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FULL RESEARCH PAPER
Cardiovascular disease

Burden and long-term impact of pulmonary embolism on health-related quality of life: a matched cohort study

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Aims It has not been conclusively established whether and to what extent pulmonary embolism (PE) affects health-related quality of life (HrQoL). We aimed to assess the long-term independent association of PE with HrQoL to provide reference values for interventional studies and support quantification of the burden of PE in terms of quality- or disability-adjusted life years (QALYs and DALYs).

Methods and results A total of 1005 patients from a prospective multicenter study, followed 3 and 12 months after PE, were successfully matched to 3058 individuals from the general population of the same country based on age, sex, and key comorbidities. Differences between acute PE survivors and matched controls in the ordinal EQ-5D-5L HrQoL dimensions were assessed using multivariable ordinal regression, in the HrQoL index (reflecting overall HrQoL) using multivariable-adjusted mixed linear regression. Both multiple imputation and complete case analysis were performed. Compared with controls, patients reported worse HrQoL in the dimensions self-care, usual activities, and anxiety/depression, and worse HrQoL index at both 3 [adjusted difference −0.04 (95% CI: −0.06, −0.039) in a range from 0 to 1] and 12 months [−0.02 (95% CI: −0.04, −0.01)] in the imputation analysis. Complete case analysis showed similar results. The annual disability weight of PE for DALY calculation was conservatively estimated at 0.03 (95% CI: 0.02, 0.04).

Conclusion PE was independently associated with a moderate decrease in HrQoL, which persisted 12 months after the acute episode despite partial recovery over time. This degree of impairment is comparable to that imposed by several other cardiopulmonary diseases.

Lay summary This study explored the difference in the quality of life between survivors of acute pulmonary embolism in the year after the event and individuals from the general population of the same country (Germany), similar in age, sex, and general health status.

- Survivors of acute pulmonary embolism reported poorer health-related quality of life regarding self-care, usual activities, and anxiety/depression compared to similar individuals from the general population. Pain/discomfort seemed to be of relevance only in the first few months after pulmonary embolism, while mobility was not reduced. The impairment was independent of age, sex, or other coexisting health conditions.

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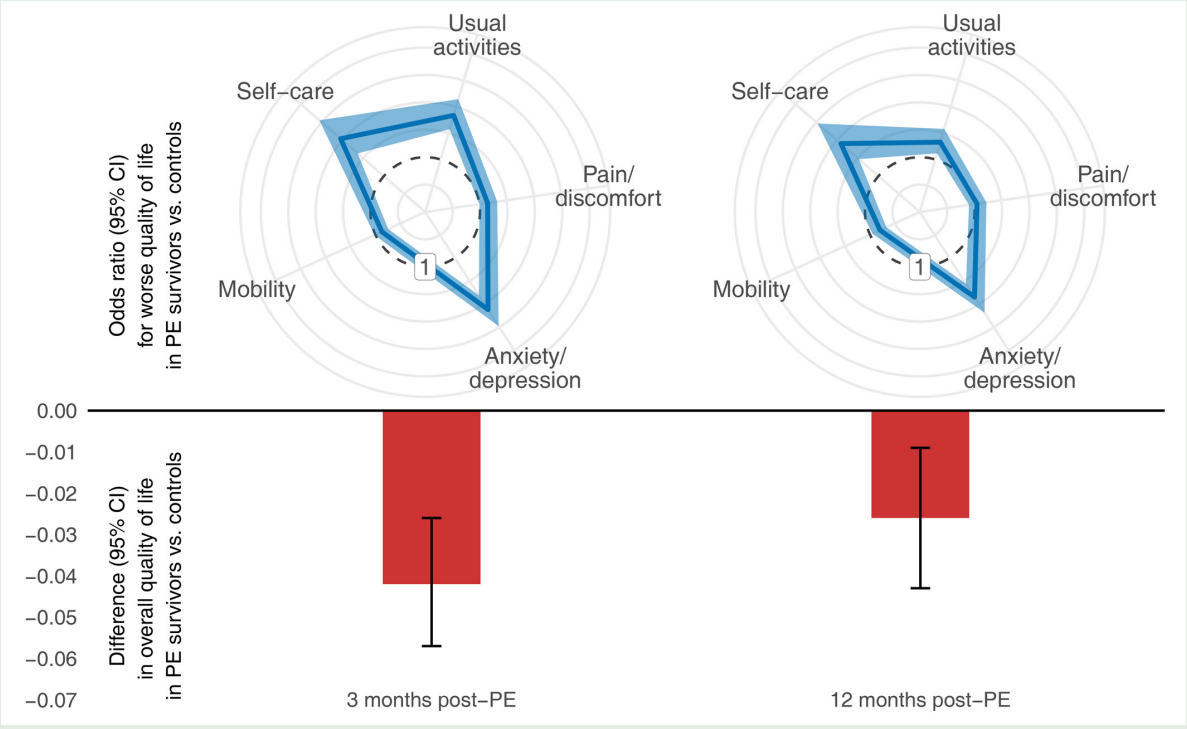
- The reduction of the patients' quality of life after pulmonary embolism is moderate but similar to that seen in some chronic diseases of the heart and the lungs, such as heart failure, asthma, or chronic obstructive lung disease. Despite showing some improvement over time, the difference is still noticeable after 12 months.

Graphical Abstract



Upper panel: radar plots depicting the multi-adjusted odds ratios (with 95% CI) of a worse score (odds ratio higher than 1) in each of the five dimensions of EQ-5D-5L health-related quality of life in 1005 patients three (left) and twelve (right) months after PE compared to 3058 matched population controls. *Lower panel*: bar plots depicting the adjusted difference (with 95% CI) in the EQ-5D-5L index, ranging from 0 (lowest overall quality of life) to 1 (highest overall quality of life), between 1005 patients three (left) and twelve (right) months after pulmonary embolism compared to 3058 matched population controls. PE = Pulmonary Embolism. CI = Confidence interval.

Keywords Pulmonary Embolism • Venous Thromboembolism • Quality of Life • Patient Reported Outcome Measures • Quality-Adjusted Life Years • Disability-Adjusted Life Years • Cost of Illness • Clinical Study • Cohort Studies • Aftercare

Introduction

Venous thromboembolism, and particularly pulmonary embolism (PE), is the third most frequent acute cardiovascular syndrome after myocardial infarction and stroke.[1] Early mortality rates due to PE keep falling.[2,3] However, functional limitation and persisting complaints characterize the long-term clinical course of acute PE survivors.[4–6] These sequelae of PE are in turn responsible for a considerable disease burden on both patients and healthcare systems.[7,8] To this date, however, the existing evidence on the reduction in quality of life attributable to PE is sparse and mostly derived from cohort studies of PE survivors, with no direct comparison with a reference population and no consideration of the impact of other concomitant factors.[9,10] Accounting and adjusting for comorbidities, in particular, is essential. As patients with PE often carry a higher overall cardiovascular risk and include a considerable proportion of individuals with cancer, poorer quality of life may be due to those comorbidities rather than PE itself. In addition, most of the existing data have been obtained from small, selected patient samples, or have not accounted for the time since the occurrence of PE[9,10] despite the fact that post-PE impairment is unlikely to remain constant over time.[6,11]

Accurately assessing the extent and temporal course of the impact of PE on long-term quality of life would provide essential reference values for interventional studies on the long-term outcomes of PE in medicine and public health.[12,13] Moreover, these assessments would enable the derivation of health state weights required for the calculation of Quality-Adjusted (QALYs) or Disability-Adjusted Life Years (DALYs), which are critical metrics for evaluating disease burden. These metrics inform priority setting, resource allocation, and evaluations of potential gains from primary prevention or improved long-term management in healthcare policy and research at both local and international levels.[13–15] The Global Burden of Disease studies have thus far provided no estimate for the QALY or the disability weight (the equivalent weight for DALYs) of venous thromboembolism or PE. Instead, previous studies used as a proxy the disability weight of diseases considered 'roughly similar', e.g. chronic obstructive pulmonary disease.[16]

We sought to quantify the impact of PE on health-related quality of life (HrQoL) in the year after the acute event and estimate a one-year QALY weight and disability weight in a matched cohort study comparing prospectively followed patients to control individuals with a similar demographic and comorbidity profile from the general population.

Methods

Study design and study population

We carried out a matched cohort study using a prospectively followed exposed population and controls from a cross-sectional survey. The patients followed up after PE from the FOllow-up after aCUte pulmonary emboliSm (FOCUS) study were used as exposed individuals. The FOCUS study has been described earlier.[17,18] In brief, this was a prospective observational study including consecutive unselected patients aged ≥18 years with a confirmed diagnosis of acute symptomatic PE, enrolled at 17 large-volume centres across Germany between 2014 and 2018 and followed up over 2 years with a predefined visit plan (3, 12, and 24 months). As the study question of the present analysis focused on the year after PE, the HrQoL at the 3-month and the 12-month visits were used. The study population consisted of the patients who survived at least until the first possible opportunity for assessment of quality of life, the 3-month follow-up visit. There were a total of 1005 patients after the exclusion of 12 patients who died between discharge and that visit. The rationale for this restriction was that, in the context of the calculation of QALYs and DALYs, the QALY weight and, in particular, the disability weight refer to *years lived with disability*, in contrast to *years of life lost,* which separately account for loss of life due to premature death. Therefore, early deaths, before a decrease in HrQoL could take place, should not contribute to the weights, but would still be accounted for by the component *years of life lost* of QALYs and DALYs.

The population from which matched control individuals were drawn consisted of 5005 individuals representative of the German adult (≥18 years) population.[19,20] In brief, data collection took place from March to April 2014 in a cross-sectional phone survey. Representativeness of the German general adult population was ensured by selecting telephone numbers randomly from a sample of registered telephone numbers proportional to the federal state residential structures, stratified by community size.[20] A sampling frame designed for telephone surveys was used, allowing for the representative selection of individuals living in German regions or urban districts and within private households.[21] The person to be interviewed in the private household was determined by the Kish selection grid.[22] Inclusion criteria of the telephone interview were being German-speaking and above the age of 18. The response rate of the survey was 47%. Additional details on this population sample can be found elsewhere.[23]

Study outcomes

Generic HrQoL was assessed in both study populations using the extensively validated EQ-5D-5L system.[24] The system consists of five items, each exploring one HrQoL dimension: Mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Each item is answered by selecting one of five ordered functional levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. For each individual, the combination of the five answers (with the five ordinal levels of each answer encoded 1 to 5 and a total of 3125 possible permutations) corresponds to their health state or profile and is mapped, using externally validated country-specific value sets reflecting cultural differences, to a single numeric value (*index* or *utility*) indicating overall HrQoL. For the present study, the 2018 German value sets were used.[25] The utility lies on a scale anchored by the values 1 (indicating full health) and 0 (indicating death). While the utility cannot take a value higher than 1, values less than 0 are rare but possible for health states considered to be 'worse than death' (down to −0.661).[24] In the patient population (FOCUS), the EQ-5D-5L of the 3- and the 12-month visits were used; in the control population, we used the single EQ-5D-5L obtained in the survey. Because the research question does not require reference values from control individuals after a specific event, but only similarity of the controls to the exposed patients in several characteristics *except* the recent diagnosis of PE, the repeated measures of HrQoL from the exposed patients were compared to the single cross-sectional assessment in the control population.

Matching procedure

Matching was conducted using cardinality matching.[26] Given a set of individuals exposed to a treatment or risk factor (here: acute PE), and a set of individuals unexposed to it, this iterative matching method identifies the largest possible number of individuals in the unexposed population that delivers a balanced set (a similar distribution) with respect to a given number of variables of interest other than the exposure. Cardinality matching achieves high covariate balance and reduces residual confounding at least as efficiently as propensity score matching, while offering some advantages: it tends to return larger sample sizes; retains all exposed individuals, thus preserving representativeness; and imposes fewer constraints on subsequent analysis (such as the need for conditional regression), thus permitting flexible modelling approaches including mixed-effects regression.[26,27] For the present analysis, the matching variables included sex, age, cardiovascular disease (defined as history of myocardial infarction, heart failure, stroke, or arterial hypertension), chronic pulmonary disease, diabetes, and cancer. These comorbidities were documented by the investigators in the patient (FOCUS) population and self-reported in the control population. More details on the matching procedure are provided in the *Supplementary Material*.

Statistical analysis

The first part of the analysis investigated the association between PE and each one of the five EQ-5D-5L dimensions in their original five-point ordinal scale using ordinal logistic regression. Because the proportional odds assumption was not met for all items in a single mixed model including both measurements (3 and 12 months post-PE) in the FOCUS patients, for each dimension, two separate models were run against the population controls for the 3-month and the 12-month post-PE values, respectively. The model was additionally adjusted for all matching variables as recommended, accounting for the increase in age across the two assessments of post-PE patients.[28]

The second part of the analysis focused on the association of PE with the continuous EQ-5D-5L index using a linear model with a random intercept accounting for the two repeated measures in the post-PE patients.[29] To obtain the required contrasts (3 months post-PE vs. controls and 12 months post-PE vs. controls), the main exposure (PE) was modelled as a categorical variable with the controls' measurement as the reference level and the 3-month and 12-month measurements among post-PE patients as indicator levels. The model was additionally adjusted for all matching variables.[28]

The *utility weight* or *HrQoL weight* is a value anchored from 0 (death) to 1 (full health) used in the calculation of QALYs.[30] An annualized utility weight can be obtained from a difference β_{annual} in a HrQoL index, such as the EQ-5D-5L index, for a health state relative to a reference over 1 year; in the present analysis, in post-PE patients vs. controls. We estimated β_{annual} using an average of the coefficients for 3 and 12 months obtained from the multivariable mixed linear regression, each weighted by the previous fraction of year in months to obtain a conservative estimate, according to the formula $\beta_{annual} = \frac{3}{12}\beta_{3\,m} + \frac{9}{12}\beta_{12\,m} = \frac{1}{4}\beta_{3\,m} + \frac{3}{4}\beta_{12\,m}$.[31] This estimate is conservative because the *end-period* coefficient (β_{3m} and β_{12m}) was used to weight each period, despite the fact that HrQoL was highest at the end of the period than during it (as HrQoL increased over time), thus underestimating the loss in HrQoL among patients. In contrast to a utility weight, a *disability* weight, used to calculate DALYs, is anchored from 0 (full health) to 1 (death).[30] While the current standard method to obtain disability weights requires discrete choice experiments for valuation of alternative health states, *disutility* (defined as *1—utility weight*) can be used as a rough estimate of a disability weight.[30,32–34] Further details on the calculation of the annual coefficients and the corresponding 95% confidence interval are provided in the *Supplementary material*.

Table 1 Characteristics of survivors of pulmonary embolism and controls from the general population before and after cardinality matching

Before matching	PE survivors ($N = 1005$)	Population controls ($N = 5005$)	SMD
Age (years), median (IQR)	64 (51, 74)	56 (42, 70)	0.42
Women, *n*/*N* (%)	458 (45.6)	2666 (53.3)	−0.15
Cardiovascular disease, *n*/*N* (%)	585 (58.2)	1705 (34.1)	0.49
Diabetes, *n*/*N* (%)	111 (11.0)	540 (10.8)	0.01
Chronic pulmonary disease, *n*/*N* (%)	156 (15.5)	809 (16.2)	−0.02
Cancer, *n*/*N* (%)	102 (10.1)	474 (9.5)	0.02
After matching	**PE survivors ($N = 1005$)**	**Population controls ($N = 3058$)**	**SMD**
Age (years), median (IQR)	64 (51, 74)	63 (51, 74)	0.05
Women, *n*/*N* (%)	458 (45.6)	1469 (48)	−0.05
Cardiovascular disease, *n*/*N* (%)	585 (58.2)	1705 (55.8)	0.05
Diabetes, *n*/*N* (%)	111 (11.0)	385 (12.6)	−0.05
Chronic pulmonary disease, *n*/*N* (%)	156 (15.5)	496 (16.2)	0.00
Cancer, *n*/*N* (%)	102 (10.1)	355 (11.6)	−0.05

Counts are averages of 40 multiply imputed datasets, medians (IQR), and proportions refer to the multiply imputed datasets as a whole.
PE, Pulmonary embolism; IQR, interquartile range; SMD, standardized mean difference.

Multiple imputation

In the cohort of population controls, only 17/5005 (0.3%) individuals displayed missing values in variables required for the analysis. In the FOCUS cohort, the EQ-5D-5L index could be calculated at neither the 3-month nor the 12-month visit in 91/1005 (9.1%) patients due to a missing visit or availability of fewer than all 5 items of the EQ-5D-5L instrument. The association of baseline variables with missing index is displayed in Supplementary material online, *Table S2*. Assuming missingness at random (MAR), multivariate imputation by chained equations was conducted.[35] The five EQ-5D-5L items were imputed individually. The imputation model included all variables used in the final analysis as well as additional auxiliary variables listed in the *Supplementary Material*. To incorporate the HrQoL of patients who were alive for at least 3 months but died during follow-up, a total of 26/1005 (2.6%) deaths between the 3rd and 12th months of follow-up in FOCUS were included in the imputation model by using a dummy indicator for death[35]; and in order to prevent imputed HrQoL after death from affecting the analysis (as deaths should not contribute to the utility or the disability weight), only imputed HrQoL measurements *before* death were considered in the subsequent analysis. A total of 40 multiply imputed datasets were generated, and results were pooled using Rubin's rules. Further details on the multiple imputation procedure and diagnostics are given in the *Supplementary Material*. A complete case analysis (CCA) was conducted as an additional analysis.

Categorical variables are presented as frequencies and percentages, and continuous variables as medians with interquartile range. Two-tailed *P*-values < 0.05 were considered significant. R version 4.4.1 with the packages *MatchIt* (version 4.5.5), *mice* (version 3.16.0), and *MatchThem* (version 1.2.1) were used for data analysis.

Ethics approval and registration

The FOCUS study was approved by the central ethics committee of Rhineland-Palatinate with number 837.137.14 (9376-F; dated 10 June 2014), and by the ethics committees of the participating sites. FOCUS was registered with the German Clinical Trials registry (DRKS00005939). Written informed consent was obtained from all FOCUS participants.

The data collection from the German general adult population through the phone survey was submitted to the local ethics committee, which did not consider an ethics vote to be required and did not mandate written informed consent; the study was not registered in advance.

Results

Study populations

The characteristics of the source populations (before matching) of 1005 post-PE patients and 5005 population controls are shown in the upper part of *Table 1*. Compared with the population controls, post-PE patients were older, more frequently women, and more often affected by cardiovascular disease, as reflected by higher standardized mean differences in these variables. The proportion of individuals reporting problems in each of the five EQ-5D-5L dimensions was consistently higher among the patients 3 months after PE than among population controls; the difference was less pronounced 12 months after PE (*Table 2*). The distribution of the values in the complete cases and the imputed data is reported in Supplementary material online, *Figure S1*.

Matching was successful, as it retained all 1005 post-PE patients in the analysis and identified 3058/5005 of the population controls with no residual imbalance, as shown by the standardized mean differences <0.1 in all covariates (lower part of *Table 1*). The mean EQ-5D-5L index in PE survivors 3 months after PE was 0.82 (95% CI: 0.80, 0.83), 12 months after PE 0.84 (95% CI: 0.82, 0.85); in the matched controls, 0.86 (95% CI: 0.85, 0.87). Its distribution is depicted in Supplementary material online, *Figure S2*. Additional details on the imputation and the diagnostics of the matching procedure are provided in the *Supplementary Material*.

Association of PE with the individual EQ-5D-5L dimensions

The results of the multivariable ordinal regression models for the association of PE either 3 or 12 months after the acute event (compared with the population controls) with the HrQoL dimensions are shown in *Figure 1* and *Table 3*. Post-PE patients reported worse HrQoL than population controls, with a chance of a worse level approximately twice as high at 3 months and slightly lower at 12 months, in the dimensions self-care, usual activities, and anxiety/depression. In these dimensions, PE affected HrQoL to a degree at least as high as female sex, 10 years of age,

Table 2 Reported problems in the EQ-5D-5L health-related quality of life dimensions in the original populations of post-pulmonary embolism patients and controls from the general population

	PE survivors ($N = 1005$)		Population controls
	3 months	12 months	($N = 5005$)
Mobility	345/872 (39.9%)	252/734 (34.3%)	1858/5002 (37.1%)
Self-care	148/875 (16.9%)	100/736 (13.6%)	377 (7.5%)
Usual activities	393/875 (44.9%)	265/735 (36.1%)	1409 (28.2%)
Pain/discomfort	528/872 (60.6%)	413/733 (56.3%)	2854/5003 (57.0%)
Anxiety/depression	356/873 (40.8%)	273/738 (37.0%)	1213/5003 (24.2%)

Proportions of individuals reporting any of the four levels other than 'No problems' are shown A denominator different from the column total reflects the presence of missing data. Percentages are column percentages of non-missing values. PE, Pulmonary embolism.

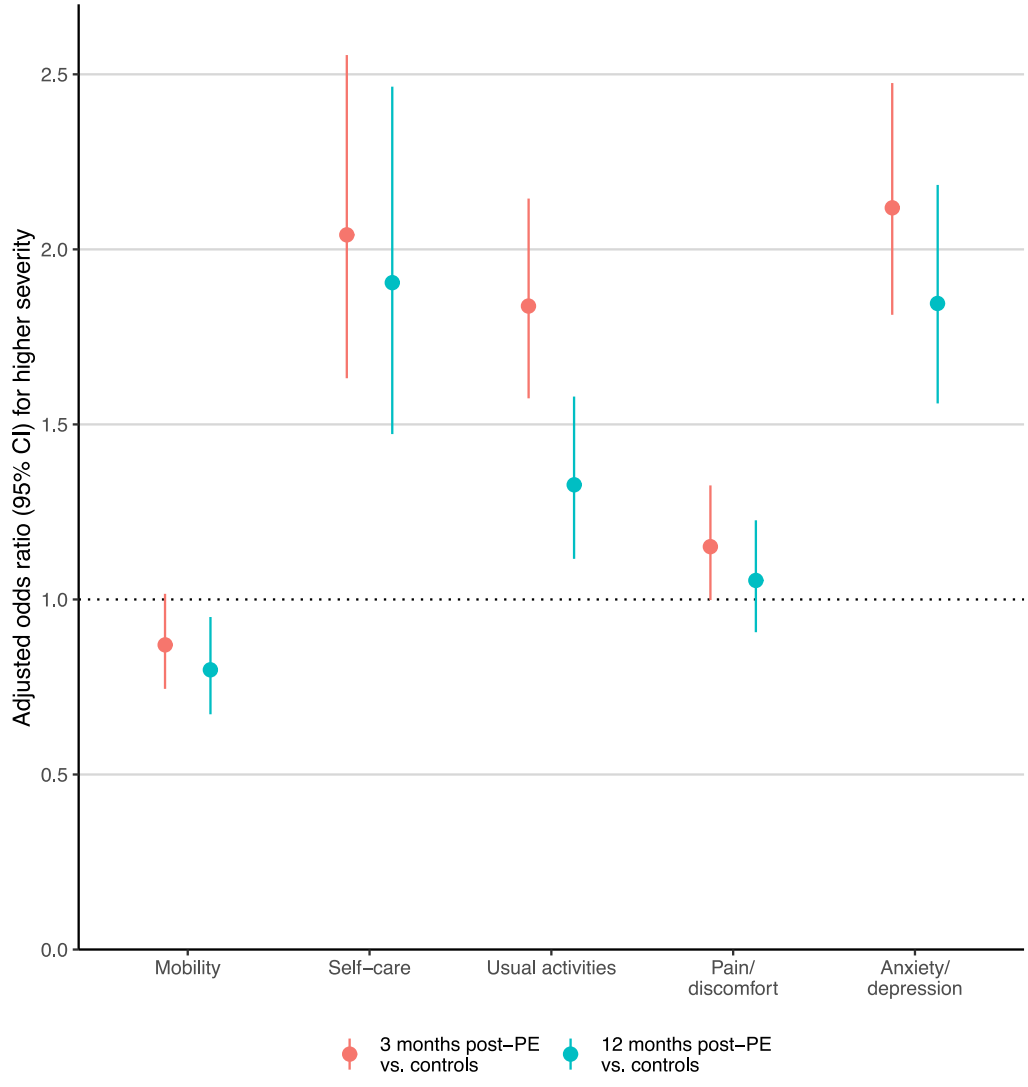


Figure 1 Adjusted odds ratios from the multivariable ordinal logistic regressions for EQ-5D-5L dimension-specific health-related quality of life 3 and 12 months after pulmonary embolism compared to matched population controls. Dots represent the point estimates of odds ratios, lines their 95% confidence interval. Adjusted odds ratios >1.0 represent higher odds of a higher level (worse health-related quality of life) in each EQ-5D-5L dimension in patients, either 3 months or 12 months after pulmonary embolism, relative to controls, while holding other variables constant. The models for either time point were adjusted for the matching variables age, sex, cardiovascular disease, diabetes, chronic pulmonary disease, and cancer. PE = pulmonary embolism.

Table 3 **Multivariable-adjusted ordinal logistic regressions of the association of the score in each EQ-5D-5L dimension with 3-month or 12-month post-pulmonary embolism status, respectively, vs. matched population controls**

	Mobility Adj. OR (95% CI)	Self-care Adj. OR (95% CI)	Usual activities Adj. OR (95% CI)	Pain/discomfort Adj. OR (95% CI)	Anxiety/depression Adj. OR (95% CI)
Three months post-PE (vs. controls)	0.87 (0.74, 1.02)	**2.04 (1.63, 2.56)**	**1.84 (1.57, 2.15)**	1.15 (1.00, 1.33)	**2.12 (1.81, 2.48)**
Age (+ 10 years)	**1.36 (1.30, 1.42)**	**1.35 (1.24, 1.46)**	**1.09 (1.04, 1.14)**	**1.09 (1.05, 1.13)**	**0.91 (0.88, 0.96)**
Women	**1.30 (1.14, 1.49)**	**1.41 (1.15, 1.73)**	**1.50 (1.31, 1.72)**	**1.46 (1.29, 1.64)**	**1.78 (1.55, 2.06)**
Cardiovascular disease	**1.70 (1.47, 1.95)**	**1.74 (1.36, 2.22)**	**1.83 (1.58, 2.12)**	**1.66 (1.46, 1.89)**	**1.52 (1.29, 1.78)**
Diabetes	**1.91 (1.58, 2.29)**	**1.85 (1.44, 2.39)**	**1.71 (1.41, 2.07)**	**1.39 (1.15, 1.68)**	1.14 (0.92, 1.41)
Chronic pulmonary disease	**2.01 (1.69, 2.39)**	**2.57 (2.03, 3.25)**	**1.93 (1.63, 2.30)**	**1.69 (1.43, 1.99)**	**1.37 (1.13, 1.66)**
Cancer	1.19 (0.97, 1.45)	1.26 (0.95, 1.68)	**1.39 (1.13, 1.70)**	1.20 (0.98, 1.47)	1.16 (0.92, 1.46)
	Mobility Adj. OR (95% CI)	**Self-care Adj. OR (95% CI)**	**Usual activities Adj. OR (95% CI)**	**Pain/discomfort Adj. OR (95% CI)**	**Anxiety/depression Adj. OR (95% CI)**
Twelve months post-PE (vs. controls)	**0.80 (0.67, 0.95)**	**1.90 (1.47, 2.46)**	**1.33 (1.12, 1.58)**	1.05 (0.91, 1.23)	**1.85 (1.56, 2.18)**
Age (+ 10 years)	**1.38 (1.31, 1.44)**	**1.33 (1.23, 1.45)**	**1.12 (1.07, 1.17)**	**1.11 (1.07, 1.16)**	**0.92 (0.88, 0.97)**
Women	**1.42 (1.25, 1.63)**	**1.31 (1.06, 1.62)**	**1.49 (1.30, 1.72)**	**1.47 (1.30, 1.66)**	**1.69 (1.47, 1.95)**
Cardiovascular disease	**1.66 (1.44, 1.92)**	**1.91 (1.47, 2.47)**	**1.82 (1.57, 2.12)**	**1.67 (1.47, 1.91)**	**1.45 (1.23, 1.70)**
Diabetes	**2.09 (1.73, 2.52)**	**1.82 (1.41, 2.35)**	**1.70 (1.48, 2.18)**	**1.38 (1.15, 1.66)**	1.07 (0.86, 1.34)
Chronic pulmonary disease	**2.11 (1.77, 2.51)**	**2.44 (1.91, 3.11)**	**1.94 (1.63, 2.31)**	**1.66 (1.40, 1.97)**	**1.41 (1.15, 1.74)**
Cancer	1.19 (0.96, 1.47)	1.32 (0.96, 1.81)	**1.29 (1.05, 1.60)**	1.21 (0.99, 1.50)	1.24 (0.98, 1.58)

Pooled results of two regression models, one per time point (3 months post-PE vs. controls, 12 months post-PE vs. controls), from 40 multiply imputed datasets. Odds ratios >1.0 represent higher chances of a worse health-related quality of life in each E5-5D-5L dimension in the condition described by the explanatory variable, while holding other variables constant. Each odds ratio is adjusted for all other variables in the table.
PE, Pulmonary embolism; Adj. OR, Adjusted odds ratio; CI, confidence interval; Bold faced values indicate $P < 0.050$.

Table 4 Multivariable-adjusted linear mixed model of the difference in EQ-5D-5L index (utility or overall health-related quality of life) between patients 3 or 12 months post-PE and matched population controls

N = 4063	EQ-5D-5L index Adj. *β* (95% CI)	*P*-value
Exposure		
Controls	Ref.	
3 months post-PE	−0.04 (−0.06, −0.03)	<0.001
12 months post-PE	−0.03 (−0.04, −0.01)	0.002
Age (+ 10 years)	−0.01 (−0.02, −0.01)	<0.001
Women (vs. men)	−0.05 (−0.07, −0.04)	<0.001
Cardiovascular disease	−0.04 (−0.06, −0.03)	<0.001
Diabetes	−0.06 (−0.08, −0.03)	<0.001
Chronic pulmonary disease	−0.09 (−0.11, −0.07)	<0.001
Cancer	−0.03 (−0.05, −0.003)	0.026

Negative β coefficients indicate worse overall generic health-related quality of life as estimated by the EQ-5D-5L index (with a maximum of 1 for full health).
Pooled results of 40 multiple imputations of a cohort of 1005 patients and an average of 3058 matched controls. Repeated measures (at 3 and 12 months) in post-PE patients are modelled using random intercepts. Each coefficient is adjusted for all other variables in the table.
PE, pulmonary embolism; Adj. , multivariable-adjusted; CI, confidence interval.

cardiovascular disease, and chronic pulmonary disease, with the exception of an inverse correlation between age and anxiety/depression. Cancer only affected usual activities. In contrast to the other comorbidities, PE affected the dimension pain and discomfort only after 3 months, while mobility was not impaired either 3 or 12 months after PE.

Association of PE with overall health-related quality of life and disability weight

The results of the multivariable mixed linear model for the difference in EQ-5D-5L index (utility or overall HrQoL) between post-PE patients and matched population controls are shown in *Table 4*. After adjusting for the matching covariates, post-PE patients reported worse overall HrQoL at both 3 (−0.04 on the utility scale; 95% CI: −0.06 to −0.03) and, to a lesser extent, 12 months (−0.03, 95% CI: −0.04 to −0.01). The association of PE with HrQoL was similar to that of female sex, cardiovascular disease, diabetes, and cancer, but lower than that of chronic pulmonary disease. Using the conservative approach detailed in *Methods*, the annual utility weight was estimated as $1+\beta_{annual}=1+\frac{1}{4}\beta_{3\,m}+\frac{3}{4}\beta_{12\,m}=0.97$ (95% CI: 0.96, 0.98) and the corresponding annual disability weight as 1–0.97 = 0.03 (95% CI: 0.02, 0.04).

Complete case analysis

Of the 1005 patients, 914 patients had at least one calculable utility either at 3 (861/1005, 85.7%) or 12 (724/1005, 72.0%) months and complete baseline variables, and could therefore be included in a mixed linear model; of the 5005 controls, 4998 had no missing variables (see Supplementary material online, *Table S3*). Cardinality matching selected 3033 controls and retained all 914 patients, with good covariate balance (see Supplementary material online, *Table S4*). The multivariable ordinal regressions on the individual dimensions returned odds ratios with direction, strength of association, and confidence intervals similar to the multiple imputation (see Supplementary material online, *Table S5*). The mixed linear model on the EQ-5D-5L index also showed similar results to the multiple imputation analysis, with the same point estimate for the 3-month difference (−0.04, 95% CI: −0.06, −0.03) and a slightly lower one for the 12-month difference (−0.02, 95% CI: −0.04 to −0.01; Supplementary material online, *Table S6*).

Discussion

In this analysis of survivors of PE and matched population controls, generic HrQoL in the year after PE was worse among PE survivors in the dimensions of usual activities, self-care, and anxiety/depression. Overall, HrQoL was poorer in patients both 3 and, to a lesser extent, 12 months after PE (*Graphical Abstract*). Based on the multi-adjusted difference in the EQ-5D-5L index (utility or overall HrQoL) between patients and controls, the annual utility weight imposed by PE was conservatively estimated at 0.97 (95% CI: 0.96, 0.98).

The management of PE extends beyond the risk of early death and encompasses the late and/or long-lasting consequences among survivors. A considerable proportion of patients have been found to report impaired quality of life or functional status in the months or even years after PE. This observation led to the concept of the disease continuum known as post-PE syndrome.[5] Until now, solid evidence on the extent and persistence of the impact of PE on quality of life was largely missing. Existing reports on this topic assessed quality of life after PE (i) by comparing patients with externally derived population reference values rather than individual controls; and (ii) with little regard to the comorbidity profile of the population of survivors of PE. It is thus still difficult to conclude whether a low quality of life is due to the PE itself or rather to the concomitant diseases. Moreover, the course of quality of life at fixed consecutive time points after PE has not thus far been assessed, preventing the establishment of time-specific reference values or annual profiles.

Two smaller studies have thus far compared generic HrQoL in PE survivors with individual controls. In a cross-sectional study conducted in Norway, the difference in EQ-5D-3L (a previous version of the EQ-5D instrument) index between patients assessed several months to years after PE and age-matched buddy controls was −0.11, using Danish value sets for the calculation of the index since Norwegian ones were unavailable.[9] In a study on patients with any form of venous thromboembolism (either deep vein thrombosis or PE) from the Netherlands and the United States, restricted to patients older than 70 years and without cancer, HrQoL as assessed by the physical and mental component summaries of the SF-36 instrument was found to be lower in patients than in population controls both shortly after venous thromboembolism and 12 months later.[36]

In an attempt to provide a reasonably accurate overview of the independent association of PE with subsequent HrQoL, our study was based on (i) an unselected population of PE survivors; (ii) assessment of HrQoL at fixed times after PE; (iii) use of the EQ-5D-5L version of the EuroQoL instrument [with some improvements in performance over the EQ-5D-3L]; (iv) a substantial sample size and limited loss to follow-up; (v) both matching and adjustment for relevant comorbidities; (vi) random selection of individual controls from a representative sample of the same country as the patients; and (vii) multiple imputation to address possible survival bias due to the longitudinal design.

The adjusted difference in EQ-5D-5L utility between patients 12 months after PE and controls in our complete case analysis is in agreement with the estimate of 0.02 (95% CI: 0.00, 0.03) obtained in a different European cohort, the PREFER registry. That study used an indirect method (comparison with population reference values) in a similar complete case analysis with exclusion of patients with cancer

or death during follow-up.[7] The fact that the estimate obtained using multiple imputation in the present study was, at least numerically, slightly higher despite matching and multivariable adjustment supports the notion that these methodological improvements may have corrected some underestimation from survival bias affecting complete case analyses in this and previous studies on long-term follow-up after PE.

Our adjusted estimates of the utility decrement associated with PE may support health economic modelling and policy decisions. In cost-effectiveness analyses, an adjusted utility decrement may be used to estimate the marginal QALY gains in Markov models, such as those deriving from interventions that prevent PE, or to conduct conservative sensitivity analyses alongside unadjusted utility weights derived from standard methods. In public health policy, our estimates can inform estimations of the net utility gain of treatments in multimorbid or older patient populations, and compare the benefits at different time points.[37]

Direct comparisons of the disability weight that we estimated using disutility derived from the EQ-5D-5L index (a measure of utility) with those available for other diseases should be made with caution. Disability weights are sensitive to the preferences of the study population that produced them, and a weight derived from disutility cannot be directly compared to disability weights derived using specific valuation methods.[38,39] With this in mind, and limiting comparisons to European populations, the estimated disability weight of 0.03 (95% CI: 0.02, 0.04) is roughly comparable in its order of magnitude to mild forms of other cardiovascular diseases such as mild heart failure,[40] or respiratory diseases such as mild to moderate asthma[40,41] or mild chronic obstructive pulmonary disease.[40] Of note, our estimates cannot be compared with previous estimates of minimal clinically important differences (MCIDs) for EQ-5D-5L disutilities. MCIDs are specific to diseases, and no reference values exist for patients with PE.[42,43] In any case, the differences in HrQoL and disability weight that we provide represent a minimal, conservative estimate for the following reasons: first, the EQ-5D-5L index is affected by the relative weight attributed by a population to each EQ-5D-5L dimension and specific combinations of values, and a moderate overall utility impairment does not exclude considerable impairment of single HrQoL dimensions as seen in our study.[29,44] Second, the differences that we found are global estimates for a heterogeneous population, covering a broad disease spectrum ranging from asymptomatic patients to substantially affected ones over the long term.[5,18] Third, the differences in HrQoL may have been underestimated due to (i) the possible presence of patients recovering from PE among the general population controls, which would dilute the difference between exposed patients and controls; (ii) known paradox effects due to rescaling of HrQoL perception occurring after an acute event[45]; or (iii) improvements of lifestyle and self-care after hospital discharge among post-PE patients.

Some limitations should be noted. First, the comorbidities in the control population were self-reported, whereas in the exposed population, they were documented by the medical investigators. Thus, some degree of misclassification bias cannot be ruled out. Second, residual confounding by unmeasured variables cannot be excluded. In particular, it was not possible to account for post-discharge events or to adjust for the patients' socio-economic status.[8] However, variables with known association with socio-economic status, including smoking status and German State of residence were included as auxiliary variables in the multiple imputation model. Third, as previous studies suggested a non-linear course of generic health-related and disease-specific quality of life in the year after PE,[6,11] future prospective studies including more time points may lead to a more precise estimate of the disability profile over time.

In conclusion, PE results in a measurable impairment of quality of life that persists over at least 1 year, predominantly affecting the domains of usual activities, self-care, and anxiety/depression. These findings substantiate the long-term consequences of PE, underscoring the importance of incorporating this lasting impact into assessments of disease burden at the population level, estimates of potential gains from primary prevention, and evaluation of management interventions aimed at improving outcomes in PE survivors.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Authors' contributions

L.V. conceptualized and conducted the statistical analysis and wrote the original draft. A.C.M. verified the methods used in the existing literature and previous findings across all manuscript drafts. I.T.F. contributed to the initial concept of the study, the identification of the control population, and manuscript editing. C.A. contributed to the selection of the methods, to the statistical analysis, and to the development of the manuscript. T.N., K.M., K.C.C., L.H., K.K., and S.B. supported the development of the methods and critically reviewed the manuscript. T.G. and A.K. curated the data management of the control population, supported data management, and reviewed the final manuscript. S.V.K. supported conceptualization and was responsible for resource provision, supervision, and editing the original draft. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Data availability

Proposals for access to the FOCUS study data will be considered by the FOCUS Steering Committee in accordance with the data access policy of the study sponsor (University Medical Centre Mainz, Germany).

The data sets of the representative sample of the German general adult population generated and/or analysed during the current study are not

publicly available due to ethical and confidentiality concerns. A proposal to access can be submitted to the Department of Health Economics and Health Services Research, University Medical Center Hamburg-Eppendorf.

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