Post-Pulmonary Embolism Syndrome and Functional Outcomes after Acute Pulmonary Embolism

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Abstract

Survivors of acute pulmonary embolism (PE) are at risk of developing persistent, sometimes disabling symptoms of dyspnea and/or functional limitations despite adequate anticoagulant treatment, fulfilling the criteria of the post-PE syndrome (PPES). PPES includes chronic thromboembolic pulmonary hypertension (CTEPH), chronic thromboembolic pulmonary disease, post-PE cardiac impairment (characterized as persistent right ventricle impairment after PE), and post-PE functional impairment. To improve the overall health outcomes of patients with acute PE, adequate measures to diagnose PPES and strategies to prevent and treat PPES are essential. Patient-reported outcome measures are very helpful to identify patients with persistent symptoms and functional impairment. The primary concern is to identify and adequately treat patients with CTEPH as early as possible. After CTEPH is ruled out, additional diagnostic tests including cardiopulmonary exercise tests, echocardiography, and imaging of the pulmonary vasculature may be helpful to rule out non-PE–related comorbidities and confirm the ultimate diagnosis. Most PPES patients will show signs of physical deconditioning as main explanation for their clinical presentation. Therefore, cardiopulmonary rehabilitation provides a good potential treatment option for this patient category, which warrants testing in adequately designed and executed randomized trials. In this review, we describe the definition and characteristics of PPES and its diagnosis and management.

Keywords
- pulmonary embolism
- cardiopulmonary rehabilitation
- pulmonary hypertension
- patient-reported outcome measures
- echocardiography

Acute pulmonary embolism (PE) remains a frequently occurring disease. Improved treatment options and identification of less severe cases of PE using sensitive diagnostic tools have resulted in lower PE-related mortality rates in recent years.[1,2] PE survivors are faced with a wide range of complications and long-term sequelae, such as recurrent PE,

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anticoagulation-associated major bleeding, and/or arterial cardiovascular complications.[3–6] Follow-up after acute PE therefore usually largely focuses on determining the optimal duration of anticoagulant therapy and the prevention of both recurrent PE and anticoagulation-associated bleeding.[7]

In recent years, a lot of attention has been given to patient-reported outcomes such as quality of life (QoL) that complement the perspective from the above-mentioned traditional outcomes.[5,8–13] Remarkably, up to half of the PE patients report persistent dyspnea, exercise intolerance, and/or functional limitations despite adequate anticoagulant treatment 3 to 6 months after the acute PE event.[8,11,14–17] Functional limitations include all adaptations in level of intensity or structural modifications in the ability of carrying out duties and/or activities at home or at work, due to physical, cognitive, and/or mental complaints after acute PE. These patients qualify for the post-PE syndrome (PPES).[18–20] A patient can be diagnosed with PPES after at least 3 months of adequate anticoagulant treatment. PPES is defined as the presence of any of the following: chronic thromboembolic pulmonary disease (CTEPD) with or without pulmonary hypertension (PH), i.e., chronic thromboembolic pulmonary hypertension (CTEPH) or CTEPD without PH post-PE cardiac dysfunction (characterized as persistent right ventricle [RV] impairment after PE), or post-PE functional impairment.[5,21] In this review, we discuss the definition and characteristics of PPES, and what is currently known about its diagnosis and management.

Case Scenario

A 50-year-old woman visits the outpatient clinic for a follow-up consultation 3 months after being diagnosed with an uncomplicated, unprovoked acute PE, which has been treated with a direct oral anticoagulant. Her medical history shows hypertension, for which she receives an angiotensin-converting enzyme inhibitor. She reports persistent dyspnea and functional limitations: she has not resumed her work, needs assistance from her neighbor in shopping for groceries, and is unable to attend social activities due to fatigue. The treating physician wonders how these symptoms may be objectified, what diagnostic tests should be done, and how the patient should be treated.

The Post-PE Syndrome

The first category of PPES is caused by persisting thrombus after acute PE. In CTEPH, the acute thromboemboli fail to resolve adequately, causing fibrotic obstruction of the pulmonary artery tree, increased pulmonary vasculature resistance, and ultimately RV pressure overload and RV failure.[22,23] The detailed pathophysiology of CTEPH and the reason for incomplete thrombus resolution remain unknown, although a proinflammatory state, abnormal fibrinolysis, and small vessel disease likely play a role.[22,24–26] CTEPH is associated with poor QoL and is the most feared subgroup of PPES since untreated CTEPH is often fatal.[27–29] CTEPH is diagnosed by mismatched perfusion defects on ventilation/perfusion (V/Q) scan in combination with a mean pulmonary artery pressure (PAP) of $\geq$25 mm Hg and pulmonary capillary wedge pressure of $\leq$15 mm Hg measured with right heart catheterization (RHC).[7,30] However, recent data from non-PH patients showed a normal mean PAP of 14.0 ± 3.3 mm Hg, suggesting an alternative definition of PH with a mean PAP of 21 instead of 25 mm Hg (two standard deviations above the mean PAP for non-PH patients), and a change in the definition of precapillary PH with a lower threshold of pulmonary vascular resistance of 2 instead of 3 Wood units has been proposed, although this definition has not yet been incorporated into the current guidelines.[23,31]

Similar to CTEPH, CTEPD without PH is also characterized by unresolved thrombi, functional impairment, and abnormal cardiopulmonary exercise test (CPET) results, but the mean PAP at rest is normal.[32] When comparing CPET and RHC outcomes during exercise between CTEPD patients without PH and a healthy control group, CTEPD patients without PH have an increased mean PAP, inadequate increase of RV ejection fraction, and a decreased ventilatory efficiency (i.e., increased ventilation [VE]/CO_2 output [VCO_2] ratio). This means that VE is increased during exercise without an accompanying increase in VCO_2, which is suggestive of an increase of dead space ventilation.[32–34] Complicating the identification and possible treatment of CTEPD patients without PH is the debatable definition of CTEPD without PH, since clear thresholds of CPET outcomes to diagnose CTEPD patients without PH remain open for discussion. However, identifying potential CTEPD without PH is important because targeted treatment in CTEPH expertise centers could improve QoL and functional outcomes.[35,36] The International Society on Thrombosis and Haemostasis (ISTH) suggests a definition of CTEPD without PH when the following four criteria are present: (1) exertional dyspnea of the New York Heart Association (NYHA) class $\geq$II, (2) persistent thromboembolic material in the pulmonary artery tree despite 3 months of adequate anticoagulant therapy, (3) normal mean PAP at rest, and (4) dead space ventilation as determined by CPET and/or PH during exercise. Currently, it is unknown whether CTEPD without PH may progress to CTEPH, and if so, how often this occurs.[23]

The second category of PPES comprises post-PE cardiac impairment. Post-PE cardiac impairment is defined by the ISTH as presence of intermediate/high echocardiographic probability of PH according to the European Society of Cardiology (ESC) criteria, RV hypokinesis, or RV dilatation, in combination with exertional dyspnea (NYHA II–IV).[21] At diagnosis of acute PE, 20 to 50% of the patients have RV dysfunction to some extent.[11,16,17,37–39] Due to the initial ischemic and structural injury during the acute PE in combination with an inflammatory response in the RV, RV dysfunction can persist in a portion of the acute PE survivors possibly because of myocardial fibrosis.[16,40–42] For 4 to 25% of the PE patients, RV dysfunction persists after several months.[11,16,17,37,39] However, in these studies no universal definition of RV dysfunction has been used, complicating the interpretation of these results. The use of the previously described definition of the ISTH of post-PE cardiac impairment could improve comparability between studies.

In most patients with post–acute PE, persisting dyspnea and functional impairment cannot be explained by the categories described earlier. Post-PE functional impairment is defined as persistent dyspnea, exercise intolerance, and/or diminished functional status after an acute PE with no apparent non-PE–related alternative explanation.[21] Decreased daily physical activity after a PE diagnosis with resulting physical deconditioning is one of the main explanations for post-PE functional impairment.[11,18–20,43,44] In addition, persistent thoracic pain, anxiety, and postthrombotic panic syndrome, as well as fear for recurrences or complications, contribute largely to functional limitations, on both the social and professional level.[45–47] Post-PE functional impairment is associated with reduced QoL and higher prevalence of depression and permanent work-related disability.[10,13,43,48–51]

Assessing Long-term Symptoms in PE Survivors

Validated patient-reported outcome measures (PROMs) are excellent tools to reproducibly assess the presence of persisting symptoms. By using PROMs, specific symptoms such as dyspnea, pain, fatigue, and psychological complaints and the impact on QoL can be assessed. For standardized evaluation of the severity of dyspnea, the Medical Research Council (MRC) dyspnea scale has been applied in PE patients.[7,52] Alternative PROMs are PROMIS Short Form Dyspnea Severity, the (modified) Borg Dyspnea Scale, and the World Health Organization functional class.[7,53–56] Disease-specific QoL can be assessed using the validated Pulmonary Embolism Quality in Life (PEmb-QoL) questionnaire, or alternatively, generic QoL PROMs can be applied.[9,57–60] The Post-VTE Functional Status (PVFS) scale can be used to capture a general overview of the impact of persistent symptoms on functioning (►**Fig. 1**).[61] This scale was developed for assessment of overall functional status following an episode of venous thromboembolism (VTE) and refined guided by the input of VTE experts and patients.[62] The scale covers a broad spectrum of functional outcomes in six scale grades ranging from no symptoms and functional limitations to death, and captures both limitations in usual activities or duties and changes in lifestyle. The PVFS scale can be administered through self-reported questionnaire by patients or with the use of a short structured interview, and can be applied to track functional status over time providing the ability to monitor the patients' functional recovery. As the PVFS scale was considered to be useful in the Coronavirus Disease 2019 (COVID-19) pandemic to measure functional status following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the Post-COVID-19 Functional Status (PCFS) scale was proposed after slight adaptation of the PVFS scale.[63] The construct validity of the scale has been demonstrated among adults with COVID-19 at 3 months after onset of symptoms, and the scale was able to discriminate between patients with varying degrees of fatigue, health-related QoL, and functional performance, confirming that the PCFS scale can be used to assess impact on functioning.[64,65] In validation studies of translations of the

PVFS scale grade		Description
0	No functional limitations	All usual duties/activities at home or at work can be carried out at the same level of intensity. Symptoms, pain and anxiety are absent.
1	Negligible functional limitations	All usual duties/activities at home or at work can be carried out at the same level of intensity, despite some symptoms, pain, or anxiety.
2	Slight functional limitations	Some usual duties/activities at home or at work are carried out at a lower level of intensity or are occasionally avoided due to symptoms, pain, or anxiety.
3	Moderate functional limitations	Usual duties/activities at home or at work have been structurally modified (reduced) due to symptoms, pain, or anxiety.
4	Severe functional limitations	Assistance needed in activities of daily living due to symptoms, pain, or anxiety: nursing care and attention are required.
D	Death	Death occurred before the scheduled assessment.

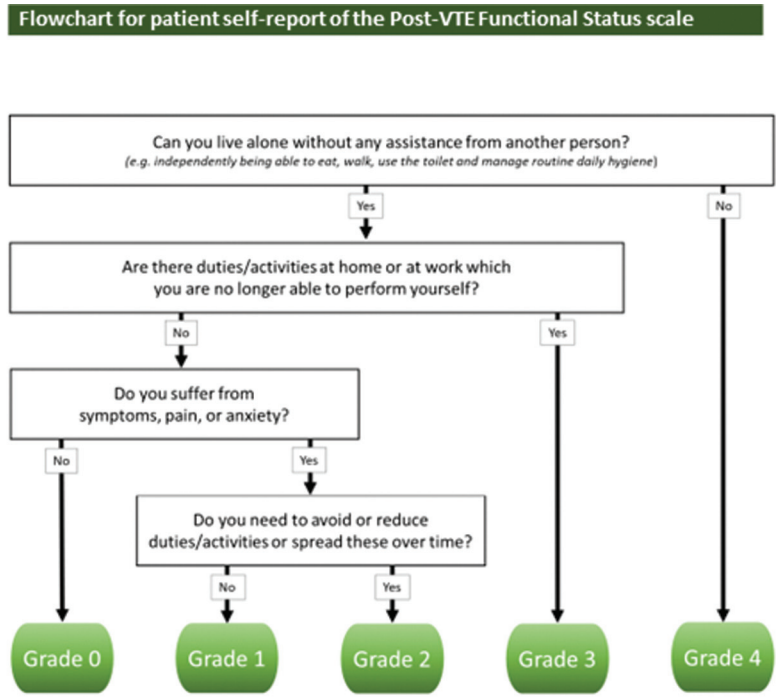

Fig. 1 Flow chart for patient self-report of the Post-VTE Functional Status scale. Image courtesy: Boon et al.[62]

PCFS scale into Turkish language, Mexican-Spanish, and Chilean-Spanish, and a cross-cultural adaptation study of the PCFS scale for the Chilean population, the scale had good psychometric properties in terms of reliability and was found to be a valid instrument.[66–69] To assess pain severity, PROMIS Short Forms for pain can be applied.[70] Psychological well-being can be assessed using the Patient Health Questionnaire-9 for depression and Generalized Anxiety Disorder-7 for anxiety, or the Hospital Anxiety and Depression Scale.[71–73] The Checklist Individual Strength with fatigue severity subscale is an adequate tool to measure fatigue.[74]

Diagnostic Evaluation in Patients with PPES

In case patients have persisting symptoms and functional limitations that qualify for PPES, the first priority should be to rule out CTEPH: an early diagnosis will lead to improved survival and better QoL.[23,75,76] The presentation of CTEPH is rather nonspecific, which makes it difficult to identify patients based on the clinical presentation, unless they show (new) signs of overt right heart failure. Patients may, however, be identified by close assessment of the index computed tomography pulmonary angiography (CTPA) performed to confirm the PE. Certain CTPA characteristics have been shown to strongly predict a future CTEPH diagnosis: these signs of CTEPH can be reliably detected by both expert and nonexpert radiologists, and the presence of these should prompt additional diagnostic tests (►**Fig. 2**).[77–81] While CTEPH can only be diagnosed through RHC, noninvasive tests can be used to rule out CTEPH. The diagnostic work-up of CTEPH starts with echocardiography.[7,23,82] A low probability of PH (peak tricuspid regurgitation of ≤2.8 m/s and no "PH signs") on transthoracic echocardiogram (TTE) rules out CTEPH.[7,30] If the echocardiography indicates intermediate or high probability of PH, further evaluation should be performed with V/Q scanning and RHC in case of persistent perfusion defects.

A noninvasive screening algorithm consisting of a clinical prediction score and the so-called "CTEPH rule-out criteria"

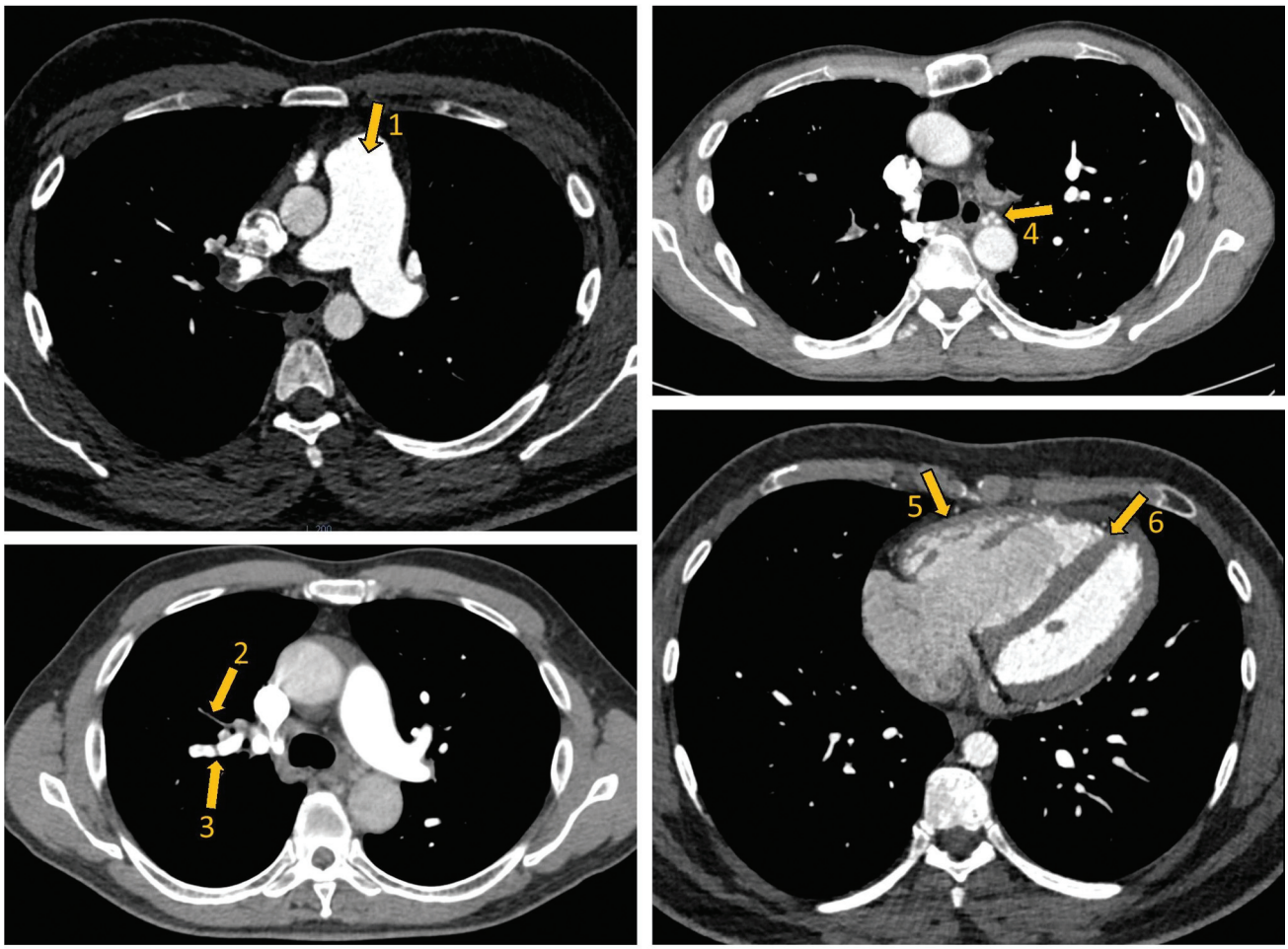

Fig. 2 Chronic thromboembolic pulmonary hypertension signs on CTPA. Image courtesy: Boon et al.[79]

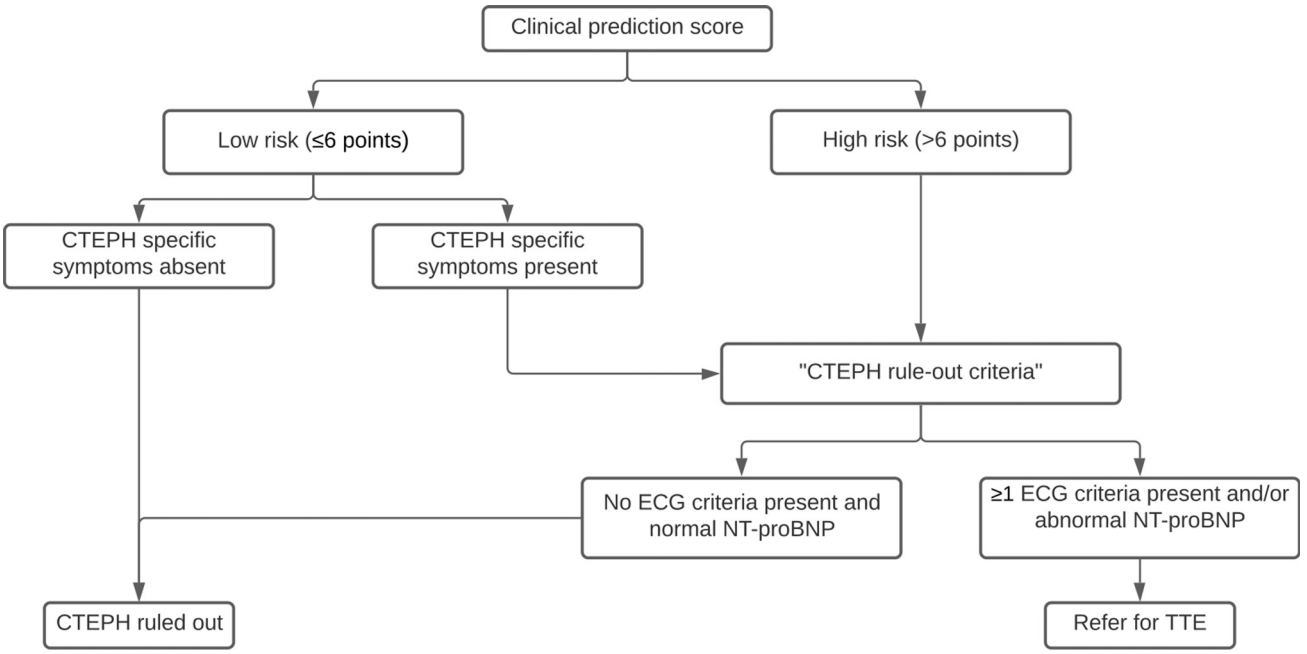

Fig. 3 Noninvasive early exclusion of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: the InShape II algorithm.[87] The ECG criteria of RV pressure overload: (1) rSR′ or rSr′ pattern in lead V1, (2) R:S > 1 in lead V1 with R > 0.5 mV, and (3) QRS axis > 90°. CTEPH, chronic thromboembolic pulmonary hypertension; ECG, electrocardiogram; NT-proBNP, N-terminal-prohormone of brain natriuretic peptide; TTE, transthoracic echocardiogram.

may also be used to rule out CTEPH.[83] The clinical prediction score can identify post-PE patients with a higher pretest probability of developing CTEPH.[84] The CTEPH rule-out criteria consist of a N-terminal-prohormone of brain natriuretic peptide (NT-proBNP; abnormal age- and gender-dependent level as defined by the assay's manufacturer) measurement and ECG reading (presence of three specific ECG characteristics of RV overload); if both are normal, CTEPH is considered ruled out (►**Fig. 3**).[85] Application of the CTEPH rule-out criteria to rule out CTEPH without further testing was deemed safe in retrospective studies.[85,86] The efficacy and safety of combining the clinical prediction score and CTEPH rule-out criteria in a noninvasive algorithm was prospectively evaluated in the Inshape II study.[87] CTEPH was considered ruled out in asymptomatic patients with a low risk of developing CTEPH according to the prediction score or in patients with normal NT-proBNP and no ECG characteristics for RV overload. Otherwise, standard evaluation with TTE as a first step was indicated. The algorithm resulted in a need for TTE in only 19% of the patients, with a low failure rate of 0.29%.[87]

If CTEPH is ruled out, further diagnostic work-up depends on the characteristics of the individual patient. Potential useful diagnostic tests involve TTE (if not yet performed), CPET, pulmonary function tests, and imaging tests to evaluate the presence of persistent perfusion defects and residual clots (►**Fig. 4**). The prevalence of post-PE cardiac impairment as well as other cardiological conditions such as systolic or diastolic dysfunction may be assessed with TTE. A recent follow-up study showed that left-sided diastolic dysfunction is the most frequent TTE abnormality in PE survivors, and out of all symptomatic subjects during follow-up, diastolic dysfunction was most frequently found to be the cause of functional limitations (34.2% of all symptomatic patients had diastolic dysfunction).[88] Notably, in patients with a normal ECG and NT-proBNP level, the incidence of relevant abnormalities on echocardiography is low.

A potential informative diagnostic test for patients with PPES without CTEPH can be CPET. CPET can be an excellent tool to further recognize pathological factors limiting exercise such as respiratory limitation, cardiovascular limitation, and peripheral muscle limitations.[89] With the recognition of the pathological limiting factor, potential therapeutic targets can be identified and prognostic information is provided.[89] Previous studies gave an interesting insight into the cardiopulmonary recovery after an acute PE. Overall, shortly after diagnosis, there is a decreased peak aerobic capacity (VO_2), which improves over time.[8,43,44,90,91] Also, increased physiological dead space proportion (the ratio of physiologic dead space over tidal volume [Vd/Vt]) and decreased stroke volume reserve are common among symptomatic post-PE patients with no residual pulmonary vascular obstruction.[90] Mostly, CPET may play a role in detecting CTEPD without PH[92,93] and post-PE functional impairment caused by deconditioning. Deconditioning (usually defined as low VO_2 at anaerobic threshold with normal cardiovascular, ventilatory, and gas exchange responses on CPET) is attributed to be the most frequent cause of post-PE persistent functional limitations and/or symptoms and no residual pulmonary vascular obstruction.[43,44] Therefore, CPET might be useful for the selection of patients who will likely benefit from cardiopulmonary exercise training or rehabilitation as treatment of PPES. Moreover, CPET might also be useful after an intervention to evaluate improvement in cardiopulmonary response

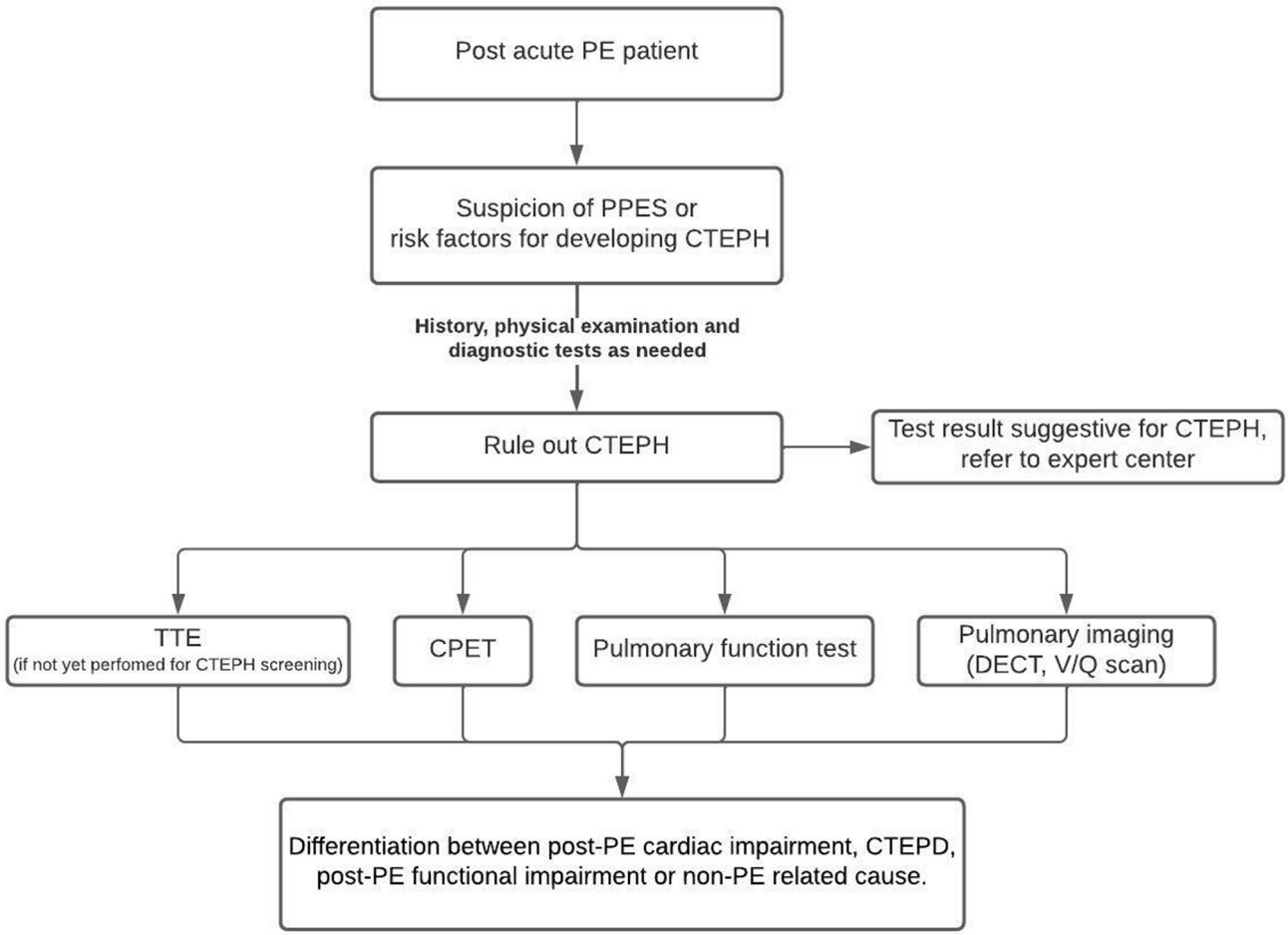

Fig. 4 Flow chart for follow-up 3 months after an acute PE for the detection of PPES. CPET, cardiopulmonary exercise test; CTEPD, chronic thromboembolic pulmonary disease; CTEPH, chronic thromboembolic pulmonary hypertension; DECT, dual-energy computed tomography; PE, pulmonary embolism; PPES, post–pulmonary embolism syndrome; TTE, transthoracic echocardiogram; V/Q, ventilation/perfusion.

to exercise. Lastly, CPET, in combination with pulmonary function tests, can be useful for the evaluation of non-PE–related alternative causes of persistent symptoms.[23] Even though CPET can provide relevant information as explained earlier, it should be noted that interpretation of CPET can be difficult. There is no clear consensus on which parameters measured during CPET are essential in diagnosing PPES subgroups. Interpretation of CPET therefore relies on pattern recognition by physicians with knowledge and expertise regarding lung physiology. Interpretation can be difficult for those with fewer expertise. For detecting persistent perfusion defects, in particular in the diagnostic work-up for CTEPH, V/Q scanning remains the diagnostic standard.[7,23] Single-photon emission computed tomography (SPECT) V/Q has shown to be superior to planar V/Q scanning.[23] Other pulmonary imaging strategies can also be used in the post-PE follow-up. Dual-energy computed tomography (DECT), in which iodine maps represent areas with decreased lung perfusion, has an emerging role in the field.[23,94] These pulmonary imaging techniques are adequate strategies to demonstrate persistent perfusion defects, but they should not be used as a routine screening test after acute PE. Perfusion defects may be associated with increased PAP and functional limitations, but 40% of patients with persistent perfusion defects do not report related symptoms.[95] Furthermore, the ELOPE study showed that the presence of persistent perfusion defects was equal in patients with a peak $VO_2 < 80\%$ of predicted compared with patients with a peak $VO_2 > 80\%$ of predicted, suggesting that persistent perfusion defects do not explain functional limitations in PPES.[43] Therefore, pulmonary imaging should only be performed in patients in whom CTEPH or CTEPD without PH is suspected based on the results of TTE and/or CPET.

Treatment

For CTEPH, pulmonary endarterectomy (PEA) is the treatment of choice (class I, level C recommendation).[7,23,30] PEA results in improved hemodynamic and exercise tolerance and is associated with low early mortality when performed in expert centers.[23,96,97] However, some patients are inoperable due to comorbidities or distal disease (even though which degree of distal disease is still operable is unknown). For these patients, potential treatment options are balloon pulmonary angioplasty (BPA), medical treatment, or a combination of both.[23,30] Two large national BPA series from Germany and France showed that BPA is safe and suggest that it is effective in the treatment of CTEPH.[98,99] Inoperable

Table 1 PH medication studies for treatment of CTEPH

Study	Year	Study type	Patients	Intervention	Outcome
CHEST-1[132]	2013	RCT	Inoperable CTEPH of residual PH after PEA ($n = 261$)	Riociguat	• PVR mean difference of -226 dyn · s · cm^{-5} for riociguat group and $+23$ dyn · s · cm^{-5} for the control group (mean difference: -246 dyn · s · cm^{-5}; 95% CI: −303 to −190) • 6MWT mean difference of +39 m for riociguat group and −6 m for placebo group (mean difference: 46 m; 95% CI: 25–67)
Reichenberger et al[133]	2007	Open label uncontrolled trial	Inoperable CTEPH ($n = 104$)	Sildenafil	• Decrease in PVR of 104 dyn · s · cm^{-5} • Increase in 6MWT of +51 m
BENEFIT[134]	2008	RCT	Inoperable CTEPH of residual PH after PEA ($n = 157$)	Bosentan	• PVR mean difference of -146 dyn · s · cm^{-5} for bosentan group and $+30$ dyn · s · cm^{-5} for the control group (mean treatment effect: −24.1%; 95% CI: −31.5 to −16.0%) • 6MWT mean difference of +2.9 m for bosentan group and +0.8 m for placebo group (mean difference: 2.2 m; 95% CI: 22.5–26.8)
MERIT-1[135]	2017	RCT	Inoperable CTEPH ($n = 80$)	Macitentan	• PVR mean difference of -206 dyn · s · cm^{-5} for macitentan group and -86 dyn · s · cm^{-5} for placebo group (geometric PVR ratio: 0.84; 95% CI: 0.70–0.99) • 6MWT mean difference of +35 m for macitentan group and +1 m for placebo group (mean difference: 34 m; 95% CI: 2.9–65.2)

Abbreviations: 6MWT, 6-minute walk test; CI, confidence interval; CTEPH, chronic thromboembolic pulmonary hypertension; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RCT, randomized controlled trial.

CTEPH patients were treated with BPA, after which they showed improvement of 6-minute walk test and reduction of mean PAP. The role of BPA in potential operable patients has not been evaluated and a randomized controlled trial comparing PEA with BPA is currently lacking. Based on clinical expertise, PEA remains the first choice of treatment for CTEPH.[23,30]

Different PH-specific medications have been evaluated in randomized controlled trials for the treatment of technically inoperable CTEPH patients or patients with persistent PH after PEA (►**Table 1**), showing beneficial value of treatment with PH-specific medication. However, the role of PH medication in relation to BPA or PEA remains unknown.[23] CTEPD patients without PH might also benefit from these treatments, but efficacy has only been evaluated in noncontrolled cohort studies with small patient populations.[35,36] Since many remain unknown in the treatment of CTEPH or CTEPD without PH, it is recommended that all patients are referred to an expert center to be discussed in a multidisciplinary team.[23]

For post-PE, functional impairment deconditioning seems to be a major component. Therefore, it is suggested that exercise training or cardiopulmonary rehabilitation is an adequate treatment for this patient category. ►**Table 2** gives an overview of the studies that have investigated the effect of exercise training in post–acute PE patients. Overall, multiple studies have shown that exercise training in patients with PPES is safe.[100–107] Rehabilitation can be effective to improve outcomes of patients with persistent symptoms several months after the acute PE. Randomized controlled trials with large sample sizes investigating the effectiveness of a rehabilitation course in patients with PPES are currently lacking. However, several cohort studies have shown an improvement in QoL, dyspnea, training intensity, and functional status after pulmonary rehabilitation.[105,107] Therefore, for patients with post-PE functional impairment, rehabilitation should be considered as a possible treatment option.

To prevent deconditioning, negative spiraling, and PPES as a result, exercise training can also be initiated shortly after diagnosis. A randomized controlled trial showed significant improvement of estimated VO_{2max}, RV/left ventricle ratio, and health-related QoL in the high-intensity interval training group after 8 weeks of training started shortly after PE diagnosis, while no improvement was found in the control group.[106] A Danish trial randomized 140 patients between an 8-week home-based exercise program with nurse consultations starting 2 to 3 weeks after PE diagnosis and a control group. The exercise program resulted in a greater improvement of incremental shuttle walk test and PE-specific QoL compared with the control group. However, between-group differences were small.[104] Since these two studies included unselected post-PE patients without considering persistent symptoms, the impact of an early exercise training program might be even larger in selected patients with persistent dyspnea and functional limitations, which should be evaluated in randomized controlled trials.

PPES in the COVID-19 Pandemic

After a COVID-19 infection, 22 to 96% of the patients have persistent symptoms qualifying for "long coronavirus

Table 2 Summary of rehabilitation studies in post-acute PE patients

Author	Year	Study type	Patients and timing of intervention	Intervention	Control	Outcome
Lakoski et al[100]	2015	RCT	VTE ≥6 weeks and <3 months before enrolment ($n=17$; 10 PE and 7 DVT)	3-month exercise and behavioral weight loss intervention	Usual care	• No AE in either group • Mean difference of exercise per week of 133 min in sfavor of intervention group • VO_{2max} improved significantly for the intervention group (26.1 to 29.8 mL O_2/kg)
Noack et al[101]	2015	Retrospective cohort study	Post-acute PE patients referred for rehabilitation; timing unknown ($n=422$)	3-week inpatient rehabilitation course	–	• 57 AEs occurred, all nonrelated to the rehabilitation course
Amoury et al[102]	2018	Prospective cohort study	Post–acute PE patients; timing unknown ($n=70$)	3-week inpatient rehabilitation course	–	• No patients died during rehabilitation; 4 patients (5.7%) died during the 12-month follow-up period • 20 patients were hospitalized during the follow-up period (28.6%), of whom 1 patient due to newly diagnosed PE (1.4%) and 2 patients due to bleeding (2.8%)
Cires-Drouet et al[103]	2020	Prospective cohort study	PE < 28 days before enrolment ($n=23$)	3-month aerobic exercise training	–	• No AE during the exercise period • 1 death, 1 DVT, and 5 readmissions due to non–exercise-related reasons • VO_{2max} improved significantly (+3.9 mL O_2/kg)
Rolving et al[104]	2020	RCT	PE 2–3 weeks before enrolment ($n=140$)	8-week home-based exercise program	Usual care with brief nurse consultation	• The exercise program resulted in a greater improvement of incremental SWT and PE-specific QoL compared with the control group (mean difference 25 m and 3.0 points on PEmb-QoL score, respectively)
Nopp et al[105]	2020	Retrospective cohort study	Acute PE median of 19 weeks before starting rehabilitation ($n=22$)	6-week outpatient pulmonary rehabilitation	–	• Mean improvement of 6MWT of 49.4 m • Improvement of self-reported health (78% of the patients reported much better or better health status)
Ghram et al[106]	2021	RCT	Acute PE 3–4 weeks before baseline measurements ($n=24$)	8-week high-intensity interval training	Usual care	• Improvement of estimated VO_{2max} (22.9 to 37.7 mL O_2/kg; $p<0.05$), RV/LV ratio (1.1 to 0.8; $p=0.005$), and health-related QoL in the intervention group • No significant improvement estimated VO_{2max} (28.6 to 33.3 mL O_2/kg; $p=0.08$), RV/LV ratio (0.8 to 0.8 $p=0.33$), and health-related QoL for the control group
Boon et al[107]	2021	Prospective cohort study	Patients with persistent moderate-to-severe dyspnea 3 months after acute PE ($n=27$)	12-week outpatient rehabilitation program	–	• Significant improvement in training intensity (+20 watt), PE-specific QoL (+3.9 points on PEmb-QoL score), fatigue (+16 points on Checklist Individual Strength scale), and functional status (67% of patients had improvement of ≥1 PVFS scale grade)

Abbreviations: 6MWT, 6-minute walk test; AE, adverse event; DVT, deep venous thromboembolism; PE, pulmonary embolism; PVFS, Post-VTE Functional Status; QoL, quality of life; RCT, randomized controlled trial; RV/LV, right ventricle/left ventricle; SWT, shuttle walk test; VTE, venous thromboembolism.

disease" also known as "long-COVID."[108–116] It can be hypothesized that since the incidence of thromboembolic events in COVID-19 is high, patients qualifying for long-COVID might also qualify for PPES. Symptoms of long-COVID might mimic post-PE functional impairment due to reduced exercise capacity and deconditioning following COVID-19.

There are several arguments to potentially expect a higher CTEPH and CTEPD without PH incidence in the COVID-19 pandemic. First, the increased number of patients with PE will result in a higher number of post-PE patients at risk for developing CTEPH or CTEPD without PH.[117–123] Second, it has been described that COVID-19 is associated with reduced fibrinolysis due to the inflammatory state. Elevated levels of plasminogen activator inhibitor-1 in COVID-19 have been shown, resulting in decreased fibrinolysis.[124–126] This hypofibrinolytic state could possibly facilitate incomplete thrombus resolution, which is part of the etiology of CTEPH and CTEPD without PH. Moreover, SARS-CoV-2 can invade endothelial cells directly or indirectly through an inflammatory effect.[124,127] This can lead to endothelial dysfunction, which is one of the hallmarks of CTEPH.[22] Third, one could argue that the presence of VTE may not have been evaluated properly in all COVID-19 patients. Most COVID-19–associated VTE events occur in patients during hospitalization or after hospitalization, and only a small proportion of the patients treated at home are tested for the presence of VTE.[128] Since they were never subjected to CTPA, a substantial number of these patients may have experienced undiagnosed VTE. Although long-term follow-up studies after COVID-19–associated PE are currently unavailable, the results of two studies may support a higher than expected incidence of CTEPH. TTE assessment in non–intensive care unit hospitalized COVID-19 patients showed a higher than expected prevalence of PH of 12% (24/200 patients), and COVID-19 survivors were found to have a 3-fold higher incidence of PH in the 4 months after the acute infection than non-COVID-19 patients (based on claims data).[129,130] While any hypothesis on incidence of CTEPH in COVID-19 patients still should be regarded as speculation, ongoing studies are expected to provide relevant answers in the next year.[131]

All in all, the possible higher incidence of CTEPH and CTEPD without PH underlines the need of adequate follow-up of patients with persistent symptoms after COVID-19 and awareness for chronic vascular COVID-19 complications.

Case Resolution

The patient reported a PVFS scale grade of 3, MRC grade of 2 ("I get short of breath when hurrying on the level or up a slight hill"), and a PEmb-QoL score of 16 points. She had a normal ECG but abnormal NT-proBNP of 192 ng/L (normal $<$125 ng/L). Follow-up TTE showed no abnormalities and a low probability of PH, and therefore CTEPH and post-PE cardiac impairment were considered excluded. The patient was subjected to CPET, which showed a decreased VO_2 at anaerobic threshold of 32% of predicted, Vd/Vt that appropriately decreased during exercise (until 0.25 at peak of exercise), VE/VCO_2 at anaerobic threshold of 31.2, and the patient reported a modified Borg score of perceived exertion of 7 ("very hard") after exercise, indicating no dead space ventilation but potential deconditioning as cause of persistent symptoms. She was referred to a rehabilitation center for an 8-week outpatient rehabilitation course consisting of 60-minute endurance and strength exercise sessions, three times a week. After 8 weeks of exercise training, the patient reported increased functional status (PVFS scale grade of 1), only breathlessness with strenuous exercise (MRC grade 1), and improved QoL (PEmb-QoL score of 10, indicating a clinically relevant improvement). She was able to resume her usual professional and social activities.

Conclusion

Many patients suffer from persistent symptoms and functional limitations after acute PE. To manage these patients properly, awareness of PPES is of utmost importance. PROMs can help objectify complaints after acute PE and select patients in whom further evaluation is necessary. Since CTEPH is the most feared subgroup of PPES, evaluation of the presence of possible CTEPH has priority. Furthermore, since most PPES patients are ultimately diagnosed with post-PE functional impairment, treatment with exercise training programs could contribute to patients' functional recovery. Lastly, it is reasonable to consider and test for PPES in patients with long-COVID, even if they were not diagnosed with acute PE.

Conflict of Interest
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References

1 Barco S, Mahmoudpour SH, Valerio L, et al. Trends in mortality related to pulmonary embolism in the European Region, 2000-15: analysis of vital registration data from the WHO Mortality Database. Lancet Respir Med 2020;8(03):277–287
2 Barco S, Valerio L, Ageno W, et al. Age-sex specific pulmonary embolism-related mortality in the USA and Canada, 2000-18: an analysis of the WHO Mortality Database and of the CDC Multiple Cause of Death database. Lancet Respir Med 2021;9 (01):33–42
3 Klok FA, Mos IC, Broek L, et al. Risk of arterial cardiovascular events in patients after pulmonary embolism. Blood 2009;114 (08):1484–1488
4 Klok FA, Zondag W, van Kralingen KW, et al. Patient outcomes after acute pulmonary embolism. A pooled survival analysis of different adverse events. Am J Respir Crit Care Med 2010;181 (05):501–506
5 Klok FA, Ageno W, Ay C, et al. Optimal follow-up after acute pulmonary embolism: a position paper of the European Society

of Cardiology Working Group on Pulmonary Circulation and Right Ventricular Function, in collaboration with the European Society of Cardiology Working Group on Atherosclerosis and Vascular Biology, endorsed by the European Respiratory Society. Eur Heart J 2022;43(03):183–189
6 Huisman MV, Barco S, Cannegieter SC, et al. Pulmonary embolism. Nat Rev Dis Primers 2018;4:18028
7 Konstantinides SV, Meyer G, Becattini C, et al; The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC) 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Respir J 2019;54(03):1901647
8 Kahn SR, Akaberi A, Granton JT, et al. Quality of life, dyspnea, and functional exercise capacity following a first episode of pulmonary embolism: results of the ELOPE cohort study. Am J Med 2017;130(08):990.e9–990.e21
9 Klok FA, Cohn DM, Middeldorp S, et al. Quality of life after pulmonary embolism: validation of the PEmb-QoL Questionnaire. J Thromb Haemost 2010;8(03):523–532
10 Klok FA, van Kralingen KW, van Dijk AP, et al. Quality of life in long-term survivors of acute pulmonary embolism. Chest 2010; 138(06):1432–1440
11 Sista AK, Miller LE, Kahn SR, Kline JA. Persistent right ventricular dysfunction, functional capacity limitation, exercise intolerance, and quality of life impairment following pulmonary embolism: systematic review with meta-analysis. Vasc Med 2017;22(01):37–43
12 Tavoly M, Utne KK, Jelsness-Jørgensen LP, et al. Health-related quality of life after pulmonary embolism: a cross-sectional study. BMJ Open 2016;6(11):e013086
13 Valerio L, Barco S, Jankowski M, et al. Quality of life 3 and 12 months following acute pulmonary embolism: analysis from a prospective multicenter cohort study. Chest 2021;159 (06):2428–2438
14 Sista AK, Klok FA. Late outcomes of pulmonary embolism: the post-PE syndrome. Thromb Res 2018;164:157–162
15 Klok FA, van Kralingen KW, van Dijk AP, Heyning FH, Vliegen HW, Huisman MV. Prevalence and potential determinants of exertional dyspnea after acute pulmonary embolism. Respir Med 2010;104(11):1744–1749
16 Stevinson BG, Hernandez-Nino J, Rose G, Kline JA. Echocardiographic and functional cardiopulmonary problems 6 months after first-time pulmonary embolism in previously healthy patients. Eur Heart J 2007;28(20):2517–2524
17 Kline JA, Steuerwald MT, Marchick MR, Hernandez-Nino J, Rose GA. Prospective evaluation of right ventricular function and functional status 6 months after acute submassive pulmonary embolism: frequency of persistent or subsequent elevation in estimated pulmonary artery pressure. Chest 2009;136(05):1202–1210
18 Klok FA, van der Hulle T, den Exter PL, Lankeit M, Huisman MV, Konstantinides S. The post-PE syndrome: a new concept for chronic complications of pulmonary embolism. Blood Rev 2014;28(06):221–226
19 Klok FA, Barco S. Follow-up after acute pulmonary embolism. Hamostaseologie 2018;38(01):22–32
20 Boon GJAM, Huisman MV, Klok FA. Determinants and management of the post-pulmonary embolism syndrome. Semin Respir Crit Care Med 2021;42(02):299–307
21 Le Gal G, Carrier M, Castellucci LA, et al; ISTH CDE Task Force. Development and implementation of common data elements for venous thromboembolism research: on behalf of SSC Subcommittee on official Communication from the SSC of the ISTH. J Thromb Haemost 2021;19(01):297–303
22 Simonneau G, Torbicki A, Dorfmüller P, Kim N. The pathophysiology of chronic thromboembolic pulmonary hypertension. Eur Respir Rev 2017;26(143):160112
23 Delcroix M, Torbicki A, Gopalan D, et al. ERS statement on chronic thromboembolic pulmonary hypertension. Eur Respir J 2021;57 (06):2002828
24 Lang IM, Dorfmüller P, Vonk Noordegraaf A. The pathobiology of chronic thromboembolic pulmonary hypertension. Ann Am Thorac Soc 2016;13(Suppl 3):S215–S221
25 Quarck R, Wynants M, Verbeken E, Meyns B, Delcroix M. Contribution of inflammation and impaired angiogenesis to the pathobiology of chronic thromboembolic pulmonary hypertension. Eur Respir J 2015;46(02):431–443
26 Sharma S, Hofbauer TM, Ondracek AS, et al. Neutrophil extracellular traps promote fibrous vascular occlusions in chronic thrombosis. Blood 2021;137(08):1104–1116
27 Mathai SC, Ghofrani HA, Mayer E, Pepke-Zaba J, Nikkho S, Simonneau G. Quality of life in patients with chronic thromboembolic pulmonary hypertension. Eur Respir J 2016;48(02): 526–537
28 Roman A, Barbera JA, Castillo MJ, Muñoz R, Escribano P. Health-related quality of life in a national cohort of patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension. Arch Bronconeumol 2013;49(05):181–188
29 Delcroix M, Lang I, Pepke-Zaba J, et al. Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. Circulation 2016;133(09):859–871
30 Galiè N, Humbert M, Vachiery J-L, et al; ESC Scientific Document Group. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37 (01):67–119
31 Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53(01):1801913
32 Held M, Kolb P, Grün M, et al. Functional characterization of patients with chronic thromboembolic disease. Respiration 2016;91(06):503–509
33 Claeys M, Claessen G, La Gerche A, et al. Impaired cardiac reserve and abnormal vascular load limit exercise capacity in chronic thromboembolic disease. JACC Cardiovasc Imaging 2019;12(8 Pt 1):1444–1456
34 van Kan C, van der Plas MN, Reesink HJ, et al. Hemodynamic and ventilatory responses during exercise in chronic thromboembolic disease. J Thorac Cardiovasc Surg 2016;152(03):763–771
35 Taboada D, Pepke-Zaba J, Jenkins DP, et al. Outcome of pulmonary endarterectomy in symptomatic chronic thromboembolic disease. Eur Respir J 2014;44(06):1635–1645
36 Coghlan JG. Balloon pulmonary angioplasty: does it have a role in CTED? Pulm Circ 2018;8(01):2045893218754887
37 Ribeiro A, Lindmarker P, Johnsson H, Juhlin-Dannfelt A, Jorfeldt L. Pulmonary embolism: one-year follow-up with echocardiography doppler and five-year survival analysis. Circulation 1999;99 (10):1325–1330
38 Kurnicka K, Lichodziejewska B, Goliszek S, et al. Echocardiographic pattern of acute pulmonary embolism: analysis of 511 consecutive patients. J Am Soc Echocardiogr 2016;29(09): 907–913
39 Golpe R, Testa-Fernández A, Pérez-de-Llano LA, et al. Long-term clinical outcome of patients with persistent right ventricle dysfunction or pulmonary hypertension after acute pulmonary embolism. Eur J Echocardiogr 2011;12(10):756–761
40 Watts JA, Zagorski J, Gellar MA, Stevinson BG, Kline JA. Cardiac inflammation contributes to right ventricular dysfunction following experimental pulmonary embolism in rats. J Mol Cell Cardiol 2006;41(02):296–307

41 Iwadate K, Doi M, Tanno K, et al. Right ventricular damage due to pulmonary embolism: examination of the number of infiltrating macrophages. Forensic Sci Int 2003;134(2–3):147–153
42 Gleditsch J, Jervan Ø, Tavoly M, et al. Association between myocardial fibrosis, as assessed with cardiac magnetic resonance T1 mapping, and persistent dyspnea after pulmonary embolism. Int J Cardiol Heart Vasc 2021;38:100935
43 Kahn SR, Hirsch AM, Akaberi A, et al. Functional and exercise limitations after a first episode of pulmonary embolism: results of the ELOPE prospective cohort study. Chest 2017;151(05): 1058–1068
44 Albaghdadi MS, Dudzinski DM, Giordano N, et al. Cardiopulmonary exercise testing in patients following massive and submassive pulmonary embolism. J Am Heart Assoc 2018;7(05): e006841
45 Hunter R, Noble S, Lewis S, Bennett P. Long-term psychosocial impact of venous thromboembolism: a qualitative study in the community. BMJ Open 2019;9(02):e024805
46 Kirchberger I, Ruile S, Linseisen J, Haberl S, Meisinger C, Berghaus TM. The lived experience with pulmonary embolism: a qualitative study using focus groups. Respir Med 2020;167:105978
47 Danielsbacka JS, Rostberg L, Olsén MF, Mannerkorpi K. "Whole life changed" - Experiences of how symptoms derived from acute pulmonary embolism affects life. A qualitative interview study. Thromb Res 2021;205:56–62
48 Keller K, Tesche C, Gerhold-Ay A, et al. Quality of life and functional limitations after pulmonary embolism and its prognostic relevance. J Thromb Haemost 2019;17(11):1923–1934
49 Braekkan SK, Grosse SD, Okoroh EM, et al. Venous thromboembolism and subsequent permanent work-related disability. J Thromb Haemost 2016;14(10):1978–1987
50 Willich SN, Chuang LH, van Hout B, et al. Pulmonary embolism in Europe - Burden of illness in relationship to healthcare resource utilization and return to work. Thromb Res 2018;170:181–191
51 Jørgensen H, Horváth-Puhó E, Laugesen K, Brækkan S, Hansen JB, Sørensen HT. Risk of a permanent work-related disability pension after incident venous thromboembolism in Denmark: a population-based cohort study. PLoS Med 2021;18(08): e1003770
52 Guérin L, Couturaud F, Parent F, et al. Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Prevalence of CTEPH after pulmonary embolism. Thromb Haemost 2014;112(03):598–605
53 Choi SW, Victorson DE, Yount S, Anton S, Cella D. Development of a conceptual framework and calibrated item banks to measure patient-reported dyspnea severity and related functional limitations. Value Health 2011;14(02):291–306
54 Crisafulli E, Clini EM. Measures of dyspnea in pulmonary rehabilitation. Multidiscip Respir Med 2010;5(03):202–210
55 Mador MJ, Rodis A, Magalang UJ. Reproducibility of Borg scale measurements of dyspnea during exercise in patients with COPD. Chest 1995;107(06):1590–1597
56 McGoon M, Gutterman D, Steen V, et al; American College of Chest Physicians. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004;126(1, Suppl):14S–34S
57 Cohn DM, Nelis EA, Busweiler LA, Kaptein AA, Middeldorp S. Quality of life after pulmonary embolism: the development of the PEmb-QoL questionnaire. J Thromb Haemost 2009;7(06): 1044–1046
58 EuroQol Group. EuroQol–a new facility for the measurement of health-related quality of life. Health Policy 1990;16(03): 199–208
59 Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30(06):473–483
60 Hays RD, Bjorner JB, Revicki DA, Spritzer KL, Cella D. Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. Qual Life Res 2009;18(07):873–880
61 Klok FA, Barco S, Siegerink B. Measuring functional limitations after venous thromboembolism: a call to action. Thromb Res 2019;178:59–62
62 Boon GJAM, Barco S, Bertoletti L, et al. Measuring functional limitations after venous thromboembolism: optimization of the Post-VTE Functional Status (PVFS) scale. Thromb Res 2020; 190:45–51
63 Klok FA, Boon GJAM, Barco S, et al. The Post-COVID-19 Functional Status scale: a tool to measure functional status over time after COVID-19. Eur Respir J 2020;56(01):2001494
64 Machado FVC, Meys R, Delbressine JM, et al. Construct validity of the Post-COVID-19 Functional Status Scale in adult subjects with COVID-19. Health Qual Life Outcomes 2021;19(01):40
65 Leite LC, Carvalho L, Queiroz DM, et al. Can the post-COVID-19 functional status scale discriminate between patients with different levels of fatigue, quality of life and functional performance? Pulmonology 2022;28(03):220–223
66 Çalik Kütükcü E, Çakmak A, Kinaci E, et al. Reliability and validity of the Turkish version of Post-COVID-19 Functional Status Scale. Turk J Med Sci 2021;51(05):2304–2310
67 Lorca LA, Torres-Castro R, Ribeiro IL, et al. Linguistic validation and cross-cultural adaptation of the Post-COVID-19 Functional Status Scale for the Chilean population. Am J Phys Med Rehabil 2021;100(04):313–320
68 Lorca LA, Leão Ribeiro I, Torres-Castro R, Sacomori C, Rivera C. Psychometric properties of the Post-COVID 19 Functional Status scale for adult COVID 19 survivors [in Spanish]. Rehabilitacion (Madr) 2022;56(04):337–343
69 Moreno-Torres LA, Ventura-Alfaro CE. Validation of the Post-Covid-19 Functional Status Scale into Mexican-Spanish. J Rehabil Med Clin Commun 2021;4:1000070
70 Alonso J, Bartlett SJ, Rose M, et al; PROMIS International Group. The case for an international patient-reported outcomes measurement information system (PROMIS®) initiative. Health Qual Life Outcomes 2013;11:210
71 Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16(09): 606–613
72 Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166(10):1092–1097
73 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67(06):361–370
74 Worm-Smeitink M, Gielissen M, Bloot L, et al. The assessment of fatigue: psychometric qualities and norms for the Checklist Individual Strength. J Psychosom Res 2017;98:40–46
75 Klok FA, Barco S, Konstantinides SV, et al. Determinants of diagnostic delay in chronic thromboembolic pulmonary hypertension: results from the European CTEPH Registry. Eur Respir J 2018;52(06):1801687
76 Boon GJAM, van den Hout WB, Barco S, et al. A model for estimating the health economic impact of earlier diagnosis of chronic thromboembolic pulmonary hypertension. ERJ Open Res 2021;7(03):00719–02020
77 Ende-Verhaar YM, Meijboom LJ, Kroft LJM, et al. Usefulness of standard computed tomography pulmonary angiography performed for acute pulmonary embolism for identification of chronic thromboembolic pulmonary hypertension: results of the InShape III study. J Heart Lung Transplant 2019;38(07): 731–738
78 Boon GJAM, Jairam PM, Groot GMC, et al. Identification of chronic thromboembolic pulmonary hypertension on CTPAs performed for diagnosing acute pulmonary embolism depending on level of expertise. Eur J Intern Med 2021;93:64–70
79 Boon GJAM, Ende-Verhaar YM, Beenen LFM, et al. Prediction of chronic thromboembolic pulmonary hypertension with

standardised evaluation of initial computed tomography pulmonary angiography performed for suspected acute pulmonary embolism. Eur Radiol 2022;32(04):2178–2187
80 Lorenz G, Saeedan MB, Bullen J, et al. CT-based biomarkers for prediction of chronic thromboembolic pulmonary hypertension after an acute pulmonary embolic event. AJR Am J Roentgenol 2020;215(04):800–806
81 Braams NJ, Boon G, de Man FS, et al. Evolution of CT findings after anticoagulant treatment for acute pulmonary embolism in patients with and without an ultimate diagnosis of CTEPH. Eur Respir J 2021;58(06):2100699
82 de Perrot M, Gopalan D, Jenkins D, et al. Evaluation and management of patients with chronic thromboembolic pulmonary hypertension - consensus statement from the ISHLT. J Heart Lung Transplant 2021;40(11):1301–1326
83 Ende-Verhaar YM, Ruigrok D, Bogaard HJ, et al. Sensitivity of a simple noninvasive screening algorithm for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. TH Open 2018;2(01):e89–e95
84 Klok FA, Dzikowska-Diduch O, Kostrubiec M, et al. Derivation of a clinical prediction score for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. J Thromb Haemost 2016;14(01):121–128
85 Klok FA, Surie S, Kempf T, et al. A simple non-invasive diagnostic algorithm for ruling out chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism. Thromb Res 2011;128(01):21–26
86 Klok FA, Tesche C, Rappold L, et al. External validation of a simple non-invasive algorithm to rule out chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Thromb Res 2015;135(05):796–801
87 Boon GJAM, Ende-Verhaar YM, Bavalia R, et al; InShape II study group. Non-invasive early exclusion of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: the InShape II study. Thorax 2021;76(10):1002–1009
88 Dzikowska-Diduch O, Kostrubiec M, Kurnicka K, et al. "The post-pulmonary syndrome - results of echocardiographic driven follow up after acute pulmonary embolism". Thromb Res 2020;186:30–35
89 Radtke T, Crook S, Kaltsakas G, et al. ERS statement on standardisation of cardiopulmonary exercise testing in chronic lung diseases. Eur Respir Rev 2019;28(154):180101
90 Fernandes TM, Alotaibi M, Strozza DM, et al. Dyspnea postpulmonary embolism from physiological dead space proportion and stroke volume defects during exercise. Chest 2020;157(04): 936–944
91 Huang D, Guo J, Yang W, Liu J. Exercise capacity and ventilatory efficiency in patients with pulmonary embolism after short duration of anticoagulation therapy. Am J Med Sci 2020;359 (03):140–146
92 McCabe C, Deboeck G, Harvey I, et al. Inefficient exercise gas exchange identifies pulmonary hypertension in chronic thromboembolic obstruction following pulmonary embolism. Thromb Res 2013;132(06):659–665
93 Held M, Hesse A, Gött F, et al. A symptom-related monitoring program following pulmonary embolism for the early detection of CTEPH: a prospective observational registry study. BMC Pulm Med 2014;14:141
94 Fuld MK, Halaweish AF, Haynes SE, Divekar AA, Guo J, Hoffman EA. Pulmonary perfused blood volume with dual-energy CT as surrogate for pulmonary perfusion assessed with dynamic multidetector CT. Radiology 2013;267(03):747–756
95 Sanchez O, Helley D, Couchon S, et al. Perfusion defects after pulmonary embolism: risk factors and clinical significance. J Thromb Haemost 2010;8(06):1248–1255
96 Jaff MR, McMurtry MS, Archer SL, et al; American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; American Heart Association Council on Peripheral Vascular Disease; American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation 2011;123(16): 1788–1830
97 Kim NH, Delcroix M, Jenkins DP, et al. Chronic thromboembolic pulmonary hypertension. J Am Coll Cardiol 2013;62(25, Suppl): D92–D99
98 Brenot P, Jaïs X, Taniguchi Y, et al. French experience of balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. Eur Respir J 2019;53(05):1802095
99 Olsson KM, Wiedenroth CB, Kamp JC, et al. Balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension: the initial German experience. Eur Respir J 2017;49(06):1602409
100 Lakoski SG, Savage PD, Berkman AM, et al. The safety and efficacy of early-initiation exercise training after acute venous thromboembolism: a randomized clinical trial. J Thromb Haemost 2015; 13(07):1238–1244
101 Noack F, Schmidt B, Amoury M, et al. Feasibility and safety of rehabilitation after venous thromboembolism. Vasc Health Risk Manag 2015;11:397–401
102 Amoury M, Noack F, Kleeberg K, et al. Prognosis of patients with pulmonary embolism after rehabilitation. Vasc Health Risk Manag 2018;14:183–187
103 Cires-Drouet RS, Mayorga-Carlin M, Toursavadkohi S, et al. Safety of exercise therapy after acute pulmonary embolism. Phlebology 2020;35(10):824–832
104 Rolving N, Brocki BC, Bloch-Nielsen JR, et al. Effect of a physiotherapist-guided home-based exercise intervention on physical capacity and patient-reported outcomes among patients with acute pulmonary embolism: a randomized clinical trial. JAMA Netw Open 2020;3(02):e200064
105 Nopp S, Klok FA, Moik F, et al. Outpatient pulmonary rehabilitation in patients with persisting symptoms after pulmonary embolism. J Clin Med 2020;9(06):1811
106 Ghram A, Jenab Y, Soori R, et al. High-intensity interval training in patients with pulmonary embolism: a randomized controlled trial. Med Sci Sports Exerc 2021;53(10):2037–2044
107 Boon GJAM, Janssen SMJ, Barco S, et al. Efficacy and safety of a 12-week outpatient pulmonary rehabilitation program in Post-PE Syndrome. Thromb Res 2021;206:66–75
108 Bliddal S, Banasik K, Pedersen OB, et al. Acute and persistent symptoms in non-hospitalized PCR-confirmed COVID-19 patients. Sci Rep 2021;11(01):13153
109 Carfì A, Bernabei R, Landi FGemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. JAMA 2020;324(06):603–605
110 Chopra V, Flanders SA, O'Malley M, Malani AN, Prescott HC. Sixty-day outcomes among patients hospitalized with COVID-19. Ann Intern Med 2021;174(04):576–578
111 Crook H, Raza S, Nowell J, Young M, Edison P. Long covid-mechanisms, risk factors, and management. BMJ 2021;374 (1648):n1648
112 Davis HE, Assaf GS, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine 2021;38:101019
113 Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 2021;397(10270):220–232
114 Naeije R, Caravita S. Phenotyping long COVID. Eur Respir J 2021; 58(02):2101763
115 Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. Nat Med 2021;27(04):601–615
116 Vaes AW, Goërtz YMJ, Van Herck M, et al. Recovery from COVID-19: a sprint or marathon? 6-month follow-up data from online

long COVID-19 support group members. ERJ Open Res 2021;7 (02):00141–02021
117 Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145–147
118 Kaptein FHJ, Stals MAM, Grootenboers M, et al; Dutch COVID & Thrombosis Coalition. Incidence of thrombotic complications and overall survival in hospitalized patients with COVID-19 in the second and first wave. Thromb Res 2021;199:143–148
119 Nopp S, Moik F, Jilma B, Pabinger I, Ay C. Risk of venous thromboembolism in patients with COVID-19: A systematic review and meta-analysis. Res Pract Thromb Haemost 2020;4 (07):1178–1191
120 Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost 2020;18(07):1743–1746
121 Helms J, Tacquard C, Severac F, et al; CRICS TRIGGERSEP Group (Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis) High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 2020;46(06):1089–1098
122 Lodigiani C, Iapichino G, Carenzo L, et al; Humanitas COVID-19 Task Force. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 2020;191:9–14
123 Klok FA, Kruip MJHA, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. Thromb Res 2020;191:148–150
124 Loo J, Spittle DA, Newnham M. COVID-19, immunothrombosis and venous thromboembolism: biological mechanisms. Thorax 2021;76(04):412–420
125 Wright FL, Vogler TO, Moore EE, et al. Fibrinolysis shutdown correlation with thromboembolic events in severe COVID-19 infection. J Am Coll Surg 2020;231(02):193–203.e1
126 Whyte CS, Morrow GB, Mitchell JL, Chowdary P, Mutch NJ. Fibrinolytic abnormalities in acute respiratory distress syndrome (ARDS) and versatility of thrombolytic drugs to treat COVID-19. J Thromb Haemost 2020;18(07):1548–1555
127 Ackermann M, Verleden SE, Kuehnel M, et al. pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med 2020;383(02):120–128
128 Pasha AK, McBane RD, Chaudhary R, et al. Timing of venous thromboembolism diagnosis in hospitalized and non-hospitalized patients with COVID-19. Thromb Res 2021;207:150–157
129 Pagnesi M, Baldetti L, Beneduce A, et al. Pulmonary hypertension and right ventricular involvement in hospitalised patients with COVID-19. Heart 2020;106(17):1324–1331
130 Daugherty SE, Guo Y, Heath K, et al. Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. BMJ 2021;373(1098):n1098
131 Kruip MJHA, Cannegieter SC, Ten Cate H, et al; Dutch COVID Thrombosis Coalition study group. Caging the dragon: research approach to COVID-19-related thrombosis. Res Pract Thromb Haemost 2021;5(02):278–290
132 Ghofrani H-A, D'Armini AM, Grimminger F, et al; CHEST-1 Study Group. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. N Engl J Med 2013;369(04):319–329
133 Reichenberger F, Voswinckel R, Enke B, et al. Long-term treatment with sildenafil in chronic thromboembolic pulmonary hypertension. Eur Respir J 2007;30(05):922–927
134 Jaïs X, D'Armini AM, Jansa P, et al; Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension Study Group. Bosentan for treatment of inoperable chronic thromboembolic pulmonary hypertension: BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension), a randomized, placebo-controlled trial. J Am Coll Cardiol 2008;52(25):2127–2134
135 Ghofrani HA, Simonneau G, D'Armini AM, et al; MERIT study investigators. Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension (MERIT-1): results from the multicentre, phase 2, randomised, double-blind, placebo-controlled study. Lancet Respir Med 2017;5(10): 785–794