRQoL after both short- and long-term follow-up. Two cohort studies showed that disease-specific HRQoL improved during the year after PE [13,17]. Several studies demonstrated that patients with DVT had impaired long-term (ie, 2-10 years) disease-specific HRQoL compared with healthy controls and population norms [9,11,15]. However, 2 other studies, including a meta-analysis, concluded that in patients who suffered from DVT, the disease-specific HRQoL remained similar to population norms after at least 1 year [10,18]. Furthermore, it is currently unknown if disease-specific HRQoL improves after VTE in older patients with VTE.

Our aim was to assess the potential recovery in generic HRQoL and disease-specific HRQoL in patients 1 year after the VTE. We also studied whether the generic HRQoL 1 year after VTE would reach the level of control subjects.

2 | METHODS

2.1 | Study design

The Age and Thrombosis, Acquired and Genetic risk factors in the elderly study is a two-center, population-based, case-control study designed to study risk factors for VTE in older people. The design of the Age and Thrombosis, Acquired and Genetic risk factors in the elderly study was described in detail previously [22]. From June 2008 to August 2011 in Leiden, the Netherlands, and December 2008 to July 2011 in Vermont, United States, all consecutive patients aged ≥70 years with a first-time imaging-confirmed DVT or PE (with or without DVT) were identified. Patients were identified from the anticoagulation clinics in Haarlem and Leiden and from the Vascular Laboratory and the Radiology Department of the University of Vermont Medical Center (Burlington, Vermont, United States). Control subjects (aged ≥70 years) were randomly selected from 5 primary care practices in Leiden and 4 in Vermont. Individuals with active malignancy or severe psychiatric or cognitive disorders (measured with Mini-Mental State Exam) were excluded. Active malignancy was defined as diagnosis of cancer within 6 months before the thrombotic event (or date of telephone call for the control subjects) or chemotherapy or radiation therapy for cancer in the last 6 months. For data collection on HRQoL and risk factors for VTE, patients were visited twice, ie, soon after the VTE event and 1 year after the event, allowing us to assess the change in HRQoL after 1 year. Control subjects were visited once. Data collection was performed by a trained research nurse.

In total, 401 patients and 431 control subjects were included in the original study. For the current study, we included only those patients who were visited twice for this study and those who filled in HRQoL questionnaires, ie, 316 patients and 427 control subjects. The study was approved by the Medical Ethical Committee of the Leiden University Medical Centre (protocol number: P08.066) and by the Committee on Human Research of the University of Vermont (protocol number: CHRMS M09-008). All participants provided written informed consent.

2.2 | Quality of life instruments

The generic SF-36 questionnaire has 8 domains (vitality, physical functioning, bodily pain, general health, physical role, emotional role,

social functioning, and mental health) that generate 2 summary scores, the physical component summary (PCS) score and mental component summary (MCS) score. PCS has 4 domains (physical functioning, bodily pain, general health, and physical role), and MCS has 4 domains (vitality, emotional role, social functioning, and mental health). Previous studies using SF-36 in patients with VTE demonstrated good reliability and validity [10,13,21]. The PCS score, the MCS score, and the 8-domain score values each range from 0 to 100, with a higher score indicating better HRQoL. If questionnaire items were missing, a score was calculated if a respondent answered at least half of the items, and a person-specific estimate was imputed for the missing items [23,24].

There are several disease-specific HRQoL questionnaires for patients with DVT or PE [5]. Because the Venous Insufficiency Epidemiological and Economic Study-Quality of Life/Symptoms Questionnaire (VEINES-QOL/Sym) is the most widely used in DVT [25–29] and the PE-Specific Quality of Life Questionnaire (PEmb-QoL) is the only questionnaire specifically for the PE population, these 2 questionnaires were selected for the current study [30,31].

The VEINES-QOL measures the impact of chronic venous disorders of the leg on symptoms and quality of life (QoL). The questionnaire includes 26 items providing the VEINES-QOL score (reflecting QoL) and the VEINES-Sym score (a quantitative measure of symptoms) [25,32,33]. Since little is known about patient-reported outcomes in people aged ≥70 years and symptoms were strongly associated with HRQoL [34], both VEINES-QOL and VEINES-Sym were reported in our study. Calculation of these scores was described in previous studies [35,36]. Total scores for each domain range from 0 to 100 and higher scores indicate better status. Scores for missing data were imputed using the same algorithm as for the SF-36 [23,24].

The PEmb-QoL is a 40-item, PE-specific QoL questionnaire and produces scores in 6 dimensions (frequency of complaints, activities of daily living limitations, work-related problems, social limitations, intensity of complaints, and emotional complaints) [30,31]. Scores for all dimensions are calculated by the sum of the scores for each item in the dimension divided by the number of the items. A transformed dimensions score is calculated in a 2-step process. The score of each item is rescaled such that 100 corresponds to a maximal score and 0 corresponds to a minimal score. A mean of rescaled items constitutes a given dimension. So total scores for each domain range from 0 to 100. The percentage scores obtained in each one of the 6 dimensions are averaged to obtain an overall PEmb-QoL score (0-100). A higher score indicates worse PE-related QoL. The PEmb-QoL has no standard for dealing with missing items, so we only included patients with complete data. When comparing PEmb-QoL scores, a difference of 15 points is considered clinically relevant [37].

The SF-36 was administered in patients and controls at the first visit, and 1 year later in the patients. For patients, at both time points, the disease-specific PEmb-QoL (patients with PE) and/or the VEINES-QOL/Sym (patients with DVT) questionnaires were completed, depending on their index diagnosis. Due to a form error, the PEmb-QoL questionnaire was not administered in its full form in patients in Vermont, so we analyzed PEmb-QoL data in patients included in the Netherlands only.

2.3 | Covariates

Risk factors for VTE including lifestyle factors were assessed at the first visit. Body height, body weight, and blood pressure were measured by the research nurse. Lifestyle factors were defined by self-report. For smoking, patients were categorized into nonsmokers, former smokers, and current smokers. Alcohol intake was dichotomized into current use yes or no. Blood pressure was measured with standard methods, and hypertension was defined as a systolic blood pressure of ≥140 mmHg or a diastolic blood pressure of ≥90 mmHg or the use of antihypertensive medication. Race was defined based on self-report; we collected data on the country of birth of participants and their parents and did not collect data specifically on ethnicity.

2.4 | VTE definitions

Provoked VTE was defined as VTE after hospitalization (including recent surgery), fracture, plaster cast, splint, minor injuries of lower extremities (such as a sprained ankle or contusion of the lower leg), or transient immobility at home for ≥4 successive days in the 3 months before the index date. The index date was defined as the date of diagnosis of thrombosis for the patients and the date of the home visit for the control subjects.

2.5 | Statistical analysis

2.5.1 | Association between time since VTE and PCS/MCS score

The median time between the index date (date of VTE) and the first visit of patients was 1 month. Based on the median time, we divided the patients into 2 groups: group 1 was for patients whose time frames were shorter than the median time, and group 2 was for patients whose time frames were the same as or longer than the median period. We compared the PCS and the MCS between these 2 groups by using the Independent Samples *t*-test.

2.5.2 | Change in HRQoL over 1 year

The mean change in HRQoL after 1 year and its 95% CI were calculated by linear regression analysis after adjustment for study center (for change in PEmb-QoL, which was based on Leiden data only, no adjustments were made). The above analyses were repeated

separately for patients with PE vs DVT. The unadjusted analysis was performed for the mean change in HRQoL.

2.5.3 | HRQoL in patients vs controls

We compared the SF-36 scores of patients 1 year after the VTE with the scores of controls by linear regression analysis, adjusting for potential confounders (age, sex, body mass index, smoking status, hypertension, diabetes, alcohol intake, and a history of heart failure, angina, myocardial infarction, cerebral hemorrhage, transient ischemic attack, and ischemic stroke). The unadjusted analysis was performed for the mean difference of SF-36 scores between patients and controls.

2.5.4 | Sensitivity analysis

Sensitivity analysis was conducted to estimate the possible impact of missing second visit data due to death between the 2 visits. We did this by comparing HRQoL measures from the first visit between those who died and those who did not using linear regression.

2.5.5 | Interpretation of the results

For the interpretation of the results of the generic HRQoL, we considered a difference of 5 points in any subscale as clinically or socially relevant [23]. For PEmb-QoL, the minimal clinically important difference (15 points) [37] was used for clinical relevance. There is no acknowledged clinically significant difference for VEINES-QOL/Sym.

3 | RESULTS

Of the 401 patients and 431 control subjects included in the original study, 5 patients and 3 controls had missing HRQoL questionnaires at both visits, and 4 patients and 1 control had a missing HRQoL questionnaire from the first visit. Therefore, 392 patients at the time of VTE and 427 controls had information on HRQoL. Not all patients were available for the second home visit 1 year after VTE as 21 (5.4%) of them died shortly after the thrombotic event and 24 (6.1%) declined to participate in the second visit. Furthermore, for 31 (7.9%) patients, data on HRQoL was missing at visit 2. Therefore, a total of 316 patients had HRQoL data both at the time of the VTE event as well as 1 year later.

3.1 | Correlation between timeframe for recruitment and PCS/MCS score

We found that the mean difference was −0.2 (95% CI, −5.7 to 5.2) for PCS and −0.1 (95% CI, −5.6 to 5.4) for MCS, indicating that there was no association between the time since the VTE event and the HRQoL score at the first visit.

TABLE 1 Baseline characteristics of patients and controls.

Characteristic	Patients (*N* = 316)	Controls (*N* = 427)
Men, *n* (%)	135 (42.7)	208 (48.7)
Age (y), mean (range)	78.4 (70.0-94.3)	77.5 (70.3-96.3)
Race, Caucasian, *n* (%)[a]	307 (97.2)	407 (95.3)
Location		
Leiden, *n* (%)	282 (89.2)	302 (70.7)
Vermont, *n* (%)	34 (10.8)	125 (29.3)
Body mass index (kg/m^2), mean (range)[a]	27.2 (17.3-45.4)	27.0 (17.0-49.7)
Type of VTE, *n* (%)		
Deep vein thrombosis	130 (41.1)	NA
Pulmonary embolism with deep vein thrombosis	186 (58.9)	NA
Provoked[a]	153 (49.5)	NA
Unprovoked[a]	156 (50.5)	NA
Smoking status, *n* (%)[a]		
Never	33 (10.5)	55 (12.9)
Former	188 (59.7)	252 (59.0)
Current	94 (29.8)	119 (27.9)
Alcohol intake, *n* (%)[a]		
None	124 (39.4)	159 (37.2)
Current	191 (60.6)	267 (62.5)
Hypertension, *n* (%)[a]	263 (84.6)	372 (87.1)
Diabetes, *n* (%)	51 (16.1)	66 (15.5)
Comorbidities, *n* (%)		
Heart failure	13 (4.1)	19 (4.4)
Angina	31 (9.8)	33 (7.7)
Myocardial infarction	45 (14.2)	51 (11.9)
Cerebral bleeding[a]	4 (1.4)	7 (1.6)
Cerebral infarction	16 (5.1)	23 (5.4)
Transient ischemic attack[a]	38 (12.0)	42 (9.8)

NA, not applicable; VTE, venous thromboembolism.
[a]For race, 1 missing in patients and 2 missing in controls; for body mass index, 14 missing in patients and 8 missing in controls; 7 patients could not be classified into provoked or unprovoked due to missing risk factors; for smoking status, 1 missing in patients and 1 missing in controls; for alcohol intake, 1 missing in patients and 1 missing in controls; for hypertension, 5 missing in patients and 9 missing in controls; for cerebral bleeding, 33 missing in patients; for transient ischemic attack, 3 missing in controls.

Table 1 shows the characteristics of patients and controls. In both, there were more women than men. The mean age of patients was 78.4 years, similar to controls (mean age, 77.5 years). Nearly all participants were Caucasian. Body mass index was similar in patients and controls.

TABLE 2 Change in quality of life over 1 year for the 36-item Short Form Health Survey.

SF-36	Patients at visit 1 (*N* = 316),[a] mean (95% CI)	Patients at visit 2 (*N* = 316),[a] mean (95% CI)	Controls (*N* = 427),[a] mean (95% CI)	Mean change, patients,[b] 95% CI	Mean difference, patients at visit 2 vs controls,[c] 95% CI
PCS score	49.5 (46.9 to 52.0)	55.2 (52.4 to 58.0)	66.1 (63.8 to 68.3)	5.6 (1.8 to 9.4)	−8.2 (−11.8 to −4.5)
Physical functioning	49.8 (46.4 to 53.1)	51.4 (48.1 to 54.8)	65.6 (62.8 to 68.3)	1.4 (−3.4 to 6.1)	−9.9 (−13.9 to −5.9)
Physical role	31.3 (26.8 to 35.8)	47.4 (42.5 to 52.4)	64.0 (60.0 to 67.9)	16.6 (9.9 to 23.3)	−13.3 (−20.0 to −6.5)
Bodily pain	60.3 (57.1 to 63.4)	65.8 (62.9 to 68.7)	70.5 (68.1 to 72.9)	5.3 (1.1 to 9.6)	−4.0 (−8.1 to 0.2)
General health	56.2 (54.0 to 58.5)	54.4 (52.1 to 56.7)	63.8 (61.9 to 65.6)	−1.8 (−5.0 to 1.4)	−6.5 (−9.6 to −3.5)
MCS score	62.2 (59.7 to 64.8)	68.2 (65.7 to 70.7)	76.1 (74.3 to 78.0)	5.5 (2.0 to 9.0)	−6.4 (−9.6 to −3.1)
Vitality	53.2 (50.6 to 55.7)	57.2 (54.8 to 59.5)	64.8 (62.8 to 66.8)	3.8 (0.4 to 7.3)	−7.1 (−10.4 to −3.9)
Social functioning	63.4 (60.3 to 66.5)	73.2 (70.2 to 76.2)	83.3 (81.2 to 85.5)	9.3 (5.1 to 13.6)	−9.5 (−13.4 to −5.7)
Emotional role	60.6 (55.7 to 65.6)	68.1 (63.5 to 72.7)	79.0 (75.6 to 82.5)	7.5 (0.8 to 14.2)	−8.1 (−14.3 to −1.9)
Mental health	72.0 (69.9 to 74.1)	74.1 (72.1 to 76.2)	77.0 (75.4 to 78.7)	2.1 (−0.8 to 5.0)	−1.2 (−4.0 to 1.6)

MCS, mental component summary; PCS, physical component summary; SF-36, 36-item Short Form Health Survey.

[a]In general, 85 patients and 4 controls were missing. For physical component summary, 298 patients were available for both visit 1 and visit 2 and 415 controls were available for visit 1; for physical functioning, 314 patients were available for both visit 1 and visit 2 and 427 controls were available for visit 1; for physical role, 312 patients were available for both visit 1 and visit 2 and 424 controls were available for visit 1; for bodily pain, 304 patients were available for both visit 1 and visit 2 and 418 controls were available for visit 1; for general health, 313 patients were available for both visit 1 and visit 2 and 425 controls were available for visit 1; for mental component summary, 296 patients were available for both visit 1 and visit 2 and 416 controls were available for visit 1; for vitality, 313 patients were available for both visit 1 and visit 2 and 425 controls were available for visit 1; for social functioning, 304 patients were available for both visit 1 and visit 2 and 421 controls were available for visit 1; for emotional role, 307 patients were available for both visit 1 and visit 2 and 422 controls were available for visit 1. For mental health, 312 patients were available for both visit 1 and visit 2 and 425 controls were available for visit 1.

[b]Mean change between 2 visits for 36-item Short Form Health Survey in patients with venous thromboembolism, adjusted for study center.

[c]Mean difference between second visit of patients with venous thromboembolism and controls, adjusted for age, sex, study center, body mass index, smoking, hypertension, alcohol intake, and comorbidities.

There were 130 (41.1%) patients who had DVT only, while 186 (58.9%) had PE (with or without DVT). The VTE event was provoked in 49.5% (153). The distribution of cardiovascular risk factors and comorbidities was not notably different between patients and controls. For patients, the mean time between the index date and the first visit was 1 month (95% CI, 0.9-1.1 months), and the time to the second visit was 12.0 months (95% CI, 11.9-12.3 months). The mean time between visits was 10.6 months (95% CI, 10.4-10.8 months).

3.2 | Generic HRQoL

Table 2 shows the results of the SF-36 questionnaire at both visits for the patients and the only visit for controls. In patients, HRQoL improved for both summary scores; the PCS increased by 5.6 points (95% CI, 1.8-9.4) and the MCS increased by 5.5 points (95% CI, 2.0-9.0). Improvement of HRQoL was also observed in most individual domains (except for general health), with the most pronounced improvement in the domains of physical role (mean difference, 16.6 points; 95% CI, 9.9-23.3) and social functioning (mean difference, 9.3 points; 95% CI, 5.1-13.6). The HRQoL of patients at visit 2 did not reach the level of the controls (mean difference for physical score, −8.2 points; 95% CI, −11.8 to −4.5; mean difference for mental score, −6.4 points; 95% CI, −9.6 to −3.1).

Regarding types of VTE, the SF-36 score was lower in patients with PE than in patients with DVT at both visits, and both groups of patients had a similar improvement in HRQoL over time (Supplementary Tables S1 and S2).

3.3 | Sensitivity analysis

Among patients who died between the 2 visits, the PCS and MCS scores were lower, as were most domains (except for vitality) compared to those who had both visits (Supplementary Table S3). The unadjusted results of generic HRQoL are shown in Supplementary Table S4, and there were no major differences between unadjusted and adjusted results.

3.4 | Disease-specific HRQoL

Table 3 shows the distribution of the overall and dimension-specific PEmb-QoL scores at visit 1 and visit 2 (Leiden center only). The PEmb-QoL overall score decreased from 21.7% to 15.2% (mean difference, −6.5%; 95% CI, −9.4% to −3.6%), indicating improved PE-related QoL 1 year after PE. The improvement was most pronounced for work-related problems (mean difference, −17.1%; 95% CI, −24.4%

TABLE 3 Change in Pulmonary Embolism–Specific Quality of Life Questionnaire (only Leiden) and Venous Insufficiency Epidemiological and Economic Study-Quality of Life/Symptoms Questionnaire results in patients with venous thromboembolism.

PEmb-QoL[a]	Visit 1, mean (SD)	Visits 2, mean (SD)	Mean change (95% CI)
Quality of life[b]	21.7 (19.4)	15.2 (16.6)	−6.5 (-9.4 to −3.6)
Frequency of complaints[b]	15.8 (16.0)	14.4 (15.8)	−1.4 (−3.9 to 1.1)
Activities of daily living limitations[b]	16.9 (21.6)	17.6 (23.1)	0.7 (−2.4 to 3.8)
Work-related problems[b]	41.7 (45.1)	24.5 (36.6)	−17.1 (−24.4 to −9.8)
Social limitations[b]	19.3 (29.8)	7.6 (19.7)	−11.8 (−16.4 to −7.1)
Intensity of complaints[b]	22.9 (21.7)	20.1 (19.0)	−2.7 (−6.1 to 0.6)
Emotional complaints[b]	15.3 (16.1)	7.7 (10.9)	−7.6 (−10.0 to −5.2)
VEINES-QOL/Sym[c]	Visit 1 (*N* = 142), mean (95% CI)	Visit 2 (*N* = 142), mean (95% CI)	Mean change[d] (95% CI)
VEINES-QOL	50.9 (49.3 to 52.4)	50.0 (48.3 to 51.7)	−0.8 (−3.1 to 1.4)
VEINES-Sym	50.5 (48.9 to 52.1)	49.9 (48.2 to 51.6)	−0.5 (−2.8 to 1.7)

PEmb-QoL, Pulmonary Embolism–Specific Quality of Life Questionnaire; VEINES-QOL/Sym, Venous Insufficiency Epidemiological and Economic Study-Quality of Life/Symptoms Questionnaire.
[a]Higher scores reflect lower health-related quality of life.
[b]For quality of life, 150 patients were available for both visit 1 and visit 2; for frequency of complaints, 167 patients were available for both visit 1 and visit 2; for activities of daily living limitations, 161 patients were available for both visit 1 and visit 2; for work-related problems, 165 patients were available for both visit 1 and visit 2; for social limitations, 168 patients were available for both visit 1 and visit 2; for intensity of complaints, 168 patients were available for both visit 1 and visit 2; for emotional complaints, 164 patients were available for both visit 1 and visit 2.
[c]Higher scores reflect better health-related quality of life.
[d]Adjusted for study center.

to −9.8%) and social limitations (mean difference, −11.8%; 95% CI, −16.4% to −7.1%). The VEINES-QOL and VEINES-Sym scores did not change over time (Table 3).

When taking the minimal clinically important difference of a 15-point change of the PEmb-QoL into consideration, the PEmb-QoL scores tended to improve in most domains (excluding the activities of daily living limitations), and 34% of patients had clinically meaningful improvement or deterioration change of more than 15 points. The mean intraindividual change of dimension-specific PEmb-QoL is shown in the Figure.

4 | DISCUSSION

This study demonstrated that older patients with VTE who survived on average 1 year after their event had improved HRQoL, which was most pronounced in the domains of physical role and social functioning. However, HRQoL of patients with VTE, whether they had DVT or PE, at 1 year did not reach the level of the controls without VTE. Among patients with PE, the PEmb-QoL scores tended to improve in most domains (except activities of daily living limitations) in the year after PE, but there was no difference over time for the VEINES-QOL/Sym score in patients with DVT.

Findings of improved generic and PE-specific QoL agree with 2 recent prospective studies in middle-aged patients [13,17]. However, the generic HRQoL did not improve to the level of the controls after 1-year follow-up. This finding differs from the results of a prospective Canadian study of middle-aged patients with VTE, where the HRQoL improved to the level of healthy population norms over 1 year of follow-up [13], and from the results of a recent meta-analysis, which reported that generic HRQoL after DVT was similar to population norms after 13 months in middle-aged patients [10]. The difference

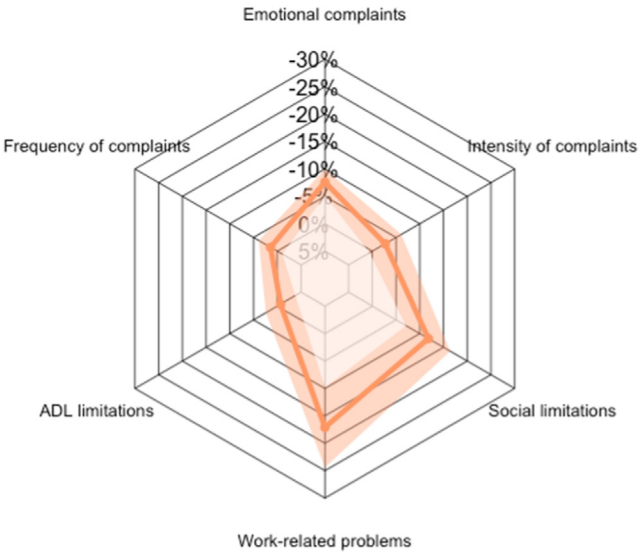

FIGURE Intraindividual change in quality of life using Pulmonary Embolism–Specific Quality of Life Questionnaire (PEmb-QoL) score between 2 visits. The dark orange line (mean value) and the orange ribbon (corresponding 95% CI) indicate the intraindividual change in the PEmb-QoL score. They are plotted as a hexagon to represent each one of the 6 PEmb-QoL dimensions. ADL, activities of daily living.

between our findings and the literature may relate to the comparison group studied; we used age-matched controls, while prior studies used population norms. The controls in our study may not be representative of the Dutch general population or the US general population, although we attempted to include a random sample of the community where the patients resided. Participation bias by healthier people for the control group may account for the control group potentially having better HRQoL than the general population.

Limited research on HRQoL has been conducted specifically in older patients with VTE. However, Cuervo et al. [21] found that older patients with VTE reported worse HRQoL than that reported by older individuals in the general Spanish population 18 months after VTE, similar to our results. The means for the 2 summary scores in that study (PCS, 45.5; 95% CI, 43.7-47.3; MCS, 47.3; 95% CI, 44.9-49.6) were lower than the second visit scores in this study (PCS, 55.2; 95% CI, 52.4-58.0; MCS, 68.2; 95% CI, 65.7-70.7), possibly since patients with active cancer were not excluded in that study.

Both generic HRQoL and PEmb-QoL improved 1 year after the VTE. The reasons for the improvement of generic HRQoL could be that the symptoms of VTE decreased, that many patients had stopped anticoagulation, or that fear of having recurrent VTE subsided. However, the differences were not observed in VEINES-QOL/Sym, which may be due to a low rate of PTS or stability in any symptoms in those with PTS. PTS is a chronic complication of DVT and may significantly impact disease-specific HRQoL that may not be captured by generic HRQoL measures [16]. In our study, the improvement of generic HRQoL did not reach the control level. Possibly, the lack of improvement was due to PTS, which was better captured by VEINES-QOL. Several studies reported that older age is a risk factor for PTS [38–40], but others showed the opposite results [41,42]. We did not measure PTS so can only speculate on the reasons for the lack of improvement of the VEINES-QOL/Sym. Nevertheless, treating physicians should take the signs of long-term effects of VTE seriously, even when there is no clinically obvious symptom, such as PTS. Other determinants of decreased QoL include anxiety and depression [43].

When comparing the mean change of generic HRQoL between patients with PE and those with DVT, we found that the improvement of PCS score and its 2 domains (physical functioning and bodily pain) was more pronounced in patients with DVT than in patients with PE. In contrast, the improvement of MCS score and its 3 domains (vitality, emotional role, and mental health) was more pronounced in patients with PE than in patients with DVT. This likely reflects ongoing symptoms of the acute event and emotional distress shortly after the VTE that improved over time. After 1 year, the generic HRQoL was better in patients with DVT than in patients with PE, similar to the pattern observed at the time of the thrombotic event. We do not have a clear explanation for this finding.

Several studies reported an improvement in the PEmb-QoL over time, albeit the improvements in the scores were not similar in all studies. The mean individual improvement for PEmb-QoL in the current study was 6.5 percentage points (95% CI, 3.6-9.4), while the mean individual change of PEmb-QoL was 4.3 percentage points between a 3- and 12-month visit after VTE in the Follow-up after Acute Pulmonary Embolism (FOCUS) study [17] and 12.1 percentage points in a Canadian study (between month 3 to month 12 after acute PE) [13]. These differences may be due to the older age, strict selection criteria, and PE severity difference.

4.1 | Clinical relevance

In the SF-36 questionnaire, a difference of 5 points or more in any subscale was accepted as clinically and socially relevant. After the multivariable analysis, the mean scores of PCS and MCS in cases over 1 year after the VTE event were clinically improved, ie, change in score >5. The mean scores of PCS and MCS remained lower in patients at visit 2 than in controls; the difference in scores being >5 indicating clinical relevance. Physical role and social functioning had the most pronounced mean change (improvement) over 1 year among patients. However, still, physical functioning, physical role, as well as social functioning had the largest mean difference between patients at visit 2 and controls, again remaining clinically relevant. These results suggest that it may be important to consider approaches to improve physical and mental health shortly after VTE diagnosis.

Several determinants of poorer HRQoL, such as pain, dyspnea, anxiety, or depression, may be targeted and improved with interventions such as compression therapy, cardiopulmonary rehabilitation, and psychosocial interventions. Small studies have shown that such interventions indeed lead to a better HRQoL and improved functional outcomes [44]. To identify patients who may qualify for such treatment, physicians should measure outcomes such as QoL and functional limitations. In addition to the need for more studies on the safety and efficacy of treatment of long-term VTE sequelae in the elderly, our findings are a call to action for physicians to measure health outcomes in elderly patients with VTE, for instance, by introducing and implementing the International Consortium for Health Outcomes Measurements-venous thromboembolism standard set of outcome measures [45].

4.2 | Strengths

We used generic and disease-specific measures to assess HRQoL in consecutive, older patients with VTE and age-matched controls. To our knowledge, this is the first study to analyze longitudinal HRQoL after VTE in people aged ≥70 years.

4.3 | Limitations

We had incomplete data for PEmb-QoL (data missing in Vermont) questionnaire, so we could not rule out differences between countries. However, data were sufficient to draw valid conclusions in the Netherlands. The controls may have had a higher HRQoL than that in the general population, which may have led to an overestimation of differences between patients and controls. The first measure of

HRQoL was done close in time to the VTE event in patients, so it may reflect acute effects of the event rather than a steady state. Lastly, we did not measure PTS or post-PE syndrome.

4.4 | Conclusion

In older patients, improvement in HRQoL was observed in the year after VTE using both the generic SF-36 and the PEmb-QoL questionnaires, while there was no improvement for patients with DVT in the VEINES-QOL/Sym questionnaire. Overall, the QoL of the VTE survivors was worse than the controls after 1 year, independent of comorbidities, indicating a major long-term impact of a VTE diagnosis on the elderly. These findings should be a call to action to increase awareness of the long-term effects of VTE in elderly patients. Patient-reported outcome measures [46,47] may be helpful to identify patients with persistent physical or mental symptoms who are likely to benefit from continuing expert care and dedicated interventions.

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ETHICS STATEMENT

The study was approved by the Medical Ethical Committee of the Leiden University Medical Centre (protocol number: P08.066) and by the Committee on Human Research of the University of Vermont (protocol number: CHRMS M09-008). All participants provided written informed consent.

AUTHOR CONTRIBUTIONS

All authors contributed substantially to the concept and design and analysis and interpretation of data. H.W. and A.v.H.V. contributed to critical writing and revising intellectual content. All authors gave final approval of the version to be published.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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SUPPLEMENTARY MATERIAL

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SUPPLEMENTAL TABLE 1 The difference of quality of life between two visits of SF-36 in deep vein thrombosis patients and the difference of quality of life between patients at second visit and controls.

SF-36	Patients Visit1 (N=130)[c] (mean, 95%CI)	Patients Visit2 (N=130)[c] (mean, 95%CI)	Controls (N=427)[c] (mean, 95%CI)	Mean change patients V2-V1[a] (95% CI)	Mean difference patients-control at V2[b] (95%CI)
PCS	52.3 (47.9 to 56.6)	58.4 (53.9 to 62.9)	66.1 (63.8 to 68.3)	5.6 (-0.6 to 11.7)	-4.5 (-9.3 to 0.3)
Physical functioning	51.0 (45.3 to 56.7)	54.9 (49.5 to 60.4)	65.6 (62.8 to 68.3)	3.1 (-4.8 to 11.0)	-6.9 (-12.3 to -1.5)
Physical role	39.3 (31.9 to 46.8)	50.4 (42.5 to 58.3)	64.0 (60.0 to 67.9)	11.4 (0.6 to 22.2)	-8.4 (-17.2 to 0.4)
Bodily pain	59.0 (54.0 to 64.1)	69.0 (64.6 to 73.3)	70.5 (68.1 to 72.9)	9.7 (3.1 to 16.3)	-1.0 (-6.4 to 4.5)
General health	58.2 (54.9 to 61.5)	57.0 (53.5 to 60.6)	63.8 (61.9 to 65.6)	-1.2 (-6.0 to 3.7)	-3.9 (-8.0 to 0.2)
MCS	65.4 (61.4 to 69.5)	70.4 (66.3 to 74.4)	76.1 (74.3 to 78.0)	4.5 (-1.1 to 10.1)	-4.8 (-9.0 to -0.6)
Vitality	57.0 (53.0 to 61.0)	59.5 (55.8 to 63.2)	64.8 (62.8 to 66.8)	2.5 (-2.9 to 7.9)	-4.7 (-9.0 to -0.4)
Social functioning	66.6 (61.6 to 71.7)	77.4 (72.7 to 82.1)	83.3 (81.2 to 85.5)	10.3 (3.6 to 17.0)	-6.1 (-11.1 to -1.1)
Emotional role	65.7 (58.1 to 73.3)	69.6 (62.6 to 76.6)	79.0 (75.6 to 82.5)	4.6 (-5.6 to 14.7)	-6.9 (-14.8 to 1.1)
Mental health	73.8 (70.3 to 77.3)	76.0 (72.7 to 79.3)	77.0 (75.4 to 78.7)	2.2 (-2.6 to 7.0)	-0.7 (-4.4 to 3.0)

CI: confidence interval; N: number; PCS: physical component summary scores; MCS: mental component summary scores.

[a]Mean change between two visits of SF-36 in deep vein thrombosis patients, adjusted for study center.

[b]Mean difference between second visit of deep vein thrombosis patients and controls, adjust for age, sex, study center, BMI, smoking, hypertension, alcohol intake and comorbidities.

[c]For PCS, 124 patients were available for both visit 1 and visit 2, 415 controls for visit1; For physical functioning, 128 patients were available for both visit 1 and visit 2, 427 controls for visit1; For physical role, 129 patients were available for both visit 1 and visit 2, 424 controls for visit1; For bodily pain, 125 patients were available for both visit 1 and visit 2, 418 controls for visit1; For general health, 130 patients were available for both visit 1 and visit 2, 425 controls for visit1; For MCS, 121 patients were available for both visit 1 and visit 2, 416 controls for visit1; For vitality, 130 patients were available for both visit 1 and visit 2, 425 controls for visit1; For social functioning, 124 patients were available for both visit 1 and visit 2, 421 controls for visit1; For emotional role, 125 patients were available for both visit 1 and visit 2, 422 controls for visit1. For mental health, 129 patients were available for both visit 1 and visit 2, 425 controls for visit1.

SUPPLEMENTAL TABLE 2 The difference of quality of life between two visits of SF-36 in pulmonary embolism patients and the difference of quality of life between patients at second visit and controls.

SF-36	Patients Visit1 (N=186)[c] (mean, 95%CI)	Patients Visit2 (N=186)[c] (mean, 95%CI)	Controls (N=427)[c] (mean, 95%CI)	Mean change patients V2-V1[a] (95% CI)	Mean difference patients-control at V2[b] (95%CI)
PCS	47.5 (44.3-50.6)	53.0 (49.3-56.6)	66.1 (63.8-68.3)	5.6 (0.9 to 10.4)	-11.3 (-15.4-(-7.2))
Physical functioning	48.9 (44.7-53.1)	49.0 (44.8-53.2)	65.6 (62.8-68.3)	0.1 (-5.8 to 6.0)	-12.4 (-17.0-(-7.9))
Physical role	25.6 (20.1-31.1)	45.4 (38.9-51.8)	64.0 (60.0-67.9)	20.2 (11.8 to 28.5)	-17.0 (-24.8-(-9.3))
Bodily pain	61.2 (57.1-65.2)	63.6 (59.7-67.5)	70.5 (68.1-72.9)	2.3 (-3.3 to 7.9)	-6.3 (-11.1-(-1.4))
General health	54.8 (51.7-57.9)	52.5 (49.5-55.5)	63.8 (61.9-65.6)	-2.3 (-6.5 to 2.0)	-9.0 (-12.5-(-5.4))
MCS	60.0 (56.7-63.2)	66.7 (63.4-70.0)	76.1 (74.3-78.0)	6.3 (1.8 to 10.8)	-7.9 (-11.6-(-4.2))
Vitality	50.5 (47.2-53.7)	55.5 (52.4-58.6)	64.8 (62.8-66.8)	4.8 (0.3 to 9.2)	-9.4 (-13.2-(-5.6))
Social functioning	61.1 (57.1-65.1)	70.3 (66.5-74.2)	83.3 (81.2-85.5)	8.8 (3.3 to 14.3)	-12.2 (-16.6-(-7.8))
Emotional role	57.1 (50.5-63.7)	67.0 (60.9-73.1)	79.0 (75.6-82.5)	9.4 (0.5 to 18.4)	-9.5 (-16.7-(-2.4))
Mental health	70.7 (68.1-73.3)	72.8 (70.2-75.4)	77.0 (75.4-78.7)	2.0 (-1.6 to 5.7)	-2.0 (-5.2-1.2)

CI: confidence interval; N: number.

[a]Mean change between two visits of SF-36 in deep vein thrombosis patients, adjusted for study center.

[b]Mean difference between second visit of deep vein thrombosis patients and controls, adjust for age, sex, study center, BMI, smoking, hypertension, alcohol intake and comorbidities.

[c]For PCS, 174 patients were available for both visit 1 and visit 2, 415 controls for visit1; For physical functioning, 186 patients were available for both visit 1 and visit 2, 427 controls for visit1; For physical role, 183 patients were available for both visit 1 and visit 2, 424 controls for visit1; For bodily pain, 179 patients were available for both visit 1 and visit 2, 418 controls for visit1; For general health, 183 patients were available for both visit 1 and visit 2, 425 controls for visit1; For MCS, 175 patients were available for both visit 1 and visit 2, 416 controls for visit1; For vitality, 183 patients were available for both visit 1 and visit 2, 425 controls for visit1; For social functioning, 180 patients were available for both visit 1 and visit 2, 421 controls for visit1; For emotional role, 182 patients were available for both visit 1 and visit 2, 422 controls for visit1. For mental health, 183 patients were available for both visit 1 and visit 2, 425 controls for visit1.

SUPPLEMENTAL TABLE 3 Compare the quality of life of patients who died between two visits and those who didn't.

SF-36	Died[c] (N=18) (mean (95%CI))	Attended both visits[b] (N=374) (mean (95%CI))	Mean difference[a] (95%CI)
PCS	33.5 (23.0-43.9)	47.8 (45.4-50.1)	-8.6 (-21.0-3.8)
Physical functioning	27.1 (12.4-41.8)	47.5 (44.4-50.6)	-15.6 (-30.5-(-0.8))
Physical role	19.1 (0.1-38.1)	29.2 (25.2-33.2)	-0.2 (-22.3-21.9)
Bodily pain	47.3 (30.8-63.7)	58.7 (55.7-61.6)	-7.3 (-23.7-9.1)
General health	45.6 (36.0-55.2)	55.8 (53.7-57.9)	-4.5 (-15.2-6.2)
MCS	56.9 (44.2-69.7)	61.7 (59.3-64.0)	2.9 (-9.9-15.7)
Vitality	53.1 (41.8-64.5)	52.2 (49.9-54.6)	6.1 (-5.8-18.1)
Social functioning	53.9 (40.0-67.8)	62.8 (59.8-65.8)	-3.8 (-20.2-12.5)
Emotional role	54.9 (30.7-79.1)	60.0 (55.4-64.6)	8.7 (-16.4-33.8)
Mental health	68.9 (60.9-76.8)	71.5 (69.5-73.5)	4.5 (-5.6-14.5)

CI: confidence interval; N: number; PCS: physical component summary scores; MCS: mental component summary scores.
[a]Adjusted for age, sex, study center, BMI, smoking, hypertension, alcohol intake and comorbidities.
[b]2 missing for PCS; 1 missing for physical role; 2 missing for bodily pain; 2 missing for general health; 2 missing for MCS; 4 missing for vitality; 11 missing for social functioning; 6 missing for emotional role; 5 missing for mental health.
[c]16 missing for PCS; 2 missing for physical functioning; 2 missing for physical role; 11 missing for bodily pain; 5 missing for general health; 16 missing for MCS; 2 missing for social functioning; 1 missing for emotional role.

SUPPLEMENTAL TABLE 4 Unadjusted change in quality of life over 1 year for SF-36.

SF-36	Patients Visit 1 (N = 316)[c] (mean, 95%CI)	Patients Visit 2 (N = 316)[c] (mean, 95%CI)	Controls (N = 427)[c] (mean, 95%CI)	Mean change Patients[a] (95% CI)	Mean difference Patients at Visit 2 vs Controls[b] (95%CI)
PCS	49.5 (46.9 to 52.0)	55.2 (52.4 to 58.0)	66.1 (63.8 to 68.3)	5.8 (3.4 to 8.1)	-10.8 (-14.4 to -7.3)
Physical functioning	49.8 (46.4 to 53.1)	51.4 (48.1 to 54.8)	65.6 (62.8 to 68.3)	1.7 (-1.0 to 4.3)	-14.3 (-18.4 to -9.9)
Physical role	31.3 (26.8 to 35.8)	47.4 (42.5 to 52.4)	64.0 (60.0 to 67.9)	16.1 (11.0 to 21.3)	-16.5 (-22.8 to -10.3)
Bodily pain	60.3 (57.1 to 63.4)	65.8 (62.9 to 68.7)	70.5 (68.1 to 72.9)	5.5 (2.2 to 8.8)	-4.7 (-8.5 to -0.9)
General health	56.2 (54.0 to 58.5)	54.4 (52.1 to 56.7)	63.8 (61.9 to 65.6)	-1.8 (-3.7 to 0)	-9.4 (-12.3 to -6.4)
MCS	62.2 (59.7 to 64.8)	68.2 (65.7 to 70.7)	76.1 (74.3 to 78.0)	6.0 (3.6 to 8.4)	-7.9 (-11.0 to -4.8)
Vitality	53.2 (50.6 to 55.7)	57.2 (54.8 to 59.5)	64.8 (62.8 to 66.8)	4.0 (1.8 to 6.1)	-7.6 (-10.7 to -4.5)
Social functioning	63.4 (60.3 to 66.5)	73.2 (70.2 to 76.2)	83.3 (81.2 to 85.5)	9.8 (6.6 to 13.2)	-10.1 (-13.7 to -6.5)
Emotional role	60.6 (55.7 to 65.6)	68.1 (63.5 to 72.7)	79.0 (75.6 to 82.5)	7.4 (1.9 to 13.0)	-11.0 (-16.6 to -5.3)
Mental health	72.0 (69.9 to 74.1)	74.1 (72.1 to 76.2)	77.0 (75.4 to 78.7)	2.2 (0.3 to 4.1)	-2.9 (-5.5 to -0.3)

CI: confidence interval; N: number; PCS: physical component summary scores; MCS: mental component summary scores.
[a]Mean change between two visits of SF-36 in venous thromboembolism patients.
[b]Mean difference between second visit of venous thromboembolism patients and controls.
[c]In general, 85 patients and 4 controls were missing. For PCS, 298 patients were available for both visit 1 and visit 2, 415 controls for visit1; For physical functioning, 314 patients were available for both visit 1 and visit 2, 427 controls for visit1; For physical role, 312 patients were available for both visit 1 and visit 2, 424 controls for visit1; For bodily pain, 304 patients were available for both visit 1 and visit 2, 418 controls for visit1; For general health, 313 patients were available for both visit 1 and visit 2, 425 controls for visit1; For MCS, 296 patients were available for both visit 1 and visit 2, 416 controls for visit1; For vitality, 313 patients were available for both visit 1 and visit 2, 425 controls for visit1; For social functioning, 304 patients were available for both visit 1 and visit 2, 421 controls for visit1; For emotional role, 307 patients were available for both visit 1 and visit 2, 422 controls for visit1. For mental health, 312 patients were available for both visit 1 and visit 2, 425 controls for visit1.