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CLINICAL RESEARCH
Clinical trials

Chronic thromboembolic pulmonary hypertension and impairment after pulmonary embolism: the FOCUS study

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Aims To systematically assess late outcomes of acute pulmonary embolism (PE) and to investigate the clinical implications of post-PE impairment (PPEI) fulfilling prospectively defined criteria.

Methods and results A prospective multicentre observational cohort study was conducted in 17 large-volume centres across Germany. Adult consecutive patients with confirmed acute symptomatic PE were followed with a standardized assessment plan and pre-defined visits at 3, 12, and 24 months. The co-primary outcomes were (i) diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH), and (ii) PPEI, a combination of persistent or worsening clinical, functional, biochemical, and imaging parameters during follow-up. A total of 1017 patients (45% women, median age 64 years) were included in the primary analysis. They were followed for a median duration of 732 days after PE diagnosis. The CTEPH was diagnosed in 16 (1.6%) patients, after a median of 129 days; the estimated 2-year cumulative incidence was 2.3% (1.2–4.4%). Overall, 880 patients were evaluable for PPEI; the 2-year cumulative incidence was 16.0% (95% confidence interval 12.8–20.8%). The PPEI helped to identify 15 of the 16 patients diagnosed with CTEPH during follow-up (hazard ratio for CTEPH vs. no CTEPH 393; 95% confidence interval 73–2119). Patients with PPEI had a higher risk of re-hospitalization and death as well as worse quality of life compared with those without PPEI.

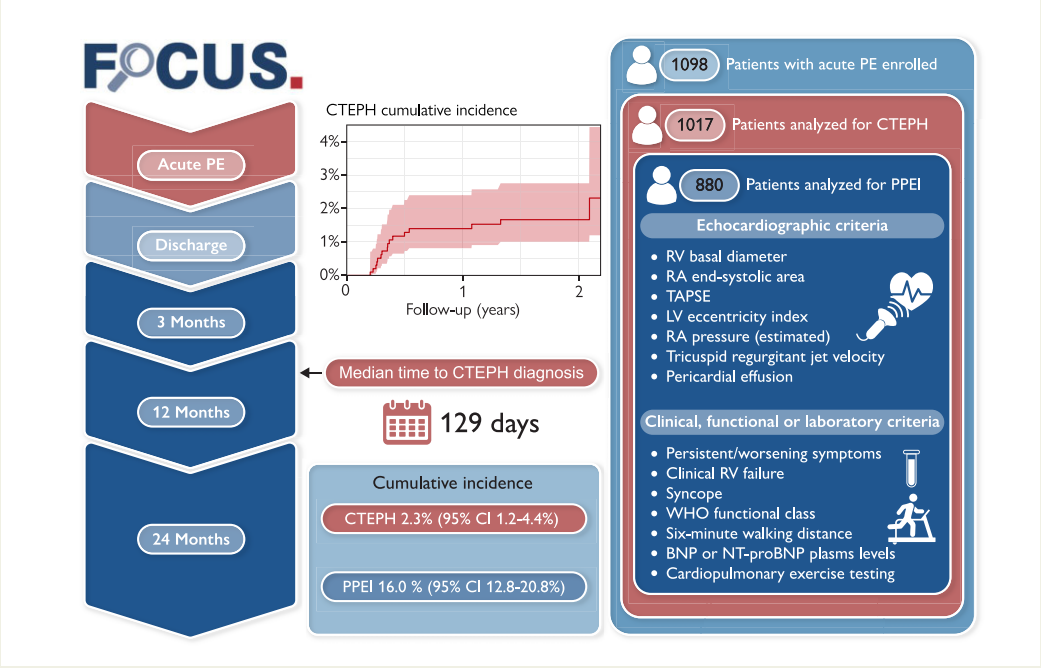
Conclusion In this prospective study, the cumulative 2-year incidence of CTEPH was 2.3%, but PPEI diagnosed by standardized criteria was frequent. Our findings support systematic follow-up of patients after acute PE and may help to optimize guideline recommendations and algorithms for post-PE care.

Structured Graphical Abstract

Key Question
What are the frequency and implications of echocardiographic, clinical, functional or laboratory impairment after acute PE?

Key Finding
Post-PE impairment was frequent and associated with CTEPH, death, hospitalization, and decreased quality of life.

Take Home Message
Systematic follow-up after acute PE using standardized criteria may help to early identify impairment & optimize patient care.



Design and main results of the FOllow-up after aCUte pulmonary emboliSm (FOCUS) study. BNP, brain natriuretic peptide; CTEPH, chronic thromboembolic pulmonary hypertension; LV, left ventricular; NT-proBNP, N-terminal probrain natriuretic peptide; PE, pulmonary embolism; PPEI, post-pulmonary embolism impairment; RA, right atrial; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; WHO, World Health Organization.

Keywords Pulmonary embolism • Follow-up • Functional impairment • Chronic thromboembolic pulmonary hypertension

Introduction

Until recently, management of pulmonary embolism (PE) has concentrated mainly on reducing the risk of early (30-day or in-hospital) death,[1] which depends on the clinical severity of the index episode, comorbidity, and the presence of acute right ventricular (RV) pressure overload and dysfunction.[2] Randomized studies focusing on the treatment of acute intermediate-risk[3] or low-risk[4] PE have been designed based on short-term primary outcomes, and therapeutic trials with long-term follow-up have primarily served the goal of determining the optimal duration and regimen of anti-coagulation and secondary prophylaxis.[5]

In parallel to acute PE, significant progress has been made in the diagnosis and treatment of chronic thromboembolic pulmonary hypertension (CTEPH).[6–8] In fact, CTEPH is considered as a late complication or sequela of acute PE, resulting from defective vascular re-modelling and resolution of pulmonary thrombi under the influence of a variety of predisposing factors.[9,10] However, the overall incidence of CTEPH after PE appears to be low,[11] a fact which does not justify routine CTEPH screening for all survivors of an acute PE episode. Therefore, there is an urgent need to develop and validate follow-up assessment strategies with the aim of identifying the 'true' candidates for advanced diagnostic work up based on a high(er) level of suspicion for CTEPH. It has further been recognized that an additional focus should be placed on patient-reported symptoms over the long-term, in order to characterize and treat a larger patient group suffering from persisting functional limitation and reduced quality of life (QoL) after PE.[12,13] The algorithm for post-PE assessment first proposed by the 2019 guidelines of the European Society of Cardiology (ESC) is a potentially useful clinical tool in this regard,[1] but it is, at the present stage, largely based on expert consensus and not on prospectively obtained data.

Aiming to contribute to closing this gap in evidence, we undertook the prospective multicentre FOllow-up after aCUte pulmonary emboliSm (FOCUS) study. The FOCUS study was conducted in large-volume tertiary centres with expertise in both acute PE and chronic pulmonary hypertension/CTEPH, which harmonized their clinical protocols and prospectively implemented a comprehensive 2-year follow-up programme in consecutive patients/all-comers with acute PE. The aim of this observational study was to systematically assess a broad range of late outcomes after acute PE, and particularly to evaluate prospectively defined criteria of clinically relevant post-PE impairment (PPEI). These might serve as a warning signal for the possible presence of CTEPH as well as for the broader clinical spectrum of clinical and functional PE sequelae.

Methods

Study design and participants

The FOCUS (German Clinical Trials registry number: DRKS00005939) prospectively enrolled consecutive unselected patients with confirmed diagnosis of acute symptomatic PE. The study was performed at 17 large-volume centres across Germany. The key aspects of the FOCUS protocol have been described previously.[14] The main inclusion criterion was objectively confirmed diagnosis of acute symptomatic PE, with or without symptomatic deep vein thrombosis, and irrespective of clinical severity, evidence of RV dysfunction, or size or extent of pulmonary emboli.[14] Patients were excluded if, among others, the diagnosis of PE was an incidental finding during diagnostic work up for another disease; if they had a documented history of confirmed CTEPH; or if they had already been enrolled in this study in the past. Patients were followed over a 2-year period after the index PE episode, with a standardized assessment plan (patient-reported health status as well as clinical, functional, laboratory, and echocardiographic examinations) at five pre-specified visits (upon enrolment, at hospital discharge, and at 3, 12, and 24 months). The visit plan and assessments were part of a clinical protocol which had been harmonized among the participating sites and served as standard of care in each one of them. The FOCUS was an observational study, and consequently the study protocol mandated neither diagnostic nor therapeutic decisions; patients were treated according to local protocols in adherence with European[6,15] and national guidelines. Detailed demographic and clinical data, diagnostic, and therapeutic procedures, and outcome variables were prospectively recorded in an electronic case report form.

Written informed consent was obtained from all patients for participation in the study. The study was approved by the central ethics committee of Rhineland-Palatinate with processing number 837.137.14 (9376-F; dated 10 June 2014), and by the ethics committees of the participating sites.

Study outcomes

The FOCUS had two co-primary outcomes. The first outcome was diagnosis of CTEPH during the 2-year follow-up period after the index episode of acute symptomatic PE. All diagnosed cases of CTEPH were adjudicated by an independent Critical Events Committee (CEC) based on a pre-defined adjudication charter. The time to CTEPH was defined as the time to confirmation of CTEPH diagnosis by the site investigator. For all patients with an adjudicated diagnosis of CTEPH, the follow-up was considered to end with the visit closest to the date of CTEPH diagnosis.

Post-PE impairment was the second co-primary outcome. Details on the assessment and classification of individual indicators of PPEI have been provided previously,[14] and are summarized in Supplementary material online, *Tables S1 and S2*. Briefly, the diagnosis of PPEI required deterioration in severity, or persistence of the highest severity, of at $\geq$ 1 'a' (echocardiographic) *and* $\geq$ 1 'b' (clinical, functional, or laboratory) parameter/abnormality. Deterioration or persistence was determined by comparison with the previous visit. For trichotomized (three-level) 'a' or 'b' parameters, the highest severity category was the one defined as 'severe/high'; for dichotomized (two-level) parameters, it was the 'moderate or severe/high' category (see Supplementary material online, *Table S2*). Patients were considered to have reached the outcome 'PPEI' if they fulfilled the above criteria at the latest available follow-up visit (3, 12, or 24 months). The rationale for the definition of the PPEI criteria used in the present study was based on previously proposed prognostic criteria related to (chronic) pulmonary hypertension[16]; practical guidance on functional, notably cardiopulmonary exercise testing for evaluation of pulmonary hypertension and chronic thromboembolic disease[17,18]; and echocardiographic probability of pulmonary hypertension as recommended by the guidelines of the ESC and the European Respiratory Society.[6,19]

Secondary outcomes included death, the cause of which was independently adjudicated by the CEC, and QoL indicators. Generic, non-disease-specific health-related QoL was assessed using the EuroQol 5-Dimension 5-Level (EQ-5D-5L) questionnaire and its corresponding visual analogue scale.[20] Briefly, the EQ-5D-5L generates an overall index that ranges from 0 (lowest generic QoL) to 1 (highest generic QoL) and is calculated based on country-specific reference value sets. The EQ-5D-5L health index was calculated with the value set for Germany. The EuroQol visual analogue scale ranges from 0 to 100,

with higher scores indicating better health. Disease-specific QoL was measured using the Pulmonary Embolism Quality of Life (PEmb-QoL) instrument,[21,22] which has been validated in many languages, including German. The PEmb-QoL includes nine questions, seven of which relate to six numeric dimensions and two provide descriptive information. The percentage scores obtained in each one of the six numeric dimensions are averaged to obtain an overall percentage score (0–100), with higher scores indicating worse QoL.[23]

Table 1 Baseline characteristics of the study population ($N = 1017$)

Variable		Missing
Patient demographics		
Women	462 (45%)	0
Age, years, median (IQR)	64 (52–74)	0
Findings related to the severity of acute PE		
Systolic/diastolic blood pressure (mmHg), median (IQR)	135 (120–150)/80 (71–90)	64/69
Oxygen saturation (pulse oximetry)	96% (93–97%)	181
Signs of RV dysfunction on CTPA or echocardiography[a]	416 (41%)	0
Troponin elevation	378/772 (49%)	245
Risk of early death		0
High	35 (3.4%)	
Intermediate	712 (70%)	
Low	270 (26.6%)	
Risk factors for venous thromboembolism and comorbidities		
Cancer or myeloproliferative disease	106/956 (11%)	61
Surgery or trauma (last 30 days)	142/990 (14%)	27
Immobilization (last 30 days)	184/984 (19%)	33
Hormonal therapies	72 (7.1%)	0
Pregnancy or puerperium	5/1005 (0.5%)	12
Recent long-distance travel	91/984 (9.2%)	33
History of venous thromboembolism	253/992 (26%)	25
Chronic pulmonary disease	157/993 (16%)	24
Chronic heart failure or coronary heart disease	127/1003 (13%)	14
Arterial hypertension	558/1004 (56%)	13
Diabetes mellitus	112/1000 (11%)	17
Chronic liver disease	34/992 (3.4%)	25
Glomerular filtration rate $<$ 50 mL/min or known chronic renal disease	172/1016 (17%)	1
Chronic inflammatory disease	101/982 (10%)	35

CTPA, computed tomography pulmonary angiography; IQR, interquartile range; PE, pulmonary embolism; RV, right ventricular.
[a]Signs of RV dysfunction on CTPA or echocardiography were diagnosed at the participating sites based on local protocols and in adherence with current (at the time of patient enrolment) European[15] and national guidelines.

Statistical analysis

Sample size calculation was based on assuming an annual CTEPH incidence rate of 0.8 per 100 patient-years among unselected patients suffering an episode of acute symptomatic PE.[14] This was a conservative estimate viewed against the background of the totality of data published until 2015 (reviewed in Ende-Verhaar *et al.*[11]), but it was still five times higher than the rate (0.16 per 100 patient-years) reported in one of the largest cohorts to that date, notably 866 unselected patients with PE.[24] Further assuming that overall death rates and case-mix would be similar to that of the previous study,[24] and that there would be $\leq 5\%$ loss to follow-up per year in addition to administrative censoring and deaths, we expected the cumulative incidence of CTEPH at 2 years to amount to 1.3%.[14] On that basis, our simulations indicated that a study population of 1000 patients would provide 90% power to reject the H_0 hypothesis that the cumulative incidence of CTEPH at 2 years is as low as 0.27% (the value corresponding to the annual incidence rate in the large previous cohort mentioned above[24]).

As it was assumed that patients with CTEPH would present with PPEI before or at the time of the diagnosis of CTEPH, hierarchical testing was used for the two co-primary outcomes. We first tested whether the cumulative incidence of PPEI was significantly higher than 0.27% at 2 years. As PPEI could only be confirmed and documented at the pre-specified study visits at 3, 12, and 24 months, its cumulative incidence was estimated using a non-parametric estimation-maximization algorithm for interval-censored data.[25] It was prospectively determined that, if our test confirmed a cumulative incidence of PPEI $>$0.27%, we would proceed with testing the cumulative incidence of CTEPH against H_0.[14] For this latter test, and because CTEPH could (in contrast to PPEI) be diagnosed at any time during the follow-up period based on diagnostic tests performed between the pre-defined study visits, the cumulative incidence of CTEPH [with the corresponding 95% confidence interval (CI)] was estimated using the Aalen–Johansen estimator. The overall two-sided level of significance was set at $\alpha = 0.05$, and both tests were expected to have a local power of at least 90%. Testing was performed by evaluating whether the 95% CIs contained the null cumulative incidence of 0.27%. Hazard ratios (HRs) of the cumulative incidence of CTEPH in patients with vs. those without PPEI, and of the cumulative incidence of death and re-hospitalization in those with vs. those without PPEI, were determined using Cox regression. The PPEI was treated as a time-dependent covariate. In patients classified as PPEI negative, it was set to 0. In the other cases, it switched from 0 to 1 at the visit when the PPEI criteria were first fulfilled and remained at that value until the end of follow-up.

For description of continuous variables, medians with the corresponding interquartile range (IQR) were calculated; for categorical variables, percentages were calculated out of the number of patients with available data for that given variable. Comparisons of continuous and ordinal variables were performed using the Wilcoxon rank sum test; for binary variables, Pearson's χ^2 test was used.

Results

Study population

Between September 2014 and October 2018, 1098 patients were included in FOCUS at the 17 study sites. Two-year follow-up of the last patient was completed in November 2020. For 81 patients, no follow-up data could be obtained after discharge, and they were

excluded from analysis (see Supplementary material online, *Figure S1*). This resulted in a total of 1017 patients who were analysed for the primary outcome(s). Supplementary material online, *Table S3* provides a comparison of baseline parameters of the patients analysed with those ($n = 81$) who were excluded from the primary analysis due to the lack of follow-up data.

An overview of the patients' demographic and baseline clinical characteristics is provided in *Table 1*. Briefly, 462 (45%) patients were women, and the median age was 64 (IQR 52–74) years. A minority ($n = 35$; 3.4%) of the patients presented with haemodynamic instability, being classified into the high-risk PE category, and 712 (70%) had intermediate-risk PE (defined as in Konstantinides *et al.*[15]). Following diagnosis of acute PE, patients were hospitalized for a median of 6 (IQR 4–10) days. A total of 80 (7.9%) patients received systemic thrombolysis upon diagnosis or during index hospitalization; use of other reperfusion modalities was reported in 13 (1.3%) patients. At discharge, use of anti-coagulants was documented in 1010 (99%) patients.

Table 2 Study outcomes

	Evaluable study population $N = 1017$
Co-primary outcomes	
Chronic thromboembolic pulmonary hypertension	
Two-year cumulative incidence (95% CI)	2.3% (1.2–4.4%)
Time to diagnosis (days), median (min-max; IQR)	129 (74–765; 97–186)
Post-pulmonary embolism impairment	Evaluable study population $N = 880$
Two-year cumulative incidence (95% CI)	16.0% (12.8–20.8%)
Visit of first documentation	
3 months	46
12 months	29
24 months	41
Secondary outcomes	
Death from any cause	56 (5.5%)
Cancer	22
Sepsis	5
Respiratory failure	3
Other, n	26
PE recurrence	19 (1.9%)
Major bleeding	87 (8.6%)
Stroke	7 (0.7%)
Re-hospitalization	318 (31%)

CI, confidence interval; IQR, interquartile range; PE, pulmonary embolism.

Patients were followed for a median of 732 (IQR 387–749) days after the diagnosis of acute PE. Of the 1017 patients included in the main analysis, follow-up was limited to 3 months in 120 (11.8%), whereas the remaining patients were followed for at least 1 year. The reasons for incomplete follow-up were death ($n = 22$), withdrawal of informed consent ($n = 45$), patient's moving to an unknown address or no response to the site's invitation for the follow-up visit ($n = 42$), or other reasons ($n = 11$).

Co-primary outcomes and individual persisting abnormalities at follow-up

The co-primary outcome CTEPH was diagnosed in 16 (1.6%) of the study patients, corresponding to an estimated 2-year cumulative incidence of 2.3% (95% CI 1.2–4.4%; *Table 2*). In all of these cases, CTEPH was confirmed by right heart catheterization. The median time to CTEPH diagnosis was 129 days (minimum to maximum 74–765; IQR 97–186 days); a graphic representation of the cumulative incidence is shown in *Figure 1*. The CTEPH was diagnosed within the first 3 months following the index acute PE event in 2 of 16 (12.5%) cases, within 6 months in 11 of 16 (68.8%), and within 12 months in 13 of 16 (81.3%) cases; in three cases (18.8%), CTEPH was diagnosed after the first 12 months. A description of the key characteristics of patients diagnosed with CTEPH at follow-up is provided in *Table 3*. A comparison of the baseline characteristics as well as of known risk factors for CTEPH[26,27] in patients with vs. without confirmed CTEPH is displayed in Supplementary material online, *Table S4*.

A total of 880 patients (86.5% of the population included in the primary analysis) were evaluable for the co-primary outcome PPEI according to the criteria described before[14] and summarized in Supplementary material online, *Tables S1* and *S2*. Of these, 116 (13.2%) fulfilled the definition of PPEI at the latest available visit, corresponding to an estimated 2-year cumulative PPEI incidence of 16.0% (95% CI 12.8–20.8%; *Table 2*). The confirmation of a cumulative incidence >0.27% allowed us to calculate, according to the hierarchical testing procedure, the CTEPH incidence reported above. Patients who fulfilled the criteria for PPEI were older, presented more frequently with a simplified Pulmonary Embolism Severity Index above 0, and were more often classified into the intermediate-risk (rather than the low-risk) PE category in the acute phase compared with patients without PPEI (*Table 4*).

At least one of the echocardiographic abnormalities that served as 'a' criteria for PPEI, was present in 524 (59.5%) patients at one or more follow-up visit(s), and at least one of the clinical, functional, or biochemical abnormalities also serving as 'b' criteria for PPEI was present in 334 (38.0%) of the study patients. The proportion of patients with vs. without confirmation of PPEI who fulfilled individual 'a' and 'b' criteria at each one of the study visits is illustrated in *Figure 2*. In patients ultimately diagnosed with PPEI, the prevalence of at least one echocardiographic 'a' abnormality was 68.2, 67.9, and 100% at the 3-, 12-, and 24-month follow-up visit, respectively (right panel, darker boxes). In comparison, in patients without PPEI, the prevalence of at least one echocardiographic abnormality was 33.4, 36.2, and 26.7%, respectively (left panel, light-coloured boxes). Similar differences were observed in the prevalence of at least one clinical, functional, or biochemical 'b' abnormality (53.3,

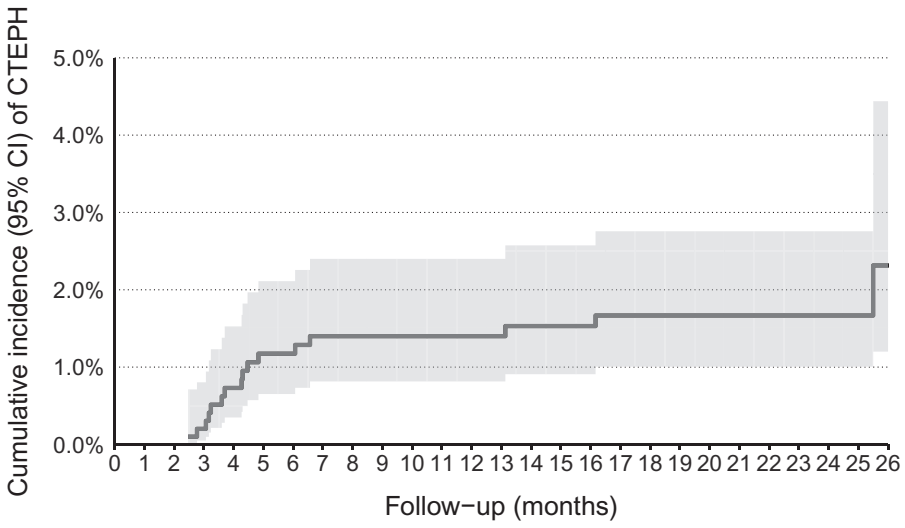


Figure 1 Cumulative incidence of chronic thromboembolic pulmonary hypertension in 1017 patients followed after acute pulmonary embolism. Estimates with the corresponding 95% confidence intervals are shown as calculated using the Aalen–Johansen estimator. In the graph, actual follow-up extends beyond 730 days because of occasional deviations from the exact date of the 2-year follow-up visit (most delays resulting from restricted access to outpatient services due to the coronavirus disease 2019 pandemic in the year 2020); the need to perform some of the visit-related examinations at a later time point; or the need for the results of all investigations to have become available to the investigator before the diagnosis of chronic thromboembolic pulmonary hypertension could be confirmed. CI, confidence interval; CTEPH, chronic thromboembolic pulmonary hypertension.

63.1, and 100%, respectively, in patients with PPEI, compared with 13.8, 18.5, and 17.2%, respectively, in those without PPEI).

During follow-up, a total of 56 deaths were recorded. The most frequent causes of death as adjudicated by the CEC were cancer ($n = 22$) and sepsis ($n = 5$). A total of 87 (8.6%) major bleeding events were recorded, as well as 19 (1.9%) recurrent PE episodes and 7 (0.7%) strokes. At least one re-hospitalization was recorded during the follow-up period in 318 (31%) patients (*Table 2*).

Association of post-pulmonary embolism impairment with clinical outcomes

Fifteen out of the sixteen patients in whom CTEPH was diagnosed at follow-up fulfilled the criteria for PPEI as stated in the Methods (*Table 3*). The corresponding estimated HR for the association of PPEI with incident CTEPH was 393 (95% CI 73–2119). Furthermore, patients with PPEI had a higher incidence of death and of re-hospitalization for any cause compared with those without PPEI [HR 7.4 (95% CI 3.0–18.4) and 4.4 (95% CI 2.7–7.1), respectively].

Differences were also found with regard to patient-reported outcomes over the long-term. Thus, patients with PPEI reported lower generic and disease-specific QoL than patients with no PPEI, as reflected by their consistently lower EuroQol utility index, lower EuroQol visual analogue scale, and higher (i.e. worse) PEmb-QoL global score during the study period (*Table 5*). Generic QoL in patients with PPEI progressively improved when assessed using the EuroQol utility index and the EuroQol visual analogue scale. However, patients with PPEI reached values similar to those without PPEI no earlier than at the 24-month visit [0.92 (IQR 0.73–1.00) vs. 0.94 (0.84–1.00) for the utility index; and 70 (50–89) vs. 80 (65–90) for the visual analogue scale]. Differences were even more pronounced regarding disease-specific QoL as estimated by the PEmb-QoL global score: while the entire evaluable population reported progressive recovery throughout the study period, median QoL was still worse in patients with PPEI at 24 months [23.3% (IQR 4.5–57.5%)] compared with patients without PPEI [9.8% (3.3–29.2%)].

As current guidelines recommend echocardiographic follow-up after PE not invariably, but as a next step to clinical assessment (i.e. in case of an abnormal clinical or functional status),[1] we also investigated the possible prognostic impact of abnormal echocardiographic findings 'alone' in the present study. Supplementary material online, *Table S5* shows the clinical outcomes of patients diagnosed with PPEI (that is, fulfilling both the 'a' and the 'b' criteria), compared with those of patients with only echocardiographic ('a') abnormalities, only clinical ('b') abnormalities, or neither. As shown in Supplementary material online, *Table S5*, patients fulfilling all criteria of PPEI, but not those with echocardiographic abnormalities alone, had significantly higher death and re-hospitalization rates as well as worse QoL indicators compared with the reference patient group without abnormal findings at follow-up. Patients with clinical abnormalities alone also had (low) death rates similar to the reference group, although their re-hospitalization rates and QoL indicators were closer to those of the PPEI population.

Discussion

In the present multicentre cohort study, we prospectively followed, over a 2-year period, a large population of 1017 unselected

Table 3 Key characteristics of patients diagnosed with chronic thromboembolic pulmonary hypertension at follow-up

Sex, age (years)	PE risk class	Days from enrolment	PPEI	PPEI 'a' criteria fulfilled	PPEI 'b' criteria fulfilled
Female, 28	Intermediate	74	Yes	RV basal diameter RA end-systolic area Eccentricity index	Clinical signs of RV failure WHO functional class
Female, 40	Intermediate	83	Yes	RA end-systolic area Eccentricity index	WHO functional class
Female, 78	Intermediate	92	Yes	RA end-systolic area Tricuspid regurgitation velocity	Symptom progression WHO functional class
Female, 60	Intermediate	95	Yes	RV basal diameter Eccentricity index	WHO functional class 6 min walking test
Male, 52	Intermediate	97	No	RV basal diameter Eccentricity index	None
Female, 77	Intermediate	108	Yes	TAPSE Eccentricity index Estimated RA pressure Tricuspid regurgitation velocity	Clinical signs of RV failure Symptom progression WHO functional class Elevated BNP/NT-proBNP
Female, 76	Intermediate	111	Yes	RA end-systolic area Eccentricity index Estimated RA pressure Tricuspid regurgitation velocity Pericardial effusion	Clinical signs of RV failure Symptom progression WHO functional class 6 min walking test Elevated BNP/NT-proBNP
Male, 67	Intermediate	128	Yes	RA end-systolic area TAPSE	Syncope WHO functional class
Male, 79	Intermediate	129	Yes	RV basal diameter Estimated RA pressure	Clinical signs of RV failure Symptom progression WHO functional class 6 min walking test Elevated BNP/NT-proBNP
Male, 76	Intermediate	134	Yes	Eccentricity index	WHO functional class
Female, 67	Intermediate	145	Yes	RA end-systolic area Eccentricity index	Clinical signs of RV failure Symptoms progression WHO functional class 6 min walking test
Male, 78	Low	182	Yes	RA end-systolic area TAPSE Tricuspid regurgitation velocity	Symptom progression
Male, 74	Intermediate	197	Yes	RV basal diameter	WHO functional class
Female, 83	Intermediate	394	Yes	RA end-systolic area	Clinical signs of RV failure Symptom progression Elevated BNP/NT-proBNP
Male, 38	Low	485	Yes	RA end-systolic area	Clinical signs of RV failure Symptom progression WHO functional class
Male, 75	Intermediate	765	Yes	RV basal diameter RA end-systolic area Eccentricity index	Clinical signs of RV failure Symptom progression 6 min walking test

BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; PE, pulmonary embolism; PPEI, post-pulmonary embolism impairment; RA, right atrial; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; WHO, World Health Organization.

Table 4 Baseline features of patients with vs. without post-pulmonary embolism impairment (evaluable population, *N* = 880)

	No PPEI (*n* = 764)	PPEI (*n* = 116)	*P*-value[a]
Women	348 (46%)	50 (43%)	0.6
Age (years), median (IQR)	61 (49–73)	72 (63–78)	<0.001
sPESI >0	322 (42%)	66 (57%)	<0.001
Signs of RV dysfunction on CTPA or echocardiography[b]	311 (41%)	55 (47%)	0.2
Troponin elevation[c]	280/596 (47%)	46/87 (53%)	0.3
Risk of early death			0.006
Low	224 (29%)	19 (16%)	
Intermediate	516 (68%)	95 (82%)	
High	24 (3%)	2 (2%)	

CTPA, computed tomography pulmonary angiography; IQR, interquartile range; PPEI, post-pulmonary embolism impairment; RV, right ventricular; sPESI, simplified Pulmonary Embolism Severity Index.
[a]For binary variables, *P*-values were obtained from Pearson's χ^2 test; for continuous and ordinal variables, Wilcoxon rank sum test was performed. Patients were grouped according to whether the PPEI criteria were satisfied in their last evaluable visit.
[b]Signs of RV dysfunction on CTPA or echocardiography were diagnosed at the participating sites based on local protocols and in adherence with current (at the time of patient enrolment) European[15] and national guidelines.
[c]Baseline troponin measurements were missing in 168/765 patients without PPEI and 29/115 patients with PPEI.

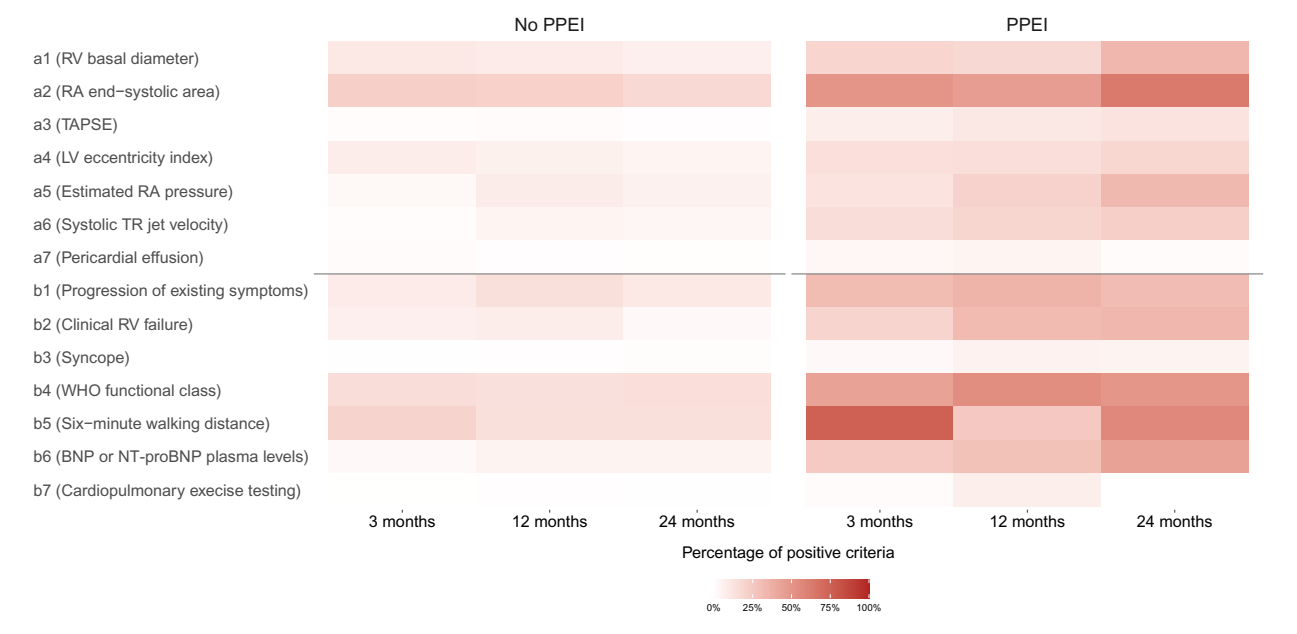


Figure 2 Proportion of patients, with and without ultimate confirmation of post-pulmonary embolism impairment, who fulfilled individual 'a' and 'b' criteria at each one of the follow-up study visits. Heat map depicting the prevalence of positive criteria for post-pulmonary embolism impairment (worsening or persistence in worst category of a parameter) in all patients in whom the parameters were evaluated at each visit. The intensity of the colour is proportional to the proportion of patients fulfilling the criterion for each parameter at each visit. BNP, brain natriuretic peptide; LV, left ventricular; NT-proBNP, N-terminal pro-brain natriuretic peptide; PPEI, post-pulmonary embolism impairment; RA, right atrial; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; WHO, World Health Organization.

consecutive patients presenting with acute symptomatic PE. Although FOCUS had an observational design, the participating sites used harmonized follow-up protocols, including a pre-defined visit and assessment plan, as their standard of care; in addition, the co-primary clinical outcomes were prospectively defined, and the diagnosis of CTEPH as well as the causes of death was independently

Table 5 Association of post-pulmonary embolism impairment with clinical outcomes other than diagnosis of chronic thromboembolic pulmonary hypertension at follow-up (evaluable population, $N = 880$[a])

Clinical outcome	No PPEI	PPEI	*P*-value[b]
Death, *n*	21	6	<0.001
Re-hospitalization for any cause, *n*	269	18	<0.001
Quality of life indicators[c]			
EQ-5D-5L utility index			
At 3 months (median, IQR)	0.91 (0.80–1.00)	0.72 (0.36–0.84)	<0.001
At 12 months (median, IQR)	0.94 (0.85–1.00)	0.82 (0.58–0.88)	<0.001
At 24 months (median, IQR)	0.94 (0.84–1.00)	0.92 (0.73–1.00)	0.3
EQ visual analogue scale			
At 3 months (median, IQR)	75 (60–89)	50 (45–70)	<0.001
At 12 months (median, IQR)	80 (65–90)	55 (45–72)	<0.001
At 24 months (median, IQR)	80 (65–90)	70 (50–89)	0.002
PEmb-QoL global score			
At 3 months (median, IQR)	20.7% (7.3–44.1%)	59.5% (40.2–71.9%)	<0.001
At 12 months (median, IQR)	12.3% (4.0–33.8%)	46.9% (24.9–58.2%)	<0.001
At 24 months (median, IQR)	9.8% (3.3–29.2%)	23.3% (4.5–57.5%)	0.003

CTEPH, chronic thromboembolic pulmonary hypertension; EQ, EuroQol; EQ-5D-5L, EuroQol 5-Dimension 5-Level; IQR, interquartile range; PEmb-QoL, Pulmonary Embolism Quality of Life; PPEI, post-pulmonary embolism impairment.

[a]Reported are the quality of life indicators for patients without vs. with documented PPEI at each specific visit. Accordingly, as more patients fulfilled the criteria for PPEI over follow-up, the number of patients in each column varies: the quality of life indicators were evaluated at 3, 12, and 24 months in 824, 716, and 583 patients without PPEI, and in 46, 56, and 73 patients with PPEI, respectively.

[b]For the time-to-event variables death and re-hospitalization, *P*-values were obtained from Cox regression; for continuous quality of life indicators, from Wilcoxon rank sum test. Patients were considered to have reached the outcome 'PPEI' from the first visit at which the PPEI criteria were fulfilled and then until the end of follow-up. Patients were censored upon diagnosis of CTEPH or at the (premature or planned) end of follow-up.

[c]The EuroQol utility index was derived from the EQ-5D-5L questionnaire using the value set for Germany; it ranges from 0 (lowest generic quality of life) to 1 (highest generic quality of life). The EuroQol visual analogue scale ranges from 0 (lowest quality of life) to 100 (highest quality of life). The PEmb-QoL global score was derived from the PEmb-QoL questionnaire by averaging the percentage scores obtained in each of its six numeric dimensions and ranges from 0 (best quality of life) to 100 (worst quality of life). Summary measures are derived from patients with available data.

adjudicated. The patients included in FOCUS were representative of the real-life risk spectrum of all-comers with acute PE.[2] The main results of FOCUS are displayed in the *Structured Graphical Abstract*, and can be summarized as follows: (i) the 2-year cumulative incidence of CTEPH was 2.3%, extending and upgrading, in view of the size and design of our study, the evidence to permit 'quantification' of the association between acute PE and CTEPH; (ii) the median time to CTEPH diagnosis after the index PE event was as short as 129 days; (iii) the 2-year cumulative incidence of the pre-defined co-primary outcome 'post-PE impairment', a combination of persistent or worsening clinical, functional, biochemical, and imaging parameters, was 16.0%; (iv) PPEI helped to narrow the target population for advanced CTEPH search among the survivors of acute PE as indicated by a HR for CTEPH as high as 393 compared with patients without PPEI; and (v) patients who met the criteria for PPEI had, compared with those without PPEI, a numerically higher all-cause mortality and incidence of re-hospitalization as well as worse generic and disease-specific QoL over the long-term.

The CTEPH is a potentially life-threatening but also treatable condition.[7,28] Previous guidelines proposed diagnostic algorithms mostly for patients in the general population, who present with progressive symptoms and/or are diagnosed with pulmonary hypertension.[6,15] However, these recommendations may not suffice to raise the (low) level of awareness among patients and general practitioners/family physicians. With approximately five new cases per million population per year,[29,30] CTEPH is a rare disease and thus likely to be often overlooked and underdiagnosed.[31,32] Moreover, clinical symptoms and signs are non-specific or absent at early stages, with signs of right heart failure only becoming evident in advanced disease. Thus, early diagnosis remains a major challenge, and the median time between symptom onset and diagnosis exceeds 1 year even in expert centres[33]; obesity and, importantly, recurrent PE itself have been identified as determinants of diagnostic delays.[34] There is, therefore, an urgent need to improve early detection of CTEPH, with the most promising approach starting at the 'source', i.e. the disease of which it is presumed to be a late complication PE.

The comprehensive visit and assessment schedule implemented by the expert centres participating in FOCUS succeeded in limiting the time to CTEPH to a median of 129 days, i.e. a little longer than 4 months (IQR 3–6 months). The time period between the index acute PE event and the diagnosis of CTEPH was thus considerably shorter compared with that reported by a previous landmark

publication on a large cohort of patients with CTEPH.[35] As that study was conducted approximately one decade before FOCUS, it is tempting to assume that awareness and timely detection of CTEPH have improved over the past years. However, any such comparisons should be interpreted with caution in view of the observational design of both studies and the fact that there was no systematic screening for CTEPH in our study population.

The FOCUS did not aim to establish a routine, comprehensive 'CTEPH screening' for all survivors of acute PE. Instead, we sought to define an 'enriched' patient population, in which advanced screening for CTEPH would indeed be justified. For this purpose, the FOCUS steering committee prospectively defined the clinical outcome of PPEI, comprising clinical, functional, biochemical (laboratory), and imaging (echocardiographic) abnormalities. The 2-year cumulative incidence of PPEI was estimated at 16.0% (95% CI 12.8–20.8%). Of note, abnormalities of one or more echocardiographic parameters were frequently (in 59.5% of the study population) reported during follow-up, but they were associated with the diagnosis of CTEPH only if they accompanied clinical, functional, or (to a lesser extent) laboratory abnormalities. Thus, although the present study did not explicitly assess a pre-determined sequence of examinations at follow-up (which would have required an interventional design), our results provide evidence to support structured algorithms which employ clinical assessment, followed by echocardiography in case of persistent symptoms, functional limitation, or risk factors for CTEPH, in post-PE care.[1,36]

The merits of follow-up and care of patients after PE extend beyond early detection and diagnosis of CTEPH. In the present study, fulfilment of the PPEI criteria also identified a patient group more frequently in need of re-hospitalization as well as with worse generic and disease-specific QoL. Importantly, abnormalities defining PPEI appeared to persist throughout the 2-year follow-up period. In this regard, it was mostly the 'b', i.e. clinical and functional criteria, which identified the patients with readmissions and poor QoL, even in the absence of echocardiographic abnormalities. Patient-reported outcomes after acute PE, often neglected in the past, are now increasingly attracting the attention of clinical research and medical care.[13,23,37] These are the patients to whom, after exclusion of CTEPH, appropriate care (exercise rehabilitation, treatment of comorbidity, behavioural education, and modification of risk factors) should be provided to restore their well-being and functional status.[1]

Some limitations of our study need to be kept in mind. All efforts were made by the FOCUS investigators to ensure adherence to existing guidelines; however, the study protocol mandated neither the treatment of patients after acute PE nor the initiation of diagnostic work up for CTEPH. It is therefore possible that the diagnosis was missed in some cases. In addition, PPEI could be evaluated in 880 (86.5%) out of the 1017 patients included in the primary analysis due to missing data in the remaining cases. Secondly, there was no central reading of echocardiograms at baseline or follow-up, and no independent adjudication of the co-primary outcome PPEI. This fact may have led to some variability, particularly concerning the interpretation of echocardiographic findings and the confirmation of fulfilment of the 'a' criteria. On the other hand, all sites were large tertiary centres with expertise in diseases of the pulmonary circulation, and focused guidance on the echocardiographic parameters of interest had been provided to the sites by the coordinating investigators (S.K. and S.R.) based on current guidelines[6] and consensus statements by European and American echocardiography societies.[38] Establishment of PPEI as a composite outcome after acute PE will require external validation in future studies.

Cardiopulmonary exercise testing is, in experienced hands, a valuable diagnostic tool in the assessment of patients with persisting symptoms or functional limitation after acute PE. Some of the parameters obtained from this test were part of the pre-defined criteria for the definition of PPEI in the FOCUS study (see Supplementary material online, *Table S2*) and were included in the analysis if available (*Figure 2*). Further parameters such as reduced ventilatory equivalent for carbon dioxide and reduced end-tidal carbon dioxide pressure may also possess a prognostic value[1] which should be investigated in future studies.

Although a higher than expected proportion of our patients underwent systemic thrombolysis or other reperfusion procedures, their possible effect on the development of CTEPH after acute PE cannot be addressed by a study with an observational design and remains questionable,[39] awaiting the results of ongoing randomized controlled trials.[40] Finally, and although known pre-existing CTEPH was an exclusion criterion for FOCUS, we cannot exclude the possibility that some of the CTEPH cases diagnosed at follow-up may have already been present at baseline. Intensive research is ongoing in this field, and recent publications identified a number of radiological findings which, when sought and found in the computed tomography pulmonary angiography performed to diagnose acute PE, may increase the level of suspicion for pre-existing CTEPH and possibly help to modify the follow-up strategy.[41]

In conclusion, the present multicentre cohort study prospectively followed and analysed a large population of 1017 patients with acute PE. Our results may help to optimize strategies aiming not only at early detection of CTEPH, but also at recognition of the broader spectrum of impairment after an index PE episode. They may thus contribute to developing integrated ambulatory care protocols after PE, with the aim to adequately support patients with persisting symptoms and limitation, and help them regain their well-being and QoL.

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Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability

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

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