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Quality of Life, Dyspnea, and Functional Exercise Capacity Following a First Episode of Pulmonary Embolism: Results of the ELOPE Cohort Study

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ABSTRACT

BACKGROUND: We aimed to evaluate health-related quality of life (QOL), dyspnea, and functional exercise capacity during the year following the diagnosis of a first episode of pulmonary embolism.

METHODS: This was a prospective multicenter cohort study of 100 patients with acute pulmonary embolism recruited at 5 Canadian hospitals from 2010-2013. We measured the outcomes QOL (by Short-Form Health Survey-36 [SF-36] and Pulmonary Embolism Quality of Life [PEmb-QoL] measures), dyspnea (by the University of California San Diego Shortness of Breath Questionnaire [SOBQ]) and 6-minute walk distance at baseline and 1, 3, 6, and 12 months after acute pulmonary embolism. Computed tomography pulmonary angiography was performed at baseline, echocardiogram was performed within 10 days, and cardiopulmonary exercise testing was performed at 1 and 12 months. Predictors of change in QOL, dyspnea, and 6-minute walk distance were assessed by repeated-measures mixed-effects models analysis.

RESULTS: Mean age was 50.0 years; 57% were male and 80% were treated as outpatients. Mean scores for all outcomes improved during 1-year follow-up: from baseline to 12 months, mean SF-36 physical component score improved by 8.8 points, SF-36 mental component score by 5.3 points, PEmb-QoL by −32.1 points, and SOBQ by −16.3 points, and 6-minute walk distance improved by 40 m. Independent predictors of reduced improvement over time were female sex, higher body mass index, and percent-predicted VO_2 peak <80% on 1 month cardiopulmonary exercise test for all outcomes; prior lung disease and higher pulmonary artery systolic pressure on 10-day echocardiogram for the outcomes SF-36 physical component score and dyspnea score; and higher main pulmonary artery diameter on baseline computed tomography pulmonary angiography for the outcome PEmb-QoL score.

CONCLUSIONS: On average, QOL, dyspnea, and walking distance improve during the year after pulmonary embolism. However, a number of clinical and physiological predictors of reduced improvement over time were identified, most notably female sex, higher body mass index, and exercise limitation on 1-month cardiopulmonary exercise test. Our results provide new information on patient-relevant prognosis after pulmonary embolism.

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KEYWORDS: Functional outcomes; Prognosis; Pulmonary embolism; Quality of life

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Pulmonary embolism leads to the hospitalization or death of over 30,000 Canadians, 225,000 Americans, and 300,000 Europeans each year.[1,2] Most research on prognosis after pulmonary embolism has focused on outcomes such as mortality and pulmonary embolism recurrence, while patient-centered outcomes such as health-related quality of life (QOL), dyspnea, and exercise capacity have been less well studied.

To characterize the effects of pulmonary embolism on patients' health and functioning, we performed the ELOPE Study, a prospective, observational, multicenter cohort study of long-term outcomes after a first episode of acute pulmonary embolism. We aimed to prospectively describe QOL, dyspnea, and functional exercise capacity during the year following pulmonary embolism diagnosis, and to evaluate predictors of changes in these measures over time.

CLINICAL SIGNIFICANCE

- On average, quality of life, dyspnea severity, and walking distance improved during the year after diagnosis of pulmonary embolism, and most of the improvement occurred during the first 3 months.
- Female sex, higher body mass index, and exercise limitation on 1-month cardiopulmonary exercise testing predicted reduced improvement quality of life, dyspnea severity, and walking distance over time.
- This research provides new information on patient-relevant prognosis after pulmonary embolism.

MATERIALS AND METHODS

Study Population

Patients with acute pulmonary embolism were recruited from the emergency departments, outpatient clinics, and inpatient wards of 5 university-affiliated hospitals in Quebec, Ontario and Nova Scotia, Canada from June 2010 to February 2013. Patients were potentially eligible to participate in the study if they were age 18 years or older, had a first episode of acute pulmonary embolism that was objectively diagnosed within the last 10 days, and were treated with anticoagulants. The diagnosis of pulmonary embolism was based on an intraluminal filling defect in segmental or larger vessels on computed tomography (CT) pulmonary angiography[3,4] or a high-probability ventilation/perfusion scan.[5]

We excluded patients if they had contraindications to or were unable to perform a cardiopulmonary exercise test or a 6-minute walk distance test, contraindications to CT pulmonary angiography, severe comorbidity, previous deep vein thrombosis (to avoid including patients with possible previous pulmonary embolism), a life expectancy of under 1 year, were pregnant or lactating, unable to read a questionnaire in English or French, unable to attend the required follow-up visits, or were unable or unwilling to provide written informed consent. A detailed list of study exclusion criteria has been published.[6] Ethics approval was obtained from the relevant committees at each hospital center, and written informed consent was obtained from all patients prior to study entry.

Study Procedures

Baseline Assessment. At study entry, demographic and clinical characteristics were recorded using a standardized case report form. Average weekly physical activity before diagnosis of pulmonary embolism was assessed using the short-form last 7 days' recall International Physical Activity Questionnaire.[7] Participants were asked to complete generic QOL (Short-Form Health Survey-36 [SF-36][8,9]), pulmonary embolism-specific QOL (Pulmonary Embolism Quality of Life [PEmb-QoL][10]), and dyspnea (University of California at San Diego Shortness of Breath Questionnaire [SOBQ])[11] questionnaires. Baseline CT pulmonary angiography was performed in all patients. An echocardiogram was performed at 10 ± 2 days after study enrollment.

Follow-up Assessments. Follow-up visits were scheduled at 1, 3, 6, and 12 months. At each visit, patients completed the above-noted QOL and dyspnea questionnaires and performed a standardized 6-minute walk distance test.[12] At the 1- and 12-month visits, a cardiopulmonary exercise test was performed in the pulmonary function laboratory of the respective hospital, which was interpreted in real-time by a respirologist who was kept blinded to patient information. Calculations of percent-predicted VO_2 peak were done centrally, using Wasserman's equation for predicted VO_2[13]; results were categorized as <80% predicted (abnormal), vs >80% predicted (normal), as per American Thoracic Society/American College of Chest Physicians guidelines.[14]

Study Outcomes

Study outcomes relevant to the present analysis included QOL, dyspnea, and 6-minute walk distance during 1-year follow-up.

We assessed generic QOL using the validated SF-36 questionnaire, which measures 8 domains (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health) and produces 2 summary scores: Physical and Mental Component Summary scores. Higher summary scores indicate better QOL. We assessed pulmonary embolism-specific QOL using the validated PEmb-QoL questionnaire, a 40-item, pulmonary embolism-specific QOL questionnaire that produces scores in 6 domains. Total scores for each domain range from 0-100; lower scores indicate better pulmonary embolism-related QOL.[10,15] To estimate a total PEmb-QoL score, the average of scores of all 6 domains was calculated. We assessed dyspnea with the validated SOBQ, a 24-item questionnaire on shortness of breath with activities of

daily living.[11] Total scores range from 0-120, with lower scores indicating less shortness of breath. Walking distance was assessed using a standardized 6-minute walk distance test, which measures distance in meters (m) covered during 6 minutes of walking laps in a hallway.[12]

Statistical Analysis

We summarized demographic and clinical characteristics of study subjects as means and standard deviations (SD), medians and interquartile ranges, or proportions, as appropriate.

Mean (SD) scores for QOL, dyspnea, and 6-minute walk distance were calculated at each time point measured. Baseline scores were compared for categories of sex, age, body mass index (BMI), inpatient vs. outpatient status, smoking history, known lung disease, concurrent deep vein thrombosis at time of pulmonary embolism diagnosis, and pulmonary embolism type (provoked [defined as having surgery and major trauma within last 3 months or acute medical conditions associated with venous thromboembolism in last month] vs unprovoked) using *t* test and analysis of variance, as appropriate. Associations between baseline CT obstruction (CTO) index on CT pulmonary angiography (a quantitative measure of the degree of arterial obstruction in pulmonary embolism)[16] and QOL and dyspnea scores were assessed using Spearman correlation coefficient.

Changes in QOL scores, dyspnea scores, and 6-minute walk distance from the first assessment to each subsequent assessment were analyzed by paired *t* test and presented graphically.

Longitudinal data for the outcomes QOL, dyspnea, and 6-minute walk distance during follow-up were analyzed by repeated-measures mixed-effects models. For linear mixed-effects models, baseline values were retained as part of the outcome vector. Akaike Information Criterion was used to select the final model for each outcome. The random effects of recruiting center, intercept, and time were included in the initial prediction models for each outcome. Unstructured was selected as the covariance structure.

In all models, time was included as a continuous variable; based on the patterns of changes in outcomes over time and the significant reductions in Akaike Information Criterion achieved, a quadratic effect of time (t^2) was included in the models as well. Time interactions for the variables sex, BMI, CTO index, contrast reflux into inferior vena cava (a sign of right heart dysfunction) on baseline CT pulmonary angiography, and pulmonary embolism type were included in the prediction models; however, to avoid multicollinearity, time interactions were not included for other variables.

To assess the stability of parameter estimation, multiple imputation using the chained equations method was done to impute missing data caused by loss to follow-up and certain incomputable variables.[17] Evaluation of missing data suggested that missingness was at random. In order to be reasonably certain about the statistical reproducibility of the results, Monte Carlo error estimates of coefficients, standard errors, and *P*-value were evaluated. Kernel density estimation was used to visually depict and compare the distribution of variables before and after multiple imputation.

Based on the literature, at least a 4-point change in Physical Component and Mental Component Summary scores,[8,18] a 5-point change in SOBQ score,[19] and a 30-m increase in 6-minute walk distance[20] from the first assessment to the 1-year assessment was considered to represent one unit of clinically meaningful improvement. As PEmb-QoL is a recently developed measure, information on clinically important differences in score is not yet available.

We performed all statistical analyses using Stata Statistical Software, version 14 IC (StataCorp LP, College Station, TX). Two-sided *P* value of .05 was considered statistically significant.

RESULTS

Patient Characteristics

Among 984 patients screened, 150 were eligible and 100 consented to be enrolled in the study. Patient flow and baseline characteristics have been previously detailed.[6] Mean age was 50.0 years, 57% were male, and 80% were diagnosed and managed in the outpatient setting. Pulmonary embolism was unprovoked in 79%, and 33% of patients had concomitant deep vein thrombosis. Median number of days from diagnosis to study enrollment was 7 days, most patients were treated with 5-7 days of low-molecular-weight heparin followed by warfarin, and mean (SD) duration of anticoagulant treatment was 5.7 (2.0) months (**Table 1**). Mean (SD) CTO[16] on baseline CT pulmonary angiography was 28.1% (18.3%); additional baseline imaging characteristics are shown in **Table 1**.

Self-reported weekly habitual physical activity was low for 41 (47.7%) participants, moderate for 30 (34.9%) participants, and high for 15 (17%) participants (14 subjects declined to respond). On 1 month and 1 year cardiopulmonary exercise test, 55 (59.1%) and 40 (46.5%) of patients had percent-predicted VO_2 peak <80%, respectively.

Baseline QOL and Dyspnea Scores

Baseline QOL and dyspnea scores are presented in **Table 2**. Women had worse QOL and dyspnea scores at baseline than men, as did those in the highest BMI category. Older patients had better PEmb-QoL scores than younger patients. Smoking status, known lung disease, concurrent deep vein thrombosis, or pulmonary embolism type did not significantly influence baseline scores. There was a statistically significant correlation between baseline CT obstruction index and baseline dyspnea scores ($P = .025$).

Change in QOL, Dyspnea, and 6-Minute Walk Distance over Follow-up

Scores for all outcomes improved over time. From baseline to 12 months, mean within-individual Physical Component Summary score improved by 8.8 points (95% confidence

Table 1 Baseline Characteristics of Study Participants (n = 100)*

Demographic Characteristics	
Age, y	
Mean (SD)	50.0 (15.2)
<40	29 (29%)
40-65	56 (56%)
>65	15 (15%)
Male	57 (57%)
Outpatient at study entry	80 (80%)
Body mass index, kg/m^2	
Mean (SD)	29.5 (6.2)
<25	27 (27%)
25-30	33 (33%)
>30	40 (40%)
Race/ethnicity, n (%)	
White	78 (78%)
Hispanic	16 (16%)
Black	2 (2%)
Aboriginal	2 (2%)
Other	2 (2%)
Asian	0 (0%)
Unknown/not answered	0 (0%)
Clinical characteristics	
Asthma or COPD	13 (13%)
MI or angina	1 (1%)
Active cancer	1 (1%)
CHF	0 (0%)
Smoker	
Never	60 (60%)
Past	33 (33%)
Current	7 (7%)
Characteristics and treatment of index pulmonary embolism	
Days from pulmonary embolism diagnosis to study enrolment — median (IQR)	7 (3-10)
Concurrent deep vein thrombosis	33 (33%)
Unprovoked pulmonary embolism†	79 (79%)
Baseline CTPA findings	
Obstruction index,‡ % — mean (SD)	28.1% (18.3%)
RV/LV ratio (normal <1.0)	
Mean (SD)	1.01 (0.34)
Abnormal	32 (32%)
PA diameter, mm (normal <30)	
Mean (SD)	26.7 (4.7)
Abnormal	26 (26%)
Contrast reflux into inferior vena cava	39 (39%)
10-d echocardiogram findings§	
PASP, mm Hg — mean (SD) (normal ≤36)	25.1 (7.3)
RV free wall systolic velocity, cm/s — mean (SD) (normal >9.5)	12.9 (2.6)
TAPSE, mm — mean (SD) (normal >17)	21.9 (4.0)
LVEF Biplane Simpson's, % — mean (SD) (normal ≥53%)	61.4 (6.8)
Initial treatment of pulmonary embolism	
Low-molecular-weight heparin	93 (93%)
Warfarin	78 (78%)
Unfractionated heparin	15 (15%)
Other‖	8 (8%)
Thrombolysis	2 (2%)
Total duration of anticoagulation treatment, mo — mean (SD)	5.7 (2.0) mo

CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CTPA = computed tomography pulmonary angiography; IQR = interquartile range; LV = left ventricle; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PA = pulmonary artery; PASP = pulmonary artery systolic pressure; PE = pulmonary embolism; RV = right ventricle; TAPSE = tricuspid annular plane systolic excursion (a parameter of global RV function).

*n (%) unless indicated otherwise.

†Defined as absence of surgery, major trauma, or acute medical conditions associated with venous thromboembolism in last 3 months.

‡Index to quantify degree of pulmonary arterial obstruction; range 0%-100%.[16]

§PA pressure, RV free wall velocity, TAPSE and LVEF noncalculable or missing in 14, 7, 9, and 9 patients, respectively.

‖Six were participants in a double-blind randomized trial of edoxaban vs warfarin; 2 were treated with rivaroxaban.

interval [CI], 6.5-11.1), Mental Component Summary score by 5.3 points (95% CI, 3.5-7.1), PEmb-QoL by −32.1 points (95% CI, −37.1 to −27.1), and SOBQ by −16.3 points (95% CI, −22.1 to −10.6). Similarly, from 1 month to 12 months, mean within-individual 6-minute walk distance improved by 40.0 m (95% CI, 26.6-53.4), from 534.0 (93.8) m to 574.0 (94.5) m. All improvements in scores were statistically significant, with $P < .0001$ (**Figure**). For all outcomes, patterns of improvement in scores over follow-up were quadratic. The greatest degree of improvement was observed in the first 3 months; further improvement from 3 to 12 months was more modest.

Assessment of clinically meaningful improvement showed that at 1 month, compared with baseline, Mental Component Summary score, Physical Component Summary score, and SOBQ improved by at least 1 clinically meaningful improvement unit in 33.3%, 47.3%, and 49.5% of patients, respectively. At 12 months, compared with the first assessment, these values were 56.8%, 72.7%, and 64.8% of patients, respectively, and 6-minute walk distance improved by at least 1 clinically meaningful improvement unit in 58.3% of patients (Supplementary Figure 1, Appendix, available online).

Based on analyses of effect size, the magnitude of improvement in QOL, its subscales, and dyspnea scores from baseline to 1 year in patients with percent-predicted VO_2 peak >80% at 1 year were greater than in patients with percent-predicted VO_2 peak <80% at 1 year. These improvements were most notable for PEmb-QoL domain scores and total score (Supplementary Figure 2, available online).

Predictors of Change in QOL, Dyspnea, and 6-Minute Walk Distance over Time

Female sex, abnormal percent-predicted VO_2 peak at 1 month, and higher BMI were identified as determinants of

Table 2 Baseline Health-Related Quality of Life and Dyspnea Severity by Patient Characteristics

	Generic Quality of Life					PE-Specific Quality of Life			Dyspnea		
Baseline Characteristic	n	SF-36 PCS Mean (SD)	*P* Value	SF-36 MCS Mean (SD)	*P* Value	n	PEmb-QoL Total Mean (SD)	*P* Value	n	SOBQ Mean (SD)	*P* Value
All patients	98	41.3 (9.6)	—	46.7 (12.1)	—	82	45.2 (24.1)	—	98	32.2 (26.8)	—
Males	56	43.1 (8.9)	.036	48.7 (11.5)	.060	49	38.8 (23.0)	.003	56	25.4 (23.3)	.003
Females	42	39.0 (10.1)		44.0 (12.6)		33	54.5 (22.9)		42	41.3 (28.7)	
Inpatients	20	42.7 (11.1)	.473	44.9 (14.3)	.463	13	33.1 (25.6)	.047	20	33.3 (32.6)	.863
Outpatients	78	41.0 (9.2)		47.2 (11.6)		69	47.4 (23.3)		78	31.9 (25.3)	
Age (y)											
<40	28	39.6 (10.5)	.169	45.4 (12.4)	.249	24	51.8 (26.0)	.041	28	40.1 (32.2)	.074
40-65	55	41.1 (9.3)		46.1 (12.0)		45	45.7 (23.3)		55	31.2 (24.4)	
>65	15	45.3 (8.4)		51.5 (11.9)		13	31.1 (18.3)		15	20.9 (20.1)	
BMI (kg/m^2)											
<25	26	42.0 (7.4)	.244	45.8 (13.0)	.002	23	42.9 (23.4)	.005	26	27.1 (22.9)	.001
25-30	33	43.1 (11.2)		52.3 (10.4)		26	34.9 (24.7)		33	22.6 (22.9)	
>30	39	39.4 (9.4)		42.6 (11.3)		33	54.8 (20.7)		39	43.7 (28.5)	
Lung Disease											
Yes	13	36.8 (13.7)	.210	46.9 (14.8)	.948	9	42.2 (28.2)	.702	13	44.8 (32.8)	.069
No	85	42.0 (8.7)		46.7 (11.8)		73	45.5 (23.7)		85	30.3 (25.4)	
Smoker											
Yes	40	40.3 (9.0)	.391	47.1 (13.2)	.788	35	42.3 (21.3)	.361	40	31.7 (26.5)	.878
No	58	42.0 (10.0)		46.4 (11.4)		47	47.3 (25.9)		58	32.5 (27.2)	
Concurrent DVT											
Yes	33	42.8 (9.3)	.293	44.7 (11.9)	.245	27	39.5 (27.7)	.171	33	30.4 (26.9)	.629
No	65	40.6 (9.7)		47.7 (12.2)		55	48.0 (21.8)		65	33.1 (26.9)	
Unprovoked PE	77	41.8 (9.5)	.368	47.1 (12.2)	.554	63	44.9 (23.2)	.839	77	33.1 (26.6)	.538
Provoked PE	21	39.6 (10.1)		45.3 (12.0)		19	46.1 (27.5)		21	29.0 (27.9)	
CT obstruction index	98	−0.101	.321	−0.026	.803	82	0.067	.551	98	0.23	.025

P value for 2-sample *t* test or analysis of variance; data shown for CT obstruction index are Spearman correlation coefficients; all other data are mean (SD).

For SF-36 PCS and MCS, lower scores signify poorer quality of life; for PEmb-QoL, higher scores signify poorer QoL; for SOBQ, higher scores indicate worse dyspnea. 6MWD not done at baseline.

Provoked pulmonary embolism defined as having surgery and major trauma within last 3 months or acute medical conditions associated with venous thromboembolism in last month; Lung disease: known chronic obstructive pulmonary disease or asthma; Smoker includes current or past smoking; CT obstruction index = index to quantify degree of pulmonary arterial obstruction; range 0%-100%.[16]

BMI = body mass index; DVT = deep vein thrombosis; MCS = Mental Component Summary score; PCS = Physical Component Summary score; PE = pulmonary embolism; PEmb-QoL = pulmonary embolism quality of life questionnaire (the average of scores of all 6 dimensions was calculated as PEmb-QOL total); SF-36 = Short-Form Health Survey-36; SOBQ = University of California at San Diego Shortness of Breath Questionnaire; 6MWD = 6-minute walk distance.

worse QOL scores, higher dyspnea scores, and lower 6-minute walk distance over 1-year follow-up (Table 3). Prior lung disease and higher values of pulmonary artery systolic pressure (mm Hg) on 10-day echocardiogram predicted lower (ie, worse) Physical Component Summary scores and higher (ie, worse) dyspnea scores over time; higher values of main pulmonary artery diameter (mm) on baseline CT pulmonary angiography predicted higher (ie, worse) PEmb-QoL scores over time; and older age and having any contrast reflux into inferior vena cava on baseline CT pulmonary angiography were predictors of lower 6-minute walk distance over time.

Modeling results after multiple imputation were similar to those using available data, and none of the significant *P*-values became nonsignificant after multiple imputation (Supplementary Table, available online).

DISCUSSION

We prospectively evaluated QOL, dyspnea, and functional exercise tolerance during the year after a first episode of pulmonary embolism in a cohort of patients recruited at 5 hospital centers in Canada. We found that, on average, generic and pulmonary embolism-specific QOL scores, dyspnea scores, and 6-minute walk distance tended to improve over time, most of the improvement occurred during the first 3 months after diagnosis, and most patients had improvement of a magnitude that was clinically meaningful. Further, we identified a number of variables that independently predicted attenuated improvement over time, including female sex, percent-predicted VO_2 peak <80% on 1-month cardiopulmonary exercise test and higher BMI for all outcomes, prior lung disease and higher values of pulmonary artery systolic pressure on 10-day echocardiogram

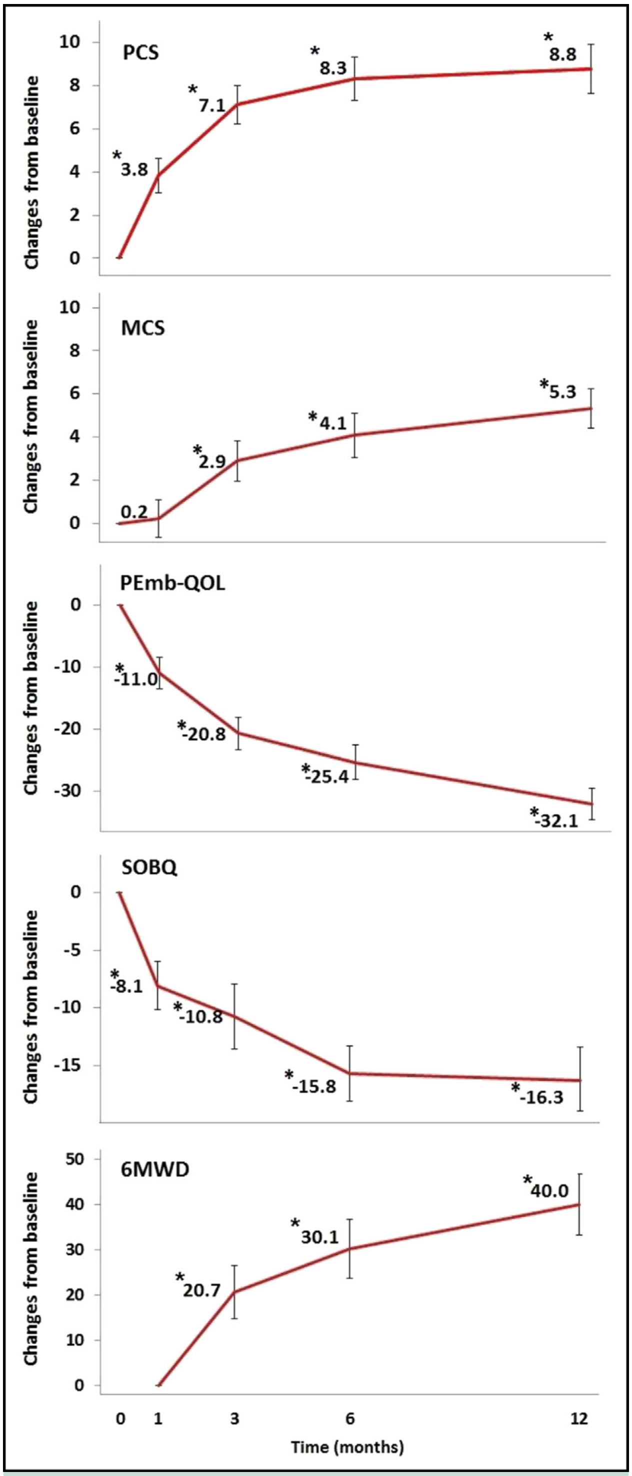

Figure Changes in health-related quality of life, dyspnea and walking distance during follow-up. All measures were assessed at baseline and at 1, 3, 6, and 12 months, except for 6-minute walk distance, which was assessed at 1, 3, 6, and 12 months. Mean within-patient change scores (Δ) at each time point compared with the first assessment are presented; error bars are standard errors. **P* value < .005. MCS = Mental Component Summary score; PCS = Physical Component Summary score; PEmb-QoL = pulmonary embolism quality of life questionnaire; SF-36 = Short-Form Health Survey-36; SOBQ = University of California at San Diego Shortness of Breath Questionnaire; 6MWD = 6-minute walk distance.

for SF-36 Physical Component Summary scores and dyspnea scores, and higher values of main pulmonary diameter on baseline CT pulmonary angiography for PEmb-QoL score. We had previously documented that close to half (46.5%) of our patients had exercise limitation (defined by percent-predicted VO_2 peak <80% on cardiopulmonary exercise test) at 1 year after pulmonary embolism,[6] and here show that such patients had attenuated improvement over 1-year for all functional outcomes, compared with patients with percent-predicted VO_2 peak >80% at 1 year.

Our findings are of direct importance to patients. At baseline, average SF-36 Physical and Mental Component Summary scores in our population of pulmonary embolism patients were similar to that reported for US patients with chronic lung disease[21] and substantially lower than population norms for a similarly aged general Canadian adult population,[18] but by 1 year, average scores had improved to the level of healthy population norms. In our study, women and those with higher BMI had less improvement in QOL, dyspnea scores, and 6-minute walk distance from baseline for reasons that are unclear but merit further study, including whether weight reduction could have potential to enhance recovery after pulmonary embolism. Exercise limitation on 1-month cardiopulmonary exercise test was predictive of worse functional outcome during follow-up, suggesting that identifying exercise-limited patients early after pulmonary embolism is of prognostic value, and that exercise rehabilitation interventions early after pulmonary embolism may have potential to improve long-term functional outcomes. Finally, we observed that evidence of higher values of pulmonary artery systolic pressure on baseline CT pulmonary angiography or echocardiogram predicted worse SF-36 Physical Component Summary score, PEmb-QoL, and dyspnea scores during follow-up, but higher CTO index on baseline CT pulmonary angiography did not. The relationship between anatomic or physiological effects of pulmonary embolism and long-term functional outcome remains to be clarified,[22] but our results suggest there could be an opportunity to use these imaging findings to help identify patients who might obtain long-term functional benefit from thrombolytic therapy for pulmonary embolism.

To our knowledge, this is the first prospective multicenter study to systematically characterize QOL, dyspnea, and walking capacity as functional outcomes after pulmonary embolism, to identify predictors of these outcomes, and to link functional outcomes with exercise limitation on cardiopulmonary exercise test. A few previous studies have addressed various aspects of functional status after acute pulmonary embolism, including those reviewed in a recent metaanalysis of the effect of venous thromboembolism on QOL.[23-29] While some of these studies suggest that functional impairment is not infrequent after pulmonary embolism, limitations include lack of baseline measures, cross-sectional data collection at a time point that was often remote from pulmonary embolism diagnosis, lack of use of validated QOL measures, and in some cases, substantial losses to follow-up.

Table 3 Predictors of QOL, Dyspnea, and 6-Minute Walk Distance over Time as Determined by Mixed-Effects Models

	PCS	MCS	PEmb-QoL	SOBQ	6MWD
Male sex					
Coeff. 95% CI	6.3 (3.1-9.5)	4.2 (.7-7.7)	−17.2 (−24.9 to −9.6)	−16.8 (−23.5 to −10.0)	88.0 (57.5-118.5)
P value	<.001	.017	<.001	<.001	<.001
Age (continuous)					
Coeff. 95% CI					−2.4 (−3.4 to −1.37)
P value					<.001
% Predicted VO_2 peak <80% at 1 mo					
Coeff. 95% CI	−6.0 (−8.6 to −3.4)	−6.3 (−9.8 to −2.8)	12.5 (5.5-19.6)	17.8 (11.6-23.9)	−62.2 (−93.0 to −31.5)
P value	<.001	<.001	<.001	<.001	<.001
Lung disease					
Coeff. 95% CI	−6.2 (−10.0 to −2.4)			14.6 (4.9-24.2)	
P value	.001			.003	
Pulmonary artery systolic pressure (continuous)					
Coeff. 95% CI	−.21 (−.39 to −.04)			.72 (.45-.99)	
P value	.019			<.001	
Contrast reflux into inferior vena cava on baseline CTPA					
Coeff. 95% CI					−45.4 (−74.6 to −16.2)
P value					.002
Main PA diameter					
Coeff. 95% CI			1.39 (1.04-1.73)		
P value			<.001		
BMI (continuous)					
Coeff. 95% CI					−2.3 (−4.8 to .2)
P value					.075
BMI*					
<25 kg/m^2					
Coeff. 95% CI	−2.4 (−6.3 to 1.5)	−4.9 (−9.4 to −.5)	8.2 (−.7 to 17.1)	5.7 (−2.6 to 13.9)	
P value	.224	.030	.070	.179	
25-30 kg/m^2	Ref	Ref	Ref	Ref	
>30 kg/m^2					
Coeff. 95% CI	−3.1 (−6.8 to .6)	−7.3 (−11.4 to −3.3)	12.5 (3.9-21.2)	14.6 (7.1-22.1)	
P value	.102	<.001	.005	<.001	
Time					
Coeff. 95% CI	2.2 (1.7-2.7)	.76 (.28-1.23)	−6.1 (−7.4 to −4.8)	−3.6 (−4.9 to −2.2)	14.2 (7.8-20.6)
P value	<.001	.002	<.001	<.001	<.001

The following variables were excluded from all models based on inability to predict main responses (ie, PCS, MCS, PEmb-QoL, SOBQ, and 6MWD): Average weekly physical activity before diagnosis of pulmonary embolism as measured by International Physical Activity Questionnaire; pulmonary embolism type; concurrent deep vein thrombosis; inpatient vs outpatient status; smoking status; CT obstruction index on baseline CTPA; right ventricle:left ventricle ratio on baseline CTPA; right ventricular free wall systolic velocity on 10-day ECHO; tricuspid annular plane systolic excursion on 10-day ECHO; left ventricular ejection fraction Biplane Simpson's on 10-day ECHO.

Final models also showed evidence of interaction between sex and time, pulmonary embolism type and time, and BMI and time; for the sake of table brevity, results not shown.

BMI = body mass index; CI = confidence interval; CTPA = computed tomography pulmonary angiography; ECHO = echocardiogram; MCS = Mental Component Summary score; PA = pulmonary artery; PCS = Physical Component Summary score; PE = pulmonary embolism; PEmb-QoL = pulmonary embolism quality of life questionnaire (the average of scores of all 6 dimensions was calculated as PEmb-QoL total); SF-36 = Short-Form Health Survey-36; SOBQ = University of California at San Diego Shortness of Breath Questionnaire; 6MWD = 6-minute walk distance.

*Because of nonlinear associations between BMI and PCS, MCS, PEmb-QoL and SOBQ, the categorical format of BMI was included in the models for these outcomes.

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Our study has a number of strengths. Our source population was well defined and we excluded patients with prior pulmonary embolism or deep vein thrombosis. We assessed a range of relevant functional outcomes prospectively, at multiple time points, using validated measures and questionnaires. To comprehensively assess QOL, we used both generic and disease-specific measures,[30,31] including a validated pulmonary embolism-specific QOL measure.[10] We collected data on various patient characteristics that could independently influence functional outcomes so that these factors could be adequately adjusted for in our analyses.

Our study also has certain limitations. We had no information on QOL, dyspnea, 6-minute walk distance, and VO_2 peak before pulmonary embolism diagnosis, and no control group. As most patients were treated with low-molecular-weight heparin followed by warfarin, we cannot comment on whether other treatments such as direct oral anticoagulants or thrombolysis would affect our results.

In conclusion, we found that, on average, QOL, dyspnea, and walking distance improve during the year after a first episode of pulmonary embolism, most notably during the first 3 months, and most patients improved to a degree that was clinically meaningful. However, a number of clinical and physiological predictors of attenuated improvement over time were identified, including female sex, higher BMI, and exercise limitation on 1-month cardiopulmonary exercise test. Our study provides prognostic information on patient-important health outcomes after pulmonary embolism and highlights the need to include measurement of one or more functional outcomes in studies of interventions to treat pulmonary embolism.

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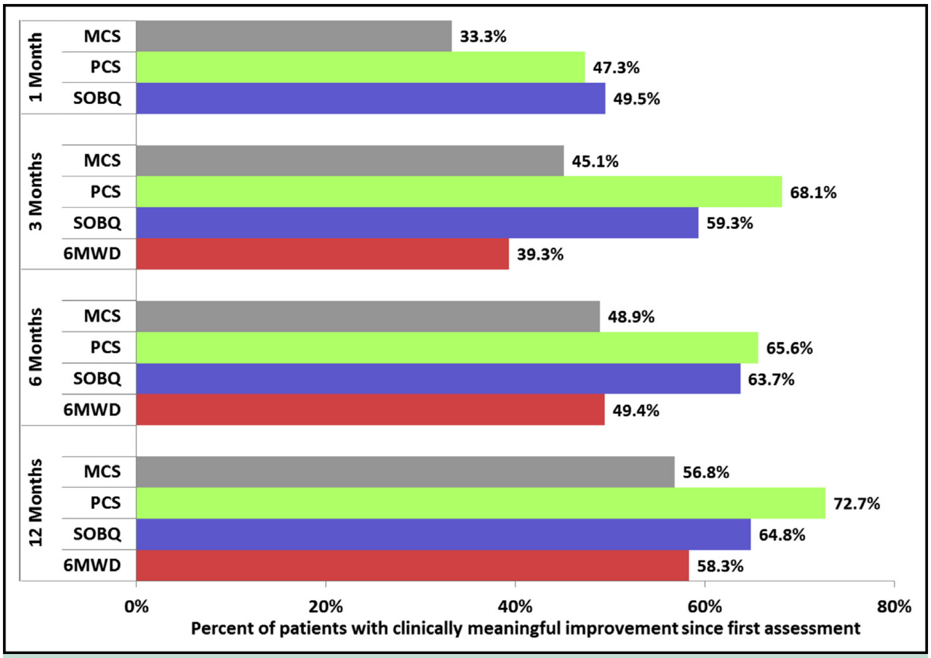
Authorship: All authors had access to the data and a role in writing the manuscript.

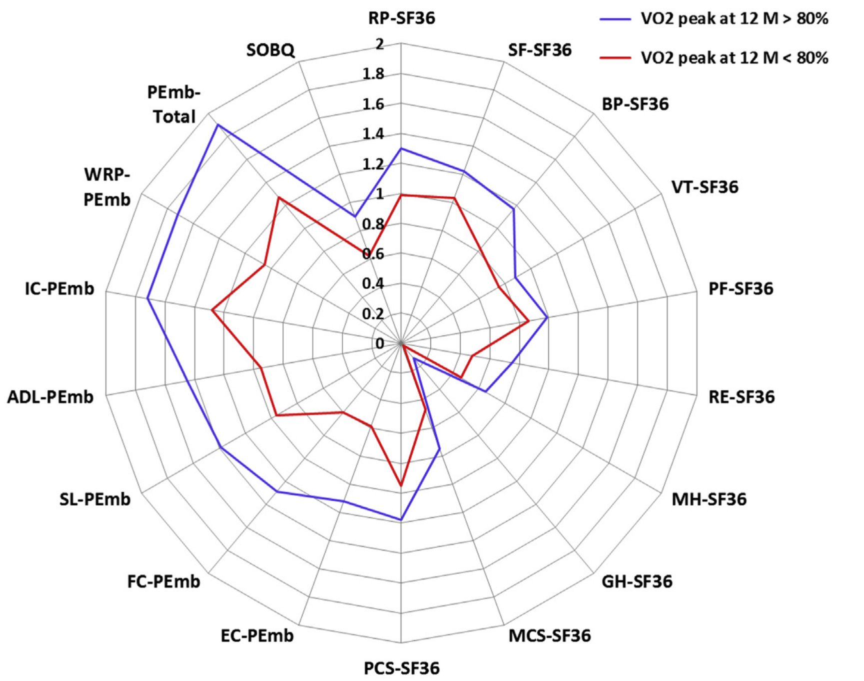
SUPPLEMENTARY DATA

Supplementary data accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.amjmed.2017.03.033.

APPENDIX



Supplementary Figure 1 Clinically meaningful improvement in health-related quality of life, dyspnea scores, and walking distance during follow-up, compared with the first assessment. SF-36 Physical Component Summary score, SF-36 Mental Component Summary score, SOBQ, and 6-minute walk distance were measured at Baseline (except 6-minute walk distance), 1, 3, 6, and 12 months after acute pulmonary embolism. For definition of clinically meaningful improvement for each measure, see manuscript text. Pulmonary embolism quality of life not presented, as information on clinically important differences in score is not yet available. MCS = Mental Component Summary score; PCS = Physical Component Summary score; SF-36 = Short-Form Health Survey-36; SOBQ = University of California at San Diego Shortness of Breath Questionnaire; 6MWD = 6-minute walk distance.



Measure		Effect size
SF-36		
PCS-SF36	Physical component summary	0.12
MCS-SF36	Mental component summary	0.16
BP-SF36	Bodily pain	0.2
MH-SF36	Mental health	0.15
VT-SF36	Vitality	0.13
RE-SF36	Role limitations due to emotional problems	0.12
RP-SF36	Role limitations due to physical health	0.11
SF-SF36	Social functioning	0.11
GH-SF36	General health perceptions	0.1
PF-SF36	Physical functioning	0.03
PEmb-QoL		
ADL-PEmb	Activities of daily living limitations	0.23
SL-PEmb	Social limitations	0.23
WRP-PEmb	Work-related problems	0.35
FC-PEmb	Frequency of complaints	0.36
EC-PEmb	Emotional complaints	0.37
IC-PEmb	Intensity of complaints	0.41
PEmb-total	PEmb-QoL total score	0.3
SOBQ	SOBQ total score	0.06

Supplementary Figure 2 Spider graph to depict the effect size values on changes in health-related quality of life and its subscales and dyspnea scores from baseline to 1 year, according to percent-predicted VO_2 peak <80% and >80% at 1 year. Concentric circles around the central target represent effect size in mean changes in scores from baseline to 1 year.[4] Health-related quality of life and dyspnea scores improved more in patients with percent-predicted VO_2 peak >80% at 1 year (distance between central point [0.0] and blue line) compared with patients with percent-predicted VO_2 peak <80% at 1 year (distance between central point [0.0] and red line). PEmb-QoL = pulmonary embolism quality of life questionnaire; SF-36 = Short-Form Health Survey-36; SOBQ = University of California at San Diego Shortness of Breath Questionnaire.

Supplementary Table Predictors of QOL, Dyspnea, and 6-Minute Walk Distance over Time Using Mixed-Effects Models, After Multiple Imputation

	PCS	MCS	PEmb-QoL	SOBQ	6MWD
Male sex					
Coeff. 95% CI	4.7 (1.7-7.7)	5.2 (1.8-8.5)	−18.1 (−25.7 to −10.5)	−12.9 (−19.7 to −6.2)	85.1 (55.6-114.6)
P value	.002	.003	<.001	<.001	<.001
Age (continuous)					
Coeff. 95% CI					−2.3 (−3.3 to −1.3)
P value					<.001
%-predicted VO_2 peak <80% at 1 mo					
Coeff. 95% CI	−4.9 (−7.5 to −2.3)	−6.3 (−9.9 to −2.7)	11.4 (4.4-18.4)	16.0 (9.8-22.2)	−61.2 (−91.3 to −31.1)
P value	<.001	.001	.001	<.001	<.001
Lung disease					
Coeff. 95% CI	−5.1 (−8.9 to −1.3)			10.1 (.4-19.9)	
P value	.008			.042	
Pulmonary artery systolic pressure (continuous)					
Coeff. 95% CI	−.22 (−.40 to −.03)			.71 (.44-.98)	
P value	.020			<.001	
Contrast reflux into inferior vena cava on baseline CTPA					
Coeff. 95% CI					−43.5 (−71.7 to −15.2)
P value					.003
Main PA diameter					
Coeff. 95% CI			1.43 (1.08-1.77)		
P value			<.001		
BMI (continuous)					
Coeff. 95% CI					−2.6 (−5.0 to −.2)
P value					.034
BMI*					
<25 kg/m^2					
Coeff. 95% CI	−1.4 (−5.3 to 2.42)	−4.9 (−9.4 to −.5)	6.6 (−2.3 to 15.6)	5.5 (−3.0 to 14.1)	
P value	.468	.030	.147	.204	
25-30 kg/m^2	Ref	Ref	Ref	Ref	
>30 kg/m^2					
Coeff. 95% CI	−3.2 (−6.6 to .21)	−7.6 (−11.6 to −3.6)	11.8 (3.2-20.4)	16.5 (9.2-23.7)	
P value	.066	<.001	.007	<.001	
Time					
Coeff. 95% CI	2.2 (1.7-2.7)	.79 (.30-1.28)	−6.3 (−7.6 to −5.0)	−3.8 (−5.1 to −2.6)	14.4 (8.0-20.8)
P value	<.001	.002	<.001	<.001	<.001

Longitudinal data imputation using the predictive mean matching (PMM) method was performed separately for each outcome. For each model, the outcome variable and all predictor variables were included in multiple imputation; in order to take advantage of available data in the previous and subsequent time point to the missing value, multiple imputation was done in wide data form.[1] We generated 40 imputed data sets for each model. To determine the number of imputation datasets needed, fraction missing information (FMI) and percentage of missing data were considered.[2,3] Highest FMI for mixed-effects models of PCS, MCS, PEmb-QoL, SOBQ, and 6MWD were .075, .066, .105, .214, and .288, respectively. Based on the criteria presented by White et al,[2] all of the Monte Carlo error estimation of coefficients and *P*-values were acceptable. The following variables were excluded from all models based on inability to predict main responses (ie, PCS, MCS, PEmb-QoL, SOBQ, and 6MWD): Average weekly physical activity before diagnosis of pulmonary embolism as measured by International Physical Activity Questionnaire; pulmonary embolism type; concurrent deep vein thrombosis; inpatient vs outpatient status; smoking status; CT obstruction index on baseline CTPA; RV:LV ratio on baseline CTPA; RV free wall systolic velocity on 10-day echocardiogram (ECHO); TAPSE on 10-day ECHO; left ventricular ejection fraction Biplane Simpson's on 10-day ECHO.

Final models also showed evidence of interaction between sex and time, pulmonary embolism type and time, and BMI and time; for the sake of table brevity, results not shown.

BMI = body mass index; CI = confidence interval; CTPA = computed tomography pulmonary angiography; MCS = Mental Component Summary score; PA = pulmonary artery; PCS = Physical Component Summary score; PE = pulmonary embolism; PEmb-QoL = pulmonary embolism quality of life questionnaire; Ref = reference category; SF-36 = Short-Form Health Survey-36; SOBQ = University of California at San Diego Shortness of Breath Questionnaire; 6MWD = 6-minute walk distance.

*Because of nonlinear associations between BMI and PCS, MCS, PEmb-QoL, and SOBQ, the categorical format of BMI was included in the models for these outcomes.

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