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Health-related quality of life after pulmonary embolism: a cross-sectional study

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ABSTRACT

Objectives: The psychological effects of acute pulmonary embolism (PE) have been scarcely studied. The aims of this study were to evaluate health-related quality of life (HRQoL) in patients with a history of PE compared to the general population and buddy controls, and to explore factors that may predict impaired HRQoL.

Design: Cross-sectional.

Setting: Haematology and Thrombosis unit in Fredrikstad, Norway.

Participants: 213 consecutive patients treated for PE were identified from hospital registries. Eligible patients were scheduled for a single study visit, including a functional capacity test (6-minute walking test). HRQoL was assessed using the EQ-5D-3L questionnaire, of which the results were compared to Danish population norms and age- and sex-matched buddy controls. Multivariable regression analyses were used to examine possible determinants of reduced HRQoL.

Results: Mean age was 61 years (SD 15), 117 (55%) were males, and median time since diagnosis was 3.8 years (range 0.3-9.5). Mean EQ VAS was 67 in PE as compared to 81 in the general population ($p<0.005$) and corresponding EQ-5D index values were 0.80 and 0.86 ($p<0.005$). Patients reported more problems in all 5 EQ-5D dimensions compared to both the buddy controls and the general population, $p<0.05$. Shorter six-minute walking distance ($B=0.09$, $p<0.005$) and patient-reported dyspnoea ($B=-11.27$, $p<0.005$) were independent predictors of lower EQ VAS scores.

Conclusion: Our findings show that patients with a history of PE have impaired HRQoL when compared to the general population and buddy controls. Reduced functional capacity and persistent dyspnoea were the main predictors of this impairment.

Strength and limitations of this study

- This study describes the long-term health-related quality of life, functional capacity and prevalence of dyspnoea in patients with a history of pulmonary embolism, which have been scarcely studied.
- A large sample size in which all aspects of a generic health-related quality of life questionnaire is reported combined with functional capacity assessment.
- The findings in this study may encourage future studies to evaluate the susceptibility of these patients to cardiopulmonary rehabilitation.
- The low response rate and the retrospective design may hamper the external validation.

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INTRODUCTION

Health-related quality of life (HRQoL) after deep vein thrombosis (DVT) has been extensively studied. The interest of studying HRQoL in DVT is believed to be related to the well characterized frequent detrimental chronic condition of post-thrombotic syndrome (PTS) that affects 30-50 % of DVT patients.[1] Unlike DVT, long-term psychological effects of acute pulmonary embolism (PE) are understudied. The equivalent long term complication of acute PE is chronic-thromboembolic pulmonary hypertension (CTEPH).[2] This condition has been shown to affect 2-4 % of the patients with a past history of PE.[3] This relatively low frequency of CTEPH may be the reason for the limited number of studies focusing on HRQoL in PE patients.[4-7] It has been suggested that CTEPH itself is the extreme manifestation of a much more common phenomenon of permanent changes in pulmonary hemodynamics, cardiac function and pulmonary gas exchange after acute PE, which is associated with dyspnoea and decreased exercise capacity. Additionally, several studies have shown that up to 50% of the patients with a history of PE complain of persistent dyspnoea long time after PE.[4,8] In analogy to PTS after DVT, it was recently proposed to refer to this phenomenon as the "post-pulmonary embolism syndrome".[9] Moreover, a recent Scandinavian study reported the overuse of antidepressants in adolescents with a history of PE, indicating that PE may develop into a chronic illness in a relevant number of patients.[10] Indeed, the few existing studies all report an impaired HRQoL in patients with a history of PE compared to the normal population,[4,6] although the results concerning possible predictors of reduced HRQoL are divergent.[7] More detailed knowledge of the determinants of HRQoL is needed to allow for identification of treatment targets and implementation of this important endpoint in future outcome studies.

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The aims of the present study were to compare HRQoL in patients with a history of PE to that of the general population and to age- and sex-matched controls, and to evaluate possible determinants of HRQoL.

MATERIAL AND METHODS

Participants and setting

Consecutive patients who were diagnosed and treated for PE at the Østfold Hospital Trust, Fredrikstad, Norway, between January 2002 and December 2011 were identified from the hospital's registries including the thrombosis registry by searching for ICD-10 codes of PE (ICD-10 I26.0 and I26.9). All patients alive at the beginning of March 2012, and with a PE diagnosis confirmed by computed tomography pulmonary angiogram (CTPA) or high probability perfusion scintigraphy, were eligible for study participation.

Patients were excluded if they were <18 or >90 years old or deemed incapable to comply with study procedures, including language barriers, geographical unavailability, known dementia, psychiatric diagnosis such as major depression as well as affective disorders or any degree of psychotic disorder. Patients living in nursing homes or receiving major help from social care services were excluded as well.

The study was approved by the Regional Committee for Medical and Health Research Ethics, Norway (Approval no 2011/2557b); and written informed consent was obtained for all patients.

Study design

All eligible patients were contacted by telephone and invited to participate in the study. Patients who responded to our invitation were scheduled for a visit during which they underwent physical examination and functional capacity test using the 6-minute walking test.

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The 6-minute walking test is a standardized functional capacity test, which is widely used to objectively assess patients' cardiopulmonary capacity.[11] The test was performed according to published guidelines,[12] by one of the study investigators (M.T.). For each patient we derived predicted values from the recommendations of the literature.[13] Evaluation of patients comprised blood tests including brain natriuretic peptide (BNP), which were obtained at the study visit. Socio-demographic data were recorded on standardized case record forms.

Prior to the study visit, the HRQoL questionnaire was sent to the patients either by e-mail or post. Patients were asked to complete the form at home and return it at scheduled study visit. Incomplete forms were completed during the visit at the hospital.

Quality of life questionnaire

The validated Norwegian version of Euroqol-5 dimension-3 level (EQ-5D-3L) questionnaire was used in order to assess quality of life. EQ-5D-3L consists of a descriptive system and the Euroqol visual analogue scale (EQ VAS).[14,15] The EQ-5D-3L is a validated, generic, preference-based, health-status measure consisting of five descriptive questions encompassing five domains of HRQoL: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each question is answered based on three response options (1= "no problems", 2= "moderate problems", 3= "severe problems"). The 243 (3^5) potential patterns of responses each indicate a unique health state ranging from 11111 for perfect health to 33333 for the worst possible state. The health states can then be converted into a single summary index value, which ranges from 1 (state of full health) to values lower than 0 (states regarded as worse than being dead).

The EQ VAS is a self-rated health on a vertical visual analogue scale (0-100) where the endpoints are labelled "worst imaginable health state" and "best imaginable health state".

Control groups

Although several European countries have established normative population data for the EQ-5D instrument, these are not available for Norway. Therefore, we compared our results to the Danish population norms that were established in 2009.[16]

To correct for incident cases with venous thrombosis in the normative population, we included a second control group by asking our study subjects to recruit two age- (+/- five years) and sex-matched relatives or friends without a history of venous thrombosis, hereafter referred to as buddy controls, to complete the EQ-5D form. Buddy controls were asked to return the anonymous questionnaire in prepaid envelopes.

Predictors

Based on clinical experience and previous research, we hypothesized that the following determinants may be relevant predictors of HRQoL after PE: a) age, b) sex, c) disease duration (time in years from PE diagnosis to study visit), d) body mass index (BMI; kg/m²), e) recurrent venous thromboembolism, f) occupation, g) persistent patient-reported dyspnoea, h) performance at 6-minute walking test, i) BNP, j) active malignancy, k) ongoing anti-coagulant treatment, l) known cardiopulmonary comorbidity, including interstitial pulmonary diseases, congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD) and m) proximal clot location at PE diagnosis as assessed by a previously published radiological score by Ghanima et al.[17]

STATISTICAL ANALYSES

Continuous variables were expressed as means and standard deviations if normally distributed and medians with ranges if skewed distributed. Categorical variables were

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presented as percentages and/or frequencies. Comparisons were made using Students T-test or Mann-U-Whitney (depending on normal or skewed distribution) for continues variables and Chi-square tests for categorical variables.

Since very few patients and controls had “extreme problems”, the EQ-5D dimensions were dichotomised to either ”no problems” or ”problems”.

Age and gender adjustment of controls were made by weighing the population norm EQ-5D index values and EQ VAS with the distribution of our sample, as recommended by Hjermstad et al.[18]

Variables deemed predictive of HRQoL where first screened using univariate analysis (Spearman’s rho). Correlations below the significance level of $\alpha=0.1$ were retained for the multivariate regression analysis. Potential multicollinearity was checked before inclusion in the multivariate models. Then, multivariate regression analyses comprising both standard linear regression and binary logistic regression models were performed. For the former, the possible determinants were tested for independency against EQ VAS and the R-squared (r^2) was used to estimate the percentage of effect explained by the model. For the latter, retained determinants from the univariate analysis were tested for independency against each of the EQ-5D dimensions. The Hosmer and Lemeshow test was used to estimate the goodness of fit of the model.

Multiple imputation model was used in order to deal with missing values in the EQ-5D questionnaires of the buddy controls in whom we did not have the possibility to check and complete the questionnaires during a study visit.[19] Cases with more than 50% of the items or EQ VAS missing were omitted. All analyses were performed using the Statistical Package for Social Science version 22.0 (SPSS Inc., Chicago, IL, USA), and considered significant at a two-sided alpha of ≤ 0.05 .

RESULTS

Study flow

A total of 836 patients were identified and assessed for eligibility in this study. As shown in the study flow chart (Figure 1), 430 (51%) patients were excluded according to the predefined exclusion criteria. Of the 406 remaining and thus invited patients, 189 (46%) declined to participate. Of the remaining 217 eligible patients, 213 completed both the EQ-5D questionnaire and underwent the six-minute walking test. Hence, the response rate for our study cohort was fifty-two percent.

The number of buddy controls who returned the EQ-5D form was 205, of whom 28 returned questionnaires had more than 50% of data missing. After excluding these 28, 177 were left for analysis. The response rate for the buddy controls was thus 42%, assuming all study patients indeed forwarded the questionnaire to two ‘buddies’.

Study patients

Patients had a mean age of 61 years (SD 15) and 55 % were men (n=117). Socio-demographic characteristics are presented in Table 1. Median time since diagnosis was 3.8 years (range 0.3-9.5) with 89% being diagnosed with PE more than a year prior to study inclusion.

Mean distance covered on 6-minute walking test by the study cohort was 449 meters (SD 135). The mean 6-minute walking distance was 97 meters (95% CI 76-117) less in male patients and 84 meters (95% CI 65-104) less in female patients as compared to their gender-predicted value, $p<0.005$.

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Table 1. Socio-demographic and clinical characteristics of the study sample.

Variable	Study sample	
	n	(%)
Female	96	(45)
Age in years, mean (SD)	61	(15)
Years since diagnosis, median (range)	3.8	(0.3-9.5)
Occupation		
-Unemployed	50	(24)
-Working	71	(33)
-Retired	92	(43)
Diagnosis		
-PE	149	(70)
-PE + DVT	64	(30)
Recurrent VTE	34	(16)
Cardiopulmonary comorbidity	19	(9)
BMI, mean (SD)	28.7	(4.9)
Obesity	73	(34)
Active malignancy	15	(7)
Reporting dyspnoea	99	(46)
Smoking		
-Current	38	(18)
-Former	52	(24)
Ongoing AC treatment	81	(38)
6MWT, mean (SD)		
-Total	449	(135)
-Men	488	(124)
-Women	402	(134)
Laboratory tests at study visit	203	
-BNP, mean (SD)	48.6	(72.4)
F-score	192	
-median (range)	3	(1-4)

Unemployed=unemployed or unemployment because of long term illness or disability retirement, Working=Working or studying, PE=pulmonary embolism, PE+DVT=concomitant deep vein thrombosis reported in hospital records at PE diagnosis, BMI=body mass index (kg/m^2), Obesity=BMI $>30\text{kg/m}^2$, 6MWT=6-minute walking test measured in meters, Ongoing AC treatment=ongoing anti-coagulant treatment at inclusion, BNP= brain natriuretic peptide (mg/l), F-score=Fredrikstad radiological score (higher scores associated with more proximal location of thrombus) and SD=standard deviation.

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Comparison of HRQoL between patients, population controls and buddy controls

Table 2 shows the frequency of reported problems by dimension as well as mean and median values for EQ VAS and EQ-5D index values stratified by age group. The dimensional difference between patients and both of the control groups yielded statistically significant differences across all dimensions (Figure 2). Comparisons of EQ-5D index values and EQ VAS between patients and control groups are presented in Table 3. A comparison with the male proportion of our sample to that of the Danish population norms regarding EQ-5D index values, initially showed a statistically significant difference, $p=0.04$ (0.84 vs. 0.88). However, after adjusting for outliers, the statistical significance disappeared (0.85 vs. 0.87, $p=0.13$). The differences in mean EQ-5D index values were 0.11 and 0.06 between patients and buddy controls and between patients and the general population respectively.

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Table 2. Frequency of patients reporting no problems and problems in the EQ-5D dimensions, means and medians for EQ VAS and EQ-5D index values. All displayed by age groups.

		AGE GROUPS							
EQ-5D DIMENSION		18-29	30-39	40-49	50-59	60-69	70-79	80+	Total
Mobility	No Problems	4	12	22	31	41	35	13	158
	Problems	2	4	6	8	12	13	10	55
Self-care	No Problems	6	16	26	36	50	43	22	199
	Problems	0	0	2	3	3	5	1	14
Usual Activities	No Problems	4	12	19	29	33	37	11	145
	Problems	2	4	9	10	20	11	12	68
Pain and Discomfort	No Problems	3	8	13	18	25	24	6	97
	Problems	3	8	15	21	28	24	17	116
Anxiety and Depression	No Problems	3	12	19	31	30	35	13	143
	Problems	3	4	9	8	23	13	10	70
EQ VAS									
Mean (SD)		61 (22)	65 (23)	67 (23)	70 (22)	70 (21)	70 (18)	57 (21)	67 (21)
Median		60	73	70	75	70	70	51	70
-25th		45	49	50	50	53	51	40	50
-75th		80	84	85	87	90	82	75	83
EQ-5D index values									
Mean (SD)		0.67 (0.40)	0.81 (0.26)	0.81 (0.23)	0.84 (0.21)	0.81 (0.16)	0.80 (0.25)	0.74 (0.18)	0.80 (0.22)
Median		0.82	0.82	0.82	0.82	0.79	0.82	0.77	0.82
-25th		0.27	0.73	0.76	0.77	0.71	0.73	0.71	0.72
-75th		1.00	1.00	1.00	1.00	1.00	1.00	0.82	1.00

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Table 3. Comparisons of mean EQ-5D index values and EQ VAS between patients vs. Danish population and patients vs. buddy controls.

	Patients			Danish population†			Buddy controls
	Male	Female	Total	Male	Female	Total	Total
EQ-5D index							
Mean	0.85	0.75 (0.23)	0.80	0.87	0.84	0.86	0.91
(SD)	(0.21)		(0.22)				(0.16)
p-value				0.13*	<0.005*	<0.005*	<0.005‡
EQ VAS							
Mean	71	62	67	81	80	81	80
(SD)	(20)	(22)	(21)				(19)
p-value				<0.005*	<0.005*	<0.005*	<0.005‡

† age and sex adjusted values. *one sample t-test with the age and sex adjusted value as test-value (two-sided). ‡ Mann U Whitney (two-sided).

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Predictors of HRQoL

Table 4 summarises the results of the univariate analysis. 6-minute walking test was significantly correlated with all the EQ-5D dimensions as well as EQ VAS ($p < 0.005$), indicating patients with lower scores on EQ VAS or reporting problems in the EQ-5D dimensions tended to walk shorter distances. Similar associations were found concerning dyspnoea, as those complaining of dyspnoea reported problems in 4 out of 5 EQ-5D dimensions ($p < 0.05$; Table 4). Patients reporting dyspnoea also tended to cover shorter distances on the 6MWT (481 vs. 413 meters, $p < 0.005$). In the multiple linear regression model following variables were shown to be independently predictive of the dependant variable EQ VAS: performance on 6-minute walking test ($B = 0.09$, $p < 0.005$), complaints of dyspnoea ($B = -11.27$, $p < 0.005$) and unemployment ($B = -8.98$, $p < 0.005$; Table 5). In addition to the EQ VAS, performance on 6-minute walking test consistently proved to be an independent determinant of every EQ-5D dimension, except for the dimension Pain and discomfort. Dyspnoea was a significant predictor of the dimension Usual activities and Pain and discomfort. However, regarding the latter the goodness of fit of the model showed a value beneath the significance level of 0.05 (Hosmer and Lemeshow = 0.02) indicating poor fit of the model. None of the other evaluated variables were significant determinants of HRQoL. The results from both the multiple linear and binary logistic regression analyses are displayed in Table 5.

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Table 4. Univariate analysis displaying correlations of the predefined determinants to EQ-5D dimensions and EQ VAS.

	EQ-5D DIMENSIONS										EQ VAS		
		¹ MO		² SC		³ UA		⁴ PD		⁵ AD			
	N	Corr.coef	p-value	Corr.coef	p-value	Corr.coef	p-value	Corr.coef	p-value	Corr.coef	p-value	Corr.coef	p-value
Age	213	0.091	0.185	0.048	0.487	0.068	0.323	0.059	0.388	0.061	0.376	-0.062	0.316
Sex	213	-0.199*	<0.005	-0.026	0.703	-0.230*	<0.005	-0.127*	0.064	-0.270*	<0.005	0.226*	<0.005
6MWT	213	-0.427*	<0.005	-0.284*	<0.005	-0.424*	<0.005	-0.299*	<0.005	-0.248*	<0.005	0.511*	<0.005
BMI	213	0.131*	0.056	0.139*	0.043	0.097	0.159	0.026	0.709	0.046	0.502	0.220*	<0.005
BNP	203	0.192*	0.006	0.010	0.892	0.157*	0.026	0.130*	0.066	0.187*	0.008	-0.103	0.144
Ongoing AC	213	0.090	0.189	-0.052	0.453	0.024	0.731	0.017	0.803	-0.013	0.853	-0.061	0.378
Cardiopulmonary comorbidity	213	0.154*	0.025	0.050	0.469	0.174*	0.011	0.088	0.202	0.062	0.202	-0.189*	0.006
Active cancer	213	0.089	0.195	0.001	0.988	0.008	0.904	-0.006	0.928	0.003	0.968	-0.020	0.767
Reporting dyspnoea	213	0.160*	0.020	0.133*	0.053	0.291*	<0.005	0.399*	<0.005	0.110	0.111	-0.365*	<0.005
F-score	192	0.058	0.423	0.151*	0.037	0.109	0.132	0.066	0.360	-0.006	0.936	-0.123*	0.089
Recurrent VTE	213	0.006	0.925	-0.064	0.354	-0.023	0.733	0.064	0.353	-0.005	0.945	-0.020	0.769
Unemployed	213	0.103	0.132	0.077	0.266	0.215*	<0.005	0.240*	<0.005	0.273*	<0.005	-0.241*	0.005
Disease duration	213	-0.020	0.769	-0.018	0.789	-0.033	0.636	-0.038	0.578	-0.069	0.315	0.133*	0.052

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*All values with $\alpha < 0.10$ retained for multiple regression analysis, explanatory variables recoded to 0=not having the condition and 1=having the condition, dimensions dichotomised in reporting problems=1 and not reporting problems=0, MO=Mobility, SC=Self-care, UA=Usual Activities, PD=Pain and Discomfort, AD=Anxiety and Depression, Corr.coef=Spearman's rho correlation coefficient, Age=age at inclusion, male sex =1, 6MWT=6-minute walking test, BMI=Body mass index (kg/m^2), BNP=Brain natriuretic peptide, Ongoing AC=Ongoing anti-coagulant treatment, F-score=Fredrikstad radiological score (higher scores associated with more proximal location of thrombus), Unemployed=Unemployed or unemployment because of long-term illness or disability retirement and Disease duration=time in years from PE diagnosis to study inclusion.

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Table 5. Multiple binary logistic and standard linear regression models with retained determinants from the univariate analysis for possible independency tested against EQ-5D dimensions and EQ VAS.

	EQ-5D DIMENSIONS										EQ VAS	
	¹ MO		² SC		³ UA		⁴ PD		⁵ AD			
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	B [†]	SE [‡]
6MWT	0.991	0.987-0.995**	0.990	0.984-0.997**	0.991	0.988-0.995**	0.996	0.992-0.999*	0.997	0.994-1.000	0.090	0.012**
BMI	1.038	0.965-1.118	1.056	0.938-1.190	--	--	--	--	--	--	-0.068	0.257
BNP	1.004	0.999-1.010	--	--	1.001	0.996-1.007	0.999	0.994-1.003	1.000	0.996-1.005	--	--
Cardiopulmonary comorbidity	0.566	0.139-2.301	--	--	0.777	0.197-3.067	--	--	--	--	1.627	4.690
Reporting dyspnoea	1.332	0.633-2.806	1.748	0.378-8.071	2.333	1.138-4.782*	3.737	1.971-7.083**	--	--	-11.270	2.558**
F-score	--	--	3.117	0.788-5.685	--	--	--	--	--	--	1.714	1.131
Unemployed	--	--	--	--	2.550	1.148-5.668*	2.756	1.235-6.152*	3.942	1.881-8.263**	-8.979	2.972**
Disease duration	--	--	--	--	--	--	--	--	--	--	-0.193	0.466
Hosmer and Lemeshow	0.08		0.87		0.35		0.02		0.62			
r ²	0.455											

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* ** : p-value <0.05 and <0.005, all regression models adjusted for age and sex, explanatory variables recoded to 0=not having the condition and 1=having the condition, dimensions dichotomised in reporting problems=1 and not reporting problems=0, MO=Mobility, SC=Self-care, UA=Usual Activities, PD=Pain and Discomfort, AD=Anxiety and Depression, higher scores in EQ VAS associated with better HRQoL, OR=Odds Ratio, 6MWT=6-minute walking test, BMI=Body mass index (kg/m²), BNP=Brain natriuretic peptide, F-score=Fredrikstad radiological score (higher scores associated with more proximal location of thrombus), Unemployed= unemployed or unemployment because of long-term illness or disability retirement, Disease duration=time in years from diagnosis to study inclusion, r²=R-squared, [†]Unstandardized beta coefficient, [‡]Standard error of beta.

DISCUSSION

In this population-based, cross-sectional study, we found that the long-term HRQoL assessed by EQ-5D-3L was significantly impaired among PE patients compared to buddy controls and population norms. Moreover, we found that poorer performance on 6-minute walking test, persistent patient-reported dyspnoea and unemployment were independent predictors of reduced HRQoL. To our knowledge this is the second largest study to compare long-term HRQoL after PE to a control group. Despite using a different instrument (EQ-5D-3L versus Short-Form 36), our results of impaired HRQoL after PE, confirms previously published studies.[6,7]

The challenge of quality of life studies is to judge whether identified differences are clinically relevant or not. Across various HRQoL research papers using the EQ-5D instrument, authors have suggested threshold values for minimal (clinical) important difference (MID/MCID), i.e., the least amount of difference suggesting clinical relevance or mandating a change in clinical practice,[20] ranging from 0.04-0.08.[21-23] In our study, the delta EQ-5D index value between study population and buddy controls was 0.11 and between study population and the general population was 0.06. This indicates that we have identified clinically relevant difference in HRQoL between the patients and both control cohorts. Of note, the cut-off value for MID/MCID is various and probably depends on both the disease and valuation sets used. Moreover, because we did not include a longitudinal within-person measurement of QoL, the differences must be interpreted with caution.[24]

Compared to those without dyspnoea, the 46.5% of our study patients who reported persistent dyspnoea performed worse in the 6-minute walking test, objectively verifying this complaint. In the multivariable analyses, performance on 6-minute walking test and persistent dyspnoea appeared to be independent predictors of worse HRQoL. This may indicate that PE patients suffer from a reduced functional capacity that persists for many years after the event

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and that the declining functional capacity is one of the main determinants of impaired HRQoL in patients with a history of PE. The finding that patients on average underperformed in the 6-minute walking test may thus be an important explanation for their overall reduced HRQoL. Again however, cut-off values for clinical relevant abnormal 6-minute walking test performance regarding PE are lacking which makes it difficult to put the observed results in further perspective.

Numerous studies have shown the beneficial effects of pulmonary rehabilitation in other cardiovascular diseases, resulting in improved functional capacity as well as HRQoL.[25-28] In this context, our findings support the hypothesis that PE patients with persistent dyspnoea and poor functional status may benefit of cardiopulmonary rehabilitation programs.[29]

Although the majority of studies focusing on the long-term effects of PE have not excluded patients with established chronic thromboembolic pulmonary hypertension (CTEPH) diagnosis, there is consistent reporting that approximately half of the patients assessed more than 6 months after experiencing an episode of acute PE complain of dyspnoea, which is also correlated to a decline in physical performance measured by 6-minute walking test.[4,8,30,31] Our results confirm these findings and support the concept of “post-PE syndrome” which has recently been presented as an analogy to PTS, referring to the persistent dyspnoea and reduced functional capacity after PE.[9] The authors discuss whether PE could in some cases, CTEPH excluded, be classified as a chronic illness and postulate the “post-PE syndrome” being a state just prior to development of CTEPH. This reasoning is further strengthened by a Danish study reporting overuse of antidepressants in adolescents long after they experienced their first episode of PE.[10] However, whether persistent dyspnoea after PE should be the subject of further standardized work-up including HRQoL questionnaires and 6-minute walking test is still debatable since some studies attribute the

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high prevalence of dyspnoea to pre-existing comorbidities.[32] The final independent predictor of worse HRQoL in our study was unemployment. Several socio-demographic variables have previously been shown to affect HRQoL, regardless of the underlying disease or condition.[33] The fact that 24% of the study population were unemployed could possibly have contributed to the overall lower HRQoL scores in our patient cohort.

Of the predefined determinants being evaluated we found only a selected proportion predictive of worse HRQoL. Previous studies have found cardiopulmonary disease, active malignancy as well as obesity being independent predictors of HRQoL.[6,34] However, the proportions of these subgroups reported in the aforementioned studies are higher than in ours and presented multivariate regression analysis yielded rather low r^2 percentages indicating the models not being precise.[6] This may indicate, as van Es et al postulate,[7] that in the present study the patients are somewhat healthier and subsequently, perhaps emphasizing the findings regarding the reported differences in HRQoL between study subjects and the general population. Nevertheless, in our view these contradictions exemplify the heterogeneous effects of PE as a disease on both HRQoL and physical capacity and consequently rendering cumbersome evaluation of determinants of HRQoL in PE patients.

Limitations

Our study has some limitations. The low response rate may hamper external validity of our results. Moreover, a possible bias toward recruitment of patients with more persistent symptoms cannot be ruled out. However, the 6-minute walking test results and proportion reporting dyspnoea in our sample are similar to prior PE follow-up studies,[31,35,36] highlighting that our cohort is a representative PE population. Also, the buddy control group could not be assessed for potential confounders because we did not assess their

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characteristics. Therefore, we cannot rule out a bias towards “extremely” healthy buddies or poor matching. Lastly, we did not apply a disease specific questionnaire of QoL.

The strongpoints of this study are the novelty of including a second control group, i.e., the buddy controls, that did not have incidents of VTE, the sample size and the long term follow up period with 89% of the patients diagnosed with PE more than 1 year prior to inclusion. Furthermore, this study is one of the largest studies presenting a more comprehensive evaluation of HRQoL by reporting all aspects of a generic quality of life questionnaire as well as incorporating functional capacity test (6-minute walking test) in order to objectify the findings.

Conclusions

Patients with a history of acute PE were found to have worse HRQoL compared to age- and sex-matched VTE-free buddy controls and population controls. Underperformance and patient-reported dyspnoea were independent predictors of decreased HRQoL. Further studies are necessary to further evaluate the course and determinants of HRQoL after acute PE as well as to interventions aimed at improving HRQoL in these patients.

CONTRIBUTORSHIP STATEMENT

Authors M. Tavoly and W. Ghanima were responsible for study concept, design and data acquisition. M. Tavoly, H.S. Wik and W. Ghanima performed the statistical analyses. M. Tavoly wrote the first draft of the manuscript. All authors were responsible for critical revision of the manuscript, interpretation of the results, had full access to all the data in the study, and take responsibility of the integrity of the data and the accuracy of data analysis.

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COMPETING INTERESTS

The authors state that they have no conflict of interest, except W. Ghanima and L.P. Jelsness-Jørgensen. W. Ghanima reports grants and lecture honoraria from Bayer, Novartis and Roche and lecture and advisory board honoraria from Pfizer, Bayer and from Boehringer Ingelheim – none of which is relevant for the submitted work. L.P. Jelsness-Jørgensen reports unrestricted grants from Ferring pharmaceuticals and Tillots pharma, and personal fees from Abbvie, not relevant for the submitted work.

DATA SHARING STATEMENT

No additional data available.

LIST OF ABBREVIATIONS

- PTS - post-thrombotic syndrome
- DVT - deep vein thrombosis
- HRQoL - health-related quality of life
- PE - pulmonary embolism
- CTEPH - chronic thromboembolic pulmonary hypertension
- CTPA - computed tomography pulmonary angiogram
- BNP - brain natriuretic peptide
- EQ-5D-3L - euroqol-5 dimension-3 level
- EQ VAS - euroqol visual analogue scale
- VTE - venous thromboembolism
- BMI - body mass index
- CHF - congestive heart failure

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COPD - chronic obstructive pulmonary disease

MID/MCID – minimal important difference/minimal clinical important difference

SD - standard deviation

OR - odds ratio

MO - mobility

SC - self-care

UA - usual activities

PD - pain and discomfort

AD - anxiety and depression

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Table legends

Table 1	Socio-demographic and clinical characteristics of the study sample.
Table 2	Frequency of patients reporting no problems and problems in the EQ-5D dimensions, means and medians for EQ VAS and EQ-5D index values. All displayed by age groups.
Table 3	Comparisons of mean EQ-5D index values and EQ VAS between patients vs. Danish population and patients vs. buddy controls.
Table 4	Univariate analysis displaying correlations of the predefined determinants to EQ-5D dimensions and EQ VAS.
Table 5	Multiple binary logistic and standard linear regression models with retained determinants from the univariate analysis for possible independency tested against EQ-5D dimensions and EQ VAS.

Figure legends

Figure 1	Study flow chart.
Figure 2	Proportion of patients, Danish population and buddy controls reporting problems stratified by EQ-5D dimensions.

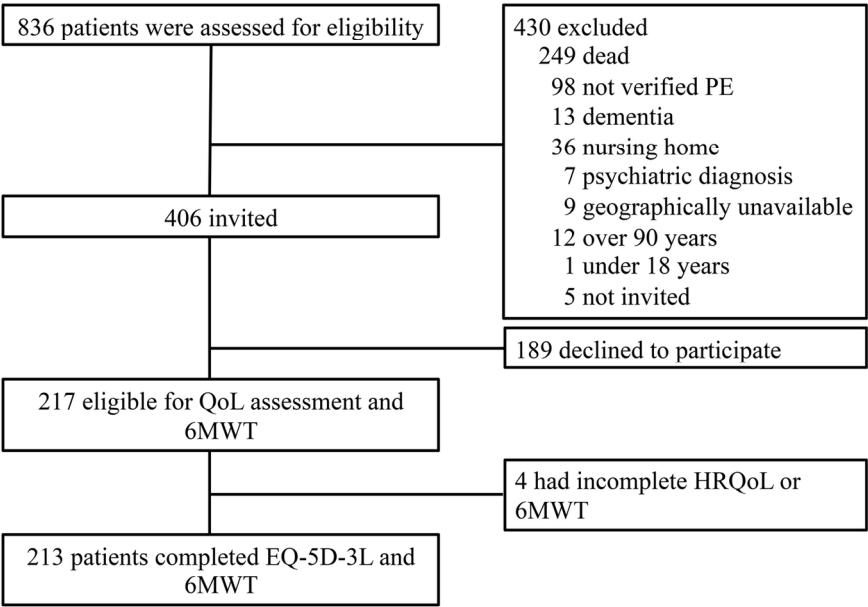


Figure 1. Study flow chart.

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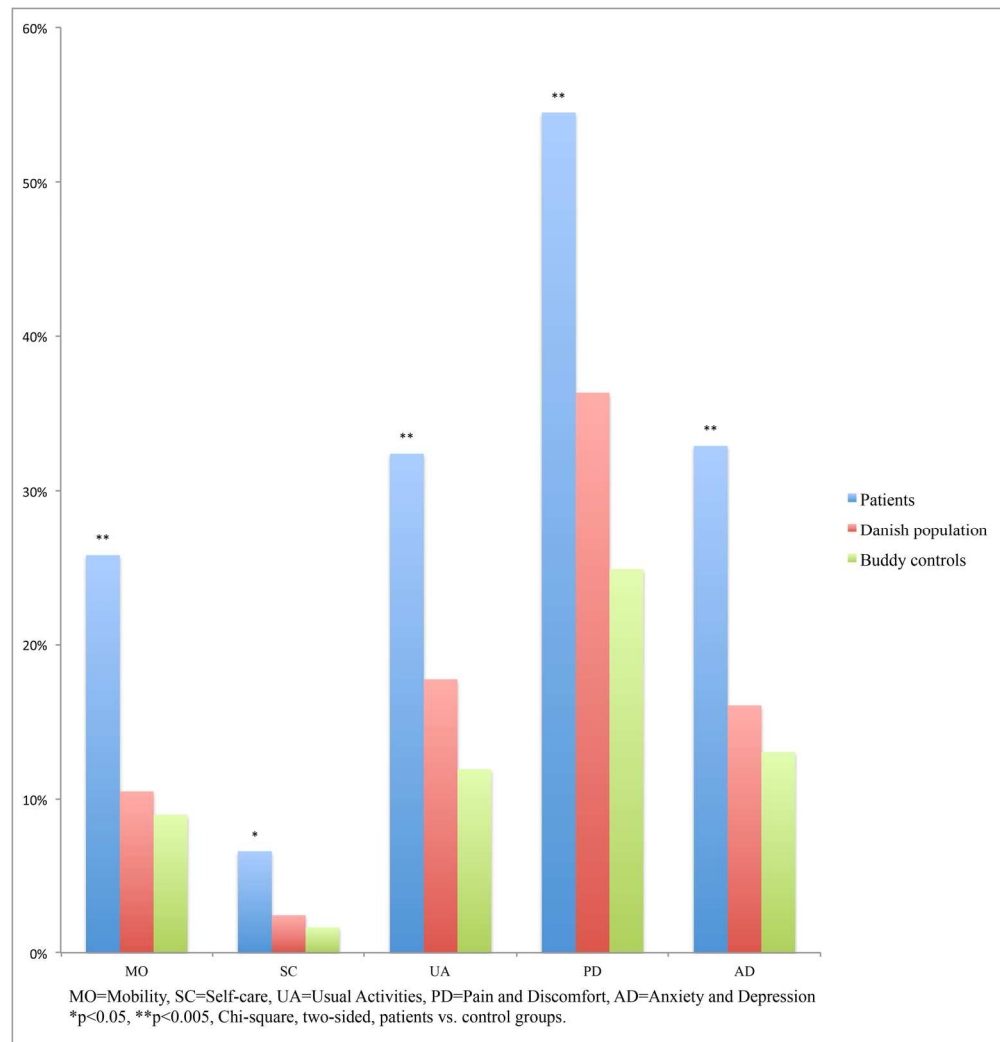


Figure 2. Proportion of patients, Danish population and buddy controls reporting problems stratified by EQ-5D dimensions.

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5, 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	7
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed	
		Case-control study—For matched studies, give matching criteria and the number of controls per case	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7, 8
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	8
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed	
		Case-control study—If applicable, explain how matching of cases and controls was addressed	

		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, 10
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	9
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-18
		(b) Report category boundaries when continuous variables were categorized	9-18
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	19
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	22
Generalisability	21	Discuss the generalisability (external validity) of the study results	22
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Health-related quality of life after pulmonary embolism: a cross-sectional study

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Health-related quality of life after pulmonary embolism: a cross-sectional study

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ABSTRACT

Objectives: The psychological effects of acute pulmonary embolism (PE) have been scarcely studied. The aims of this study were to evaluate health-related quality of life (HRQoL) in patients with a history of PE compared to the general population and buddy controls, and to explore factors that may predict impaired HRQoL.

Design: Cross-sectional.

Setting: Haematology and Thrombosis unit in Fredrikstad, Norway.

Participants: 213 consecutive patients treated for PE were identified from hospital registries. Eligible patients were scheduled for a single study visit, including a functional capacity test (6-minute walking test). HRQoL was assessed using the EQ-5D-3L questionnaire, of which the results were compared to Danish population norms and age- and sex-matched buddy controls. The buddy controls were recruited by asking every patient to hand over the EQ-5D questionnaire to two age- and sex-matched friends or relatives. Multivariable regression analyses were used to examine possible determinants of reduced HRQoL.

Results: Mean age was 61 years (SD 15), 117 (55%) were males, and median time since diagnosis was 3.8 years (range 0.3-9.5). Mean EQ VAS was 67 in PE as compared to 81 in the general population ($p<0.005$) and corresponding EQ-5D index values were 0.80 and 0.86 ($p<0.005$). Patients reported more problems in all 5 EQ-5D dimensions compared to both the buddy controls and the general population, $p<0.05$. Shorter six-minute walking distance ($B=0.09$, $p<0.005$) and patient-reported dyspnoea ($B=-11.27$, $p<0.005$) were independent predictors of lower EQ VAS scores.

Conclusion: Our findings show that patients with a history of PE have impaired HRQoL when compared to the general population and buddy controls. Reduced functional capacity and persistent dyspnoea were the main predictors of this impairment.

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Strength and limitations of this study

- This study describes the long-term health-related quality of life, functional capacity and prevalence of dyspnoea in patients with a history of pulmonary embolism, which have been scarcely studied.
- A large sample size in which all aspects of a generic health-related quality of life questionnaire is reported combined with functional capacity assessment.
- The findings in this study may encourage future studies to evaluate the susceptibility of these patients to cardiopulmonary rehabilitation.
- The low response rate and the retrospective design may hamper the external validation.

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INTRODUCTION

Health-related quality of life (HRQoL) after deep vein thrombosis (DVT) has been extensively studied. The interest of studying HRQoL in DVT is believed to be related to the well characterized frequent detrimental chronic condition of post-thrombotic syndrome (PTS) that affects 30-50 % of DVT patients.[1] Unlike DVT, long-term effects of acute pulmonary embolism (PE) on HRQoL are understudied. The equivalent long term complication of acute PE is chronic-thromboembolic pulmonary hypertension (CTEPH).[2] This condition has been shown to affect 2-4 % of the patients with a past history of PE.[3] This relatively low frequency of CTEPH may be the reason for the limited number of studies focusing on HRQoL and the psychological well-being in PE patients.[4-9] It has been suggested that CTEPH itself is the extreme manifestation of a much more common phenomenon of permanent changes in pulmonary hemodynamics, cardiac function and pulmonary gas exchange after acute PE, which is associated with dyspnoea and decreased exercise capacity. Additionally, several studies have shown that up to 50% of the patients with a history of PE complain of persistent dyspnoea long time after PE.[4,10] In analogy to PTS after DVT, it was recently proposed to refer to this phenomenon as the "post-pulmonary embolism syndrome".[11] Moreover, a recent Scandinavian study reported the overuse of antidepressants in adolescents with a history of PE, indicating that PE may develop into a chronic illness in a relevant number of patients.[12] Indeed, the few existing studies all report an impaired HRQoL in patients with a history of PE compared to the normal population,[4,6] although the results concerning possible predictors of reduced HRQoL are divergent.[7] More detailed knowledge of the determinants of HRQoL is needed to allow for identification of treatment targets and implementation of this important endpoint in future outcome studies.

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The aims of the present study were to compare HRQoL in patients with a history of PE to that of the general population and to age- and sex-matched controls, and to evaluate possible determinants of HRQoL.

MATERIAL AND METHODS

Participants and setting

Consecutive patients who were diagnosed and treated for PE at the Østfold Hospital Trust, Fredrikstad, Norway, between January 2002 and December 2011 were identified from the hospital's registries including the thrombosis registry by searching for ICD-10 codes of PE (ICD-10 I26.0 and I26.9). All patients alive at the beginning of March 2012, and with a PE diagnosis confirmed by computed tomography pulmonary angiogram (CTPA) or high probability perfusion scintigraphy, were eligible for study participation.

Patients were excluded if they were <18 or >90 years old or deemed incapable to comply with study procedures, including language barriers, geographical unavailability, known dementia, psychiatric diagnosis such as major depression as well as affective disorders or any degree of psychotic disorder. Patients living in nursing homes or receiving major help from social care services were excluded as well.

The study was approved by the Regional Committee for Medical and Health Research Ethics, Norway (Approval no 2011/2557b); and written informed consent was obtained for all patients.

Study design

All eligible patients were contacted by telephone and invited to participate in the study. Patients who responded to our invitation were scheduled for a visit during which they underwent physical examination and functional capacity test using the 6-minute walking test.

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The 6-minute walking test is a standardized functional capacity test, which is widely used to objectively assess patients' cardiopulmonary capacity.[13] The test was performed according to published guidelines,[14] by one of the study investigators (M.T.). For each patient we derived predicted values from the recommendations of the literature.[15] Evaluation of patients comprised blood tests including brain natriuretic peptide (BNP), which were obtained at the study visit. Socio-demographic data were recorded on standardized case record forms.

Prior to the study visit, the HRQoL questionnaire was sent to the patients either by e-mail or post. Patients were asked to complete the form at home and return it at scheduled study visit. Incomplete forms were completed during the visit at the hospital.

Quality of life questionnaire

The validated Norwegian version of Euroqol-5 dimension-3 level (EQ-5D-3L) questionnaire was used in order to assess quality of life. EQ-5D-3L consists of a descriptive system and the Euroqol visual analogue scale (EQ VAS).[16,17] The EQ-5D-3L is a validated, generic, preference-based, health-status measure consisting of five descriptive questions encompassing five domains of HRQoL: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each question is answered based on three response options (1= "no problems", 2= "moderate problems", 3= "severe problems"). The 243 (3^5) potential patterns of responses each indicate a unique health state ranging from 11111 for perfect health to 33333 for the worst possible state. The health states can then be converted into a single summary index value, which ranges from 1 (state of full health) to values lower than 0 (states regarded as worse than being dead).

The EQ VAS is a self-rated health on a vertical visual analogue scale (0-100) where the endpoints are labelled "worst imaginable health state" and "best imaginable health state".

Control groups

Although several European countries have established normative population data for the EQ-5D instrument, these are not available for Norway. Therefore, we compared our results to the Danish population norms that were established in 2009.[18]

To correct for incident cases with venous thrombosis in the normative population, we included a second control group by asking our study subjects to recruit two age- (+/- five years) and sex-matched relatives or friends without a history of venous thrombosis, hereafter referred to as buddy controls, to complete the EQ-5D form. Buddy controls were asked to return the anonymous questionnaire in prepaid envelopes. Due to the anonymity of the buddy controls, further baseline characteristics were not accessible.

Predictors

Based on clinical experience and previous research, we hypothesized that the following determinants may be relevant predictors of HRQoL after PE: a) age, b) sex, c) disease duration (time in years from PE diagnosis to study visit), d) body mass index (BMI; kg/m²), e) recurrent venous thromboembolism, f) occupation, g) persistent patient-reported dyspnoea, h) performance at 6-minute walking test, i) BNP, j) active malignancy, k) ongoing anti-coagulant treatment, l) known cardiopulmonary comorbidity, including interstitial pulmonary diseases, congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD) and m) proximal clot location at PE diagnosis as assessed by a previously published radiological score by Ghanima et al.[19]

STATISTICAL ANALYSES

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Continuous variables were expressed as means and standard deviations if normally distributed and medians with ranges if skewed distributed. Categorical variables were presented as percentages and/or frequencies. Comparisons were made using Students T-test or Mann-U-Whitney (depending on normal or skewed distribution) for continues variables and Chi-square tests for categorical variables.

Since very few patients and controls had “extreme problems”, the EQ-5D dimensions were dichotomised to either ”no problems” or ”problems”.

Age and gender adjustment of controls were made by weighing the population norm EQ-5D index values and EQ VAS with the distribution of our sample, as recommended by Hjermstad et al.[20]

Variables deemed predictive of HRQoL where first screened using univariate analysis (Spearman’s rho). Correlations below the significance level of $\alpha=0.1$ were retained for the multivariate regression analysis. Potential multicollinearity was checked before inclusion in the multivariate models. Then, multivariate regression analyses comprising both standard linear regression and binary logistic regression models were performed. For the former, the possible determinants were tested for independency against EQ VAS and the R-squared (r^2) was used to estimate the percentage of effect explained by the model. For the latter, retained determinants from the univariate analysis were tested for independency against each of the EQ-5D dimensions. The Hosmer and Lemeshow test was used to estimate the goodness of fit of the model.

Multiple imputation model was used in order to deal with missing values in the EQ-5D questionnaires of the buddy controls in whom we did not have the possibility to check and complete the questionnaires during a study visit.[21] Cases with more than 50% of the items or EQ VAS missing were omitted. All analyses were performed using the Statistical

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Package for Social Science version 22.0 (SPSS Inc., Chicago, IL, USA), and considered significant at a two-sided alpha of ≤ 0.05 .

RESULTS

Study flow

A total of 836 patients were identified and assessed for eligibility in this study. As shown in the study flow chart (Figure 1), 430 (51%) patients were excluded according to the predefined exclusion criteria. Of the 406 remaining and thus invited patients, 189 (46%) declined to participate. Of the remaining 217 eligible patients, 213 completed both the EQ-5D questionnaire and underwent the six-minute walking test. Hence, the response rate for our study cohort was fifty-two percent.

The number of buddy controls who returned the EQ-5D form was 205, of whom 28 returned questionnaires had more than 50% of data missing. After excluding these 28, 177 were left for analysis. The response rate for the buddy controls was thus 42%, assuming all study patients indeed forwarded the questionnaire to two ‘buddies’.

Study patients

Patients had a mean age of 61 years (SD 15) and 55 % were men (n=117). Socio-demographic characteristics are presented in Table 1. Median time since diagnosis was 3.8 years (range 0.3-9.5) with 89% being diagnosed with PE more than a year prior to study inclusion.

Mean distance covered on 6-minute walking test by the study cohort was 449 meters (SD 135). The mean 6-minute walking distance was 97 meters (95% CI 76-117) less in male

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patients and 84 meters (95% CI 65-104) less in female patients as compared to their gender-predicted value, $p < 0.005$.

Table 1. Socio-demographic and clinical characteristics of the study sample.

Variable	Study sample	
	n	(%)
Female	96	(45)
Age in years, mean (SD)	61	(15)
Years since diagnosis, median (range)	3.8	(0.3-9.5)
Occupation		
-Unemployed	50	(24)
-Working	71	(33)
-Retired	92	(43)
Diagnosis		
-PE	149	(70)
-PE + DVT	64	(30)
Recurrent VTE	34	(16)
Cardiopulmonary comorbidity	19	(9)
BMI, mean (SD)	28.7	(4.9)
Obesity	73	(34)
Active malignancy	15	(7)
Reporting dyspnoea	99	(46)
Smoking		
-Current	38	(18)
-Former	52	(24)
Ongoing AC treatment	81	(38)
6MWT, mean (SD)		
-Total	449	(135)
-Men	488	(124)
-Women	402	(134)
Laboratory tests at study visit	203	
-BNP, mean (SD)	48.6	(72.4)
F-score	192	
-median (range)	3	(1-4)

Unemployed=unemployed or unemployment because of long term illness or disability retirement, Working=Working or studying, PE=pulmonary embolism, PE+DVT=concomitant deep vein thrombosis reported in hospital records at PE diagnosis, BMI=body mass index (kg/m^2), Obesity=BMI $> 30 \text{ kg/m}^2$, 6MWT=6-minute walking test measured in meters, Ongoing AC treatment=ongoing anti-coagulant treatment at inclusion, BNP= brain natriuretic peptide (mg/l), F-score=Fredrikstad radiological score (higher scores associated with more proximal location of thrombus) and SD=standard deviation.

Comparison of HRQoL between patients, population controls and buddy controls

Table 2 shows the frequency of reported problems by dimension as well as mean and median values for EQ VAS and EQ-5D index values stratified by age group. The dimensional difference between patients and both of the control groups yielded statistically significant differences across all dimensions (Figure 2). Comparisons of EQ-5D index values and EQ VAS between patients and control groups are presented in Table 3. A comparison with the male proportion of our sample to that of the Danish population norms regarding EQ-5D index values, initially showed a statistically significant difference, $p=0.04$ (0.84 vs. 0.88). However, after adjusting for outliers, the statistical significance disappeared (0.85 vs. 0.87, $p=0.13$). The differences in mean EQ-5D index values were 0.11 and 0.06 between patients and buddy controls and between patients and the general population respectively.

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Table 2. Frequency of patients (n=213) reporting problems in the EQ-5D dimensions, means and medians for EQ VAS and EQ-5D index values. All displayed by age groups.

		AGE GROUPS							
EQ-5D DIMENSION		18-29	30-39	40-49	50-59	60-69	70-79	80+	Total
Mobility	N (%)	2 (1)	4 (2)	6 (3)	8 (4)	12 (6)	13 (6)	10 (5)	55 (26)
Self-care	N (%)	0 (0)	0 (0)	2 (1)	3 (1)	3 (1)	5 (2)	1 (0.5)	14 (7)
Usual Activities	N (%)	2 (1)	4 (2)	9 (4)	10 (5)	20 (9)	11 (5)	12 (6)	68 (32)
Pain and Discomfort	N (%)	3 (1)	8 (4)	15 (7)	21 (10)	28 (13)	24 (11)	17 (8)	116 (54)
Anxiety and Depression	N (%)	3 (1)	4 (2)	9 (4)	8 (4)	23 (11)	13 (6)	10 (5)	70 (33)
EQ VAS									
Mean		61	65	67	70	70	70	57	67
(SD)		(22)	(23)	(23)	(22)	(21)	(18)	(21)	(21)
Median		60	73	70	75	70	70	51	70
-25th		45	49	50	50	53	51	40	50
-75th		80	84	85	87	90	82	75	83
EQ-5D index values									
Mean		0.67	0.81	0.81	0.84	0.81	0.80	0.74	0.80
(SD)		(0.40)	(0.26)	(0.23)	(0.21)	(0.16)	(0.25)	(0.18)	(0.22)
Median		0.82	0.82	0.82	0.82	0.79	0.82	0.77	0.82
-25th		0.27	0.73	0.76	0.77	0.71	0.73	0.71	0.72
-75th		1.00	1.00	1.00	1.00	1.00	1.00	0.82	1.00

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Table 3. Comparisons of mean EQ-5D index values and EQ VAS between patients vs. Danish population and patients vs. buddy controls.

	Patients			Danish population†			Buddy controls
	Male	Female	Total	Male	Female	Total	Total
EQ-5D index							
Mean	0.85	0.75	0.80	0.87	0.84	0.86	0.91
(SD)	(0.21)	(0.23)	(0.22)				(0.16)
p-value				0.13*	<0.005*	<0.005*	<0.005‡
EQ VAS							
Mean	71	62	67	81	80	81	80
(SD)	(20)	(22)	(21)				(19)
p-value				<0.005*	<0.005*	<0.005*	<0.005‡

† age and sex adjusted values. *one sample t-test with the age and sex adjusted value as test-value (two-sided). ‡ Mann U Whitney (two-sided).

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Predictors of HRQoL

Table 4 summarises the results of the univariate analysis. 6-minute walking test was significantly correlated with all the EQ-5D dimensions as well as EQ VAS ($p < 0.005$), indicating patients with lower scores on EQ VAS or reporting problems in the EQ-5D dimensions tended to walk shorter distances. Similar associations were found concerning dyspnoea, as those complaining of dyspnoea reported problems in 4 out of 5 EQ-5D dimensions ($p < 0.05$; Table 4). Patients reporting dyspnoea also tended to cover shorter distances on the 6MWT (481 vs. 413 meters, $p < 0.005$). In the multiple linear regression model following variables were shown to be independently predictive of the dependant variable EQ VAS: performance on 6-minute walking test ($B = 0.09$, $p < 0.005$), complaints of dyspnoea ($B = -11.27$, $p < 0.005$) and unemployment ($B = -8.98$, $p < 0.005$; Table 5). In addition to the EQ VAS, performance on 6-minute walking test consistently proved to be an independent determinant of every EQ-5D dimension, except for the dimension Anxiety and Depression. Dyspnoea was a significant predictor of the dimension Usual Activities and Pain and Discomfort. However, regarding the latter the goodness of fit of the model showed a value beneath the significance level of 0.05 (Hosmer and Lemeshow = 0.02) indicating poor fit of the model. None of the other evaluated variables were significant determinants of HRQoL. The results from both the multiple linear and binary logistic regression analyses are displayed in Table 5.

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Table 4. Univariate analysis displaying correlations of the predefined determinants to EQ-5D dimensions and EQ VAS.

	EQ-5D DIMENSIONS										EQ VAS		
	¹ MO			² SC		³ UA		⁴ PD		⁵ AD			
	N	Corr.coef	p-value	Corr.coef	p-value	Corr.coef	p-value	Corr.coef	p-value	Corr.coef	p-value	Corr.coef	p-value
Age	213	0.09	0.19	0.05	0.49	0.07	0.32	0.06	0.39	0.06	0.38	-0.06	0.31
Sex	213	-0.20*	<0.05	-0.03	0.70	-0.23*	<0.05	-0.13*	0.06	-0.27*	<0.05	0.23*	<0.05
6MWT	213	-0.43*	<0.05	-0.28*	<0.05	-0.42*	<0.05	-0.30*	<0.05	-0.25*	<0.05	0.51*	<0.05
BMI	213	0.13*	0.06	0.14*	0.04	0.10	0.16	0.03	0.71	0.05	0.50	0.22*	<0.05
BNP	203	0.19*	0.01	0.01	0.89	0.15*	0.03	0.13*	0.07	0.19*	0.01	-0.10	0.14
Ongoing AC	213	0.09	0.19	-0.05	0.45	0.02	0.73	0.02	0.80	-0.01	0.85	-0.06	0.38
Cardiopulmonary comorbidity	213	0.15*	0.03	0.05	0.47	0.17*	0.01	0.09	0.20	0.06	0.20	-0.19*	0.01
Active cancer	213	0.09	0.20	0.01	0.99	0.01	0.90	-0.01	0.93	0.01	0.97	-0.02	0.77
Reporting dyspnoea	213	0.16*	0.02	0.13*	0.05	0.29*	<0.05	0.40*	<0.05	0.11	0.11	-0.37*	<0.05
F-score	192	0.06	0.42	0.15*	0.04	0.11	0.13	0.07	0.36	-0.01	0.94	-0.12*	0.09
Recurrent VTE	213	0.01	0.93	-0.06	0.35	-0.02	0.73	0.06	0.35	-0.01	0.95	-0.02	0.77
Unemployed	213	0.10	0.13	0.08	0.27	0.22*	<0.05	0.24*	<0.05	0.27*	<0.05	-0.24*	0.01
Disease duration	213	-0.02	0.77	-0.02	0.79	-0.03	0.64	-0.04	0.58	-0.07	0.32	0.13*	0.05

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*All values with $\alpha < 0.10$ retained for multiple regression analysis, explanatory variables recoded to 0=not having the condition and 1=having the condition, dimensions dichotomised in reporting problems=1 and not reporting problems=0, MO=Mobility, SC=Self-care, UA=Usual Activities, PD=Pain and Discomfort, AD=Anxiety and Depression, Corr.coef=Spearman's rho correlation coefficient, Age=age at inclusion, male sex =1, 6MWT=6-minute walking test, BMI=Body mass index (kg/m^2), BNP=Brain natriuretic peptide, Ongoing AC=Ongoing anti-coagulant treatment, F-score=Fredrikstad radiological score (higher scores associated with more proximal location of thrombus), Unemployed=Unemployed or unemployment because of long-term illness or disability retirement and Disease duration=time in years from PE diagnosis to study inclusion.

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Table 5. Multiple binary logistic and standard linear regression models with retained determinants from the univariate analysis for possible independency tested against EQ-5D dimensions and EQ VAS.

	EQ-5D DIMENSIONS										EQ VAS	
	¹ MO		² SC		³ UA		⁴ PD		⁵ AD			
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	B [†]	SE [‡]
6MWT	0.991	0.987-0.995**	0.990	0.984-0.997**	0.991	0.988-0.995**	0.996	0.992-0.999*	0.997	0.994-1.000	0.09	0.01**
BMI	1.04	0.97-1.12	1.06	0.94-1.19	--	--	--	--	--	--	-0.07	0.26
BNP	1.00	1.00-1.01	--	--	1.00	1.00-1.01	1.00	0.99-1.00	1.00	1.00-1.01	--	--
Cardiopulmonary comorbidity	0.57	0.14-2.30	--	--	0.78	0.20-3.07	--	--	--	--	1.63	4.69
Reporting dyspnoea	1.33	0.63-2.81	1.74	0.38-8.07	2.33	1.14-4.78*	3.74	1.97-7.08**	--	--	-11.27	2.56**
F-score	--	--	3.12	0.79-5.69	--	--	--	--	--	--	1.71	1.13
Unemployed	--	--	--	--	2.55	1.15-5.67*	2.76	1.24-6.15*	3.94	1.88-8.26**	-8.98	2.97**
Disease duration	--	--	--	--	--	--	--	--	--	--	-0.19	0.47
Hosmer and Lemeshow	0.08		0.87		0.35		0.02		0.62			
r ²												0.46

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* ** : p-value <0.05 and <0.005, all regression models adjusted for age and sex, explanatory variables recoded to 0=not having the condition and 1=having the condition, dimensions dichotomised in reporting problems=1 and not reporting problems=0, MO=Mobility, SC=Self-care, UA=Usual Activities, PD=Pain and Discomfort, AD=Anxiety and Depression, higher scores in EQ VAS associated with better HRQoL, OR=Odds Ratio, 6MWT=6-minute walking test, BMI=Body mass index (kg/m²), BNP=Brain natriuretic peptide, F-score=Fredrikstad radiological score (higher scores associated with more proximal location of thrombus), Unemployed= unemployed or unemployment because of long-term illness or disability retirement, Disease duration=time in years from diagnosis to study inclusion, r²=R-squared, [†]Unstandardized beta coefficient, [‡]Standard error of beta.

DISCUSSION

In this population-based, cross-sectional study, we found that the long-term HRQoL assessed by EQ-5D-3L was significantly impaired among PE patients compared to buddy controls and population norms. Moreover, we found that poorer performance on 6-minute walking test, persistent patient-reported dyspnoea and unemployment were independent predictors of reduced HRQoL. To our knowledge this is the second largest study to compare long-term HRQoL after PE to a control group and the first one to incorporate a validated functional capacity test to a more comprehensive evaluation of HRQoL in PE patients. Despite using a different instrument (EQ-5D-3L versus Short-Form 36), our results of impaired HRQoL after PE, confirms previously published studies.[6,7]

The challenge of quality of life studies is to judge whether identified differences are clinically relevant or not. Across various HRQoL research papers using the EQ-5D instrument, authors have suggested threshold values for minimal (clinical) important difference (MID/MCID), i.e., the least amount of difference suggesting clinical relevance or mandating a change in clinical practice,[22] ranging from 0.04-0.08.[23-25] In our study, the delta EQ-5D index value between study population and buddy controls was 0.11 and between study population and the general population was 0.06. This indicates that we have identified clinically relevant difference in HRQoL between the patients and both control cohorts. Of note, the cut-off value for MID/MCID is various and probably depends on both the disease and valuation sets used. Moreover, because we did not include a longitudinal within-person measurement of QoL, the differences must be interpreted with caution.[26]

Compared to those without dyspnoea, the 46.5% of our study patients who reported persistent dyspnoea performed worse in the 6-minute walking test, objectively verifying this complaint. As for the whole study cohort, both male and female patients walked significantly shorter distance than their gender predicted value. In the multivariable analyses, performance

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on 6-minute walking test and persistent dyspnoea appeared to be independent predictors of worse HRQoL. This may indicate that PE patients suffer from a reduced functional capacity that persists for many years after the event and that the declining functional capacity is one of the main determinants of impaired HRQoL in patients with a history of PE. The finding that patients on average underperformed in the 6-minute walking test may thus be an important explanation for their overall reduced HRQoL. This finding could be further supported by a qualitative study in PE patients revealing that modification of physical activity and exertion (avoidance or reduction) was the commonest behavior change reported by the interviewed patients.[8] Again however, cut-off values for clinical relevant abnormal 6-minute walking test performance regarding PE are lacking which makes it difficult to put the observed results in further perspective. Furthermore, we cannot exclude that this correlation also could be reversed, meaning that the reduced HRQoL is due to the low physical performance.

Numerous studies have shown the beneficial effects of pulmonary rehabilitation in other cardiovascular diseases, resulting in improved functional capacity as well as HRQoL.[27-30] In this context, our findings support the hypothesis that PE patients with persistent dyspnoea and poor functional status may benefit of cardiopulmonary rehabilitation programs.[31]

Although the majority of studies focusing on the long-term effects of PE have not excluded patients with established chronic thromboembolic pulmonary hypertension (CTEPH) diagnosis, there is consistent reporting that approximately half of the patients assessed more than 6 months after experiencing an episode of acute PE complain of dyspnoea, which is also correlated to a decline in physical performance measured by 6-minute walking test.[4,10,32,33] Our results confirm these findings and support the concept of “post-PE syndrome” which has recently been presented as an analogy to PTS, referring to the persistent dyspnoea and reduced functional capacity after PE.[11] The authors discuss

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whether PE could in some cases, CTEPH excluded, be classified as a chronic illness and postulate the “post-PE syndrome” being a state just prior to development of CTEPH. This reasoning is further strengthened by a Danish study reporting overuse of antidepressants in adolescents long after they experienced their first episode of PE.[12] However, whether persistent dyspnoea after PE should be the subject of further standardized work-up including HRQoL questionnaires and 6-minute walking test is still debatable since some studies attribute the high prevalence of dyspnoea to pre-existing comorbidities.[34] The final independent predictor of worse HRQoL in our study was unemployment. Several socio-demographic variables have previously been shown to affect HRQoL, regardless of the underlying disease or condition.[35] The fact that 24% of the study population were unemployed could possibly have contributed to the overall lower HRQoL scores in our patient cohort. Furthermore, we hypothesize that the association between impaired HRQoL and unemployment may be subject to reverse correlation, i.e. impaired HRQoL leading to unemployment. However, due to missing data on other social factors, we could not further investigate this.

Of the predefined determinants being evaluated we found only a selected proportion predictive of worse HRQoL and to our surprise malignancy appeared not to be a significant determinant of HRQoL. Previous studies have found cardiopulmonary disease, active malignancy as well as obesity being independent predictors of HRQoL.[6,36] However, the proportions of these subgroups reported in the aforementioned studies are higher than in ours and presented multivariate regression analysis yielded rather low r^2 percentages indicating the models not being precise.[6] This may indicate, as van Es et al postulate,[7] that in the present study the patients are somewhat healthier and subsequently, perhaps emphasizing the findings regarding the reported differences in HRQoL between study subjects and the general population. Nevertheless, in our view these contradictions exemplify the heterogeneous

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effects of PE as a disease on both HRQoL and physical capacity and consequently rendering cumbersome evaluation of determinants of HRQoL in PE patients.

Limitations

Our study has some limitations. The low response rate may hamper external validity of our results. Moreover, since the final study cohort comprised of one-quarter of the patients being assessed for eligibility a possible bias toward recruitment of patients with more persistent symptoms cannot be ruled out. However, the 6-minute walking test results and proportion reporting dyspnoea in our sample are similar to prior PE follow-up studies,[33,37,38] highlighting that our cohort is a representative PE population. Also, the buddy control group could not be assessed for potential confounders because we did not assess their characteristics. Therefore, we cannot rule out a bias towards “extremely” healthy buddies or poor matching. Furthermore, due to the study’s retrospective design, which carried missing data concerning the index event of the pulmonary embolism we could not classify the PE episode as low or intermediate risk.

The EQ-5D was used based on its simplicity and potential positive influence on patients’ completeness of scores. It could be argued however, that the Short-Form 36 (SF-36) might have been a good choice as well, due to its comprehensiveness and in order to compare our results with previous studies. Lastly, we did not apply a disease specific questionnaire of QoL.

The strongpoints of this study are the sample size and the long term follow up period with 89% of the patients diagnosed with PE more than 1 year prior to inclusion. Furthermore, this study is one of the largest studies presenting a more comprehensive evaluation of HRQoL by reporting all aspects of a generic quality of life questionnaire as well as

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incorporating functional capacity test (6-minute walking test) in order to objectify the findings.

Conclusions

Patients with a history of acute PE were found to have worse HRQoL compared to age- and sex-matched VTE-free buddy controls and population controls. Underperformance and patient-reported dyspnoea were independent predictors of decreased HRQoL. Further studies are necessary to further evaluate the course and determinants of HRQoL after acute PE as well as to interventions aimed at improving HRQoL in these patients.

CONTRIBUTORSHIP STATEMENT

Authors M. Tavoly and W. Ghanima were responsible for study concept, design and data acquisition. M. Tavoly, H.S. Wik and W. Ghanima performed the statistical analyses. M. Tavoly wrote the first draft of the manuscript. All authors were responsible for critical revision of the manuscript, interpretation of the results, had full access to all the data in the study, and take responsibility of the integrity of the data and the accuracy of data analysis.

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COMPETING INTERESTS

The authors state that they have no conflict of interest, except W. Ghanima and L.P. Jelsness-Jørgensen. W. Ghanima reports grants and lecture honoraria from Bayer, Novartis and Roche

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and lecture and advisory board honoraria from Pfizer, Bayer and from Boehringer Ingelheim – none of which is relevant for the submitted work. L.P. Jelsness-Jørgensen reports unrestricted grants from Ferring pharmaceuticals and Tillots pharma, and personal fees from Abbvie, not relevant for the submitted work.

DATA SHARING STATEMENT

No additional data available.

LIST OF ABBREVIATIONS

PTS - post-thrombotic syndrome

DVT - deep vein thrombosis

HRQoL - health-related quality of life

PE - pulmonary embolism

CTEPH - chronic thromboembolic pulmonary hypertension

CTPA - computed tomography pulmonary angiogram

BNP - brain natriuretic peptide

EQ-5D-3L - euroqol-5 dimension-3 level

EQ VAS - euroqol visual analogue scale

VTE - venous thromboembolism

BMI - body mass index

CHF - congestive heart failure

COPD - chronic obstructive pulmonary disease

MID/MCID – minimal important difference/minimal clinical important difference

SD - standard deviation

OR - odds ratio

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MO - mobility

SC - self-care

UA - usual activities

PD - pain and discomfort

AD - anxiety and depression

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Table legends

Table 1	Socio-demographic and clinical characteristics of the study sample.
Table 2	Frequency of patients (n=213) reporting problems in the EQ-5D dimensions, means and medians for EQ VAS and EQ-5D index values. All displayed by age groups.
Table 3	Comparisons of mean EQ-5D index values and EQ VAS between patients vs. Danish population and patients vs. buddy controls.
Table 4	Univariate analysis displaying correlations of the predefined determinants to EQ-5D dimensions and EQ VAS.
Table 5	Multiple binary logistic and standard linear regression models with retained determinants from the univariate analysis for possible independency tested against EQ-5D dimensions and EQ VAS.

Figure legends

Figure 1	Study flow chart.
Figure 2	Proportion of patients, Danish population and buddy controls reporting problems stratified by EQ-5D dimensions.

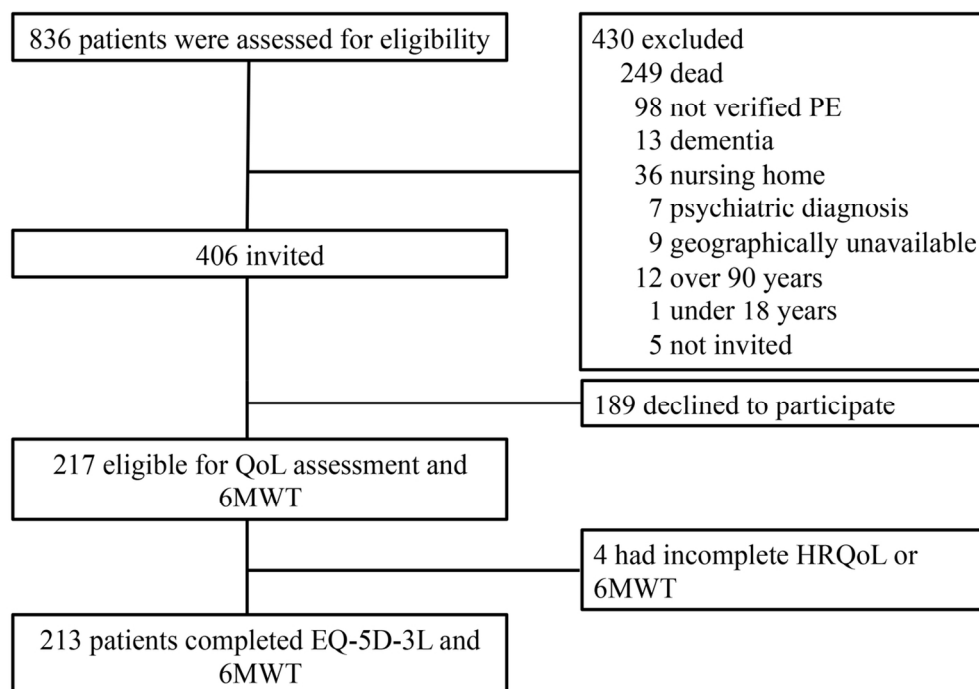


Figure 1. Study flow chart.

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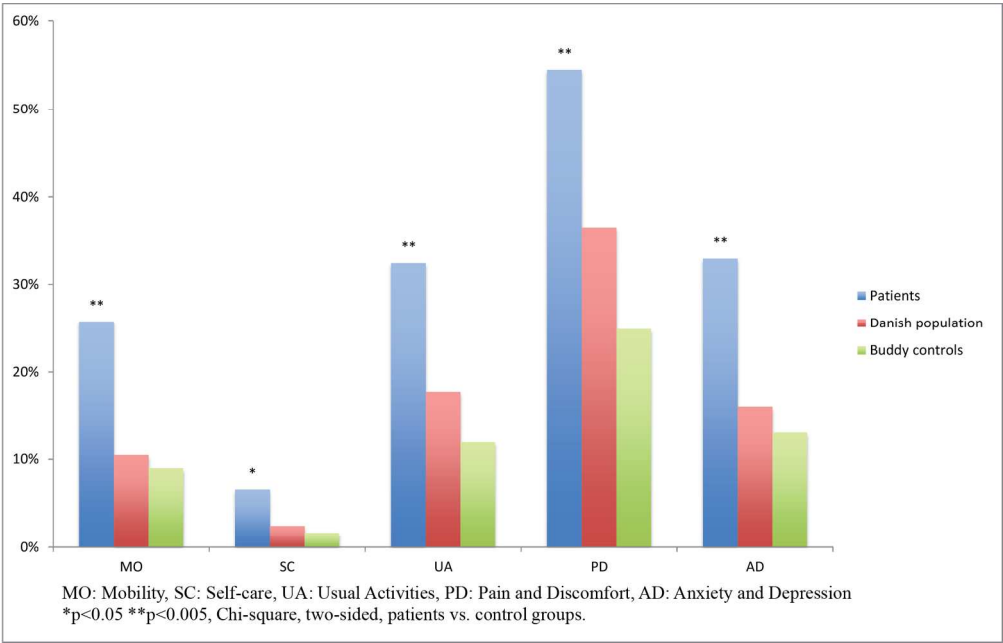


Figure 2. Proportion of patients, Danish population and buddy controls reporting problems stratified by EQ-5D dimensions.

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5, 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	7
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7, 8
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	8
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, explain how matching of cases and controls was addressed	

		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, 10
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	9
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-18
		(b) Report category boundaries when continuous variables were categorized	9-18
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	19
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	22
Generalisability	21	Discuss the generalisability (external validity) of the study results	22
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.