

# 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.<sup>1,2</sup> 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.<sup>3–6</sup> 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.<sup>7</sup>

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.<sup>5,8–13</sup> 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.<sup>8,11,14–17</sup> 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).<sup>18–20</sup> 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.<sup>5,21</sup> 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.<sup>22,23</sup> 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.<sup>22,24–26</sup> CTEPH is associated with poor QoL and is the most feared subgroup of PPES since untreated CTEPH is often fatal.<sup>27–29</sup> 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).<sup>7,30</sup> However, recent data from non-PH patients showed a normal mean PAP of  $14.0 \pm 3.3$  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.<sup>23,31</sup>

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.<sup>32</sup> 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<sub>2</sub> output [VCO<sub>2</sub>] ratio). This means that VE is increased during exercise without an accompanying increase in VCO<sub>2</sub>, which is suggestive of an increase of dead space ventilation.<sup>32–34</sup> 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.<sup>35,36</sup> 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.<sup>23</sup>

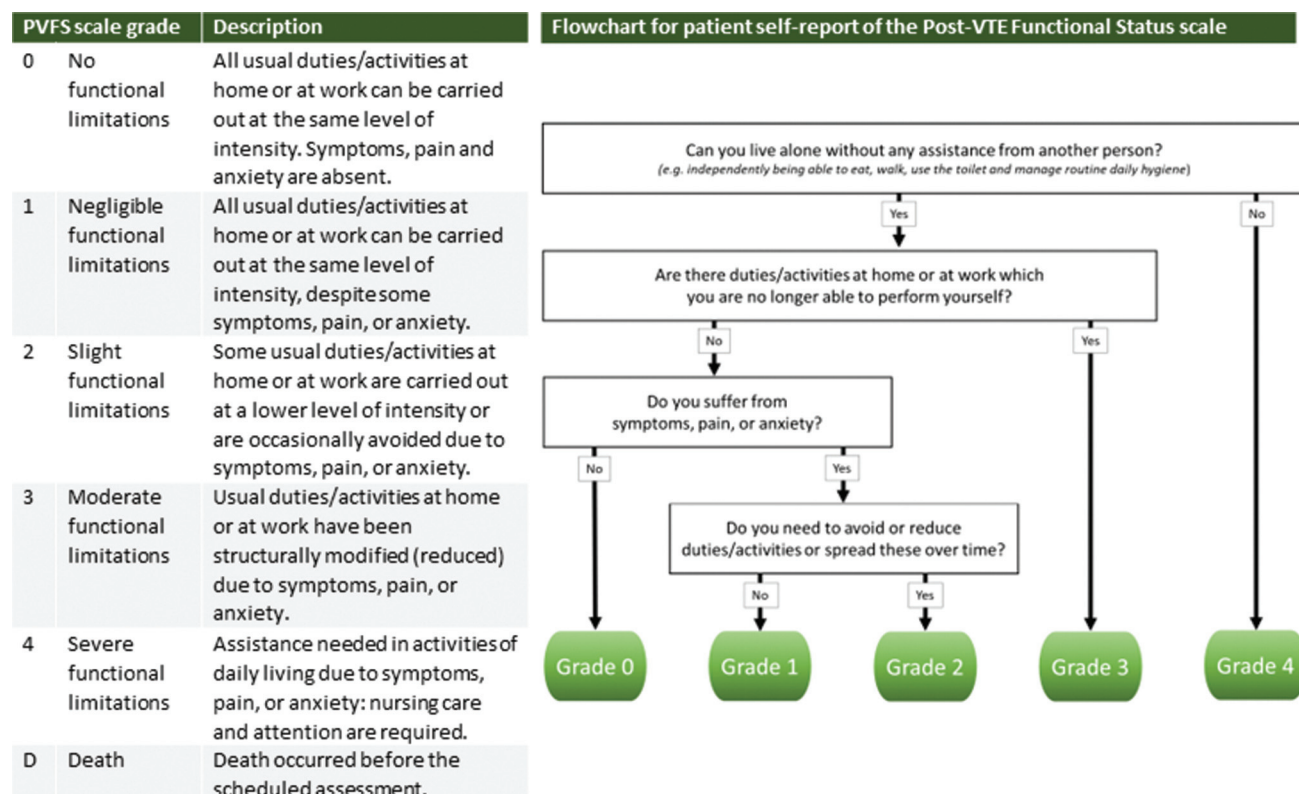
The second category of PPES comprises post-PE cardiac impairment. Post-PE cardiac impairment is defined by the ISTH as presence of intermediate/high echocardiographic probability of PH according to the European Society of Cardiology (ESC) criteria, RV hypokinesia, or RV dilatation, in combination with exertional dyspnea (NYHA II–IV).<sup>21</sup> At diagnosis of acute PE, 20 to 50% of the patients have RV dysfunction to some extent.<sup>11,16,17,37–39</sup> 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.<sup>16,40–42</sup> For 4 to 25% of the PE patients, RV dysfunction persists after several months.<sup>11,16,17,37,39</sup> 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.<sup>21</sup> Decreased daily physical activity after a PE diagnosis with resulting physical deconditioning is one of the main explanations for post-PE functional impairment.<sup>11,18–20,43,44</sup> 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.<sup>45–47</sup> Post-PE functional impairment is associated with reduced QoL and higher prevalence of depression and permanent work-related disability.<sup>10,13,43,48–51</sup>

### 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.<sup>7,52</sup> Alternative PROMs are PROMIS Short Form Dyspnea Severity, the (modified) Borg Dyspnea Scale, and the World Health Organization functional class.<sup>7,53–56</sup> 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.<sup>9,57–60</sup> 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).<sup>61</sup> 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.<sup>62</sup> 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.<sup>63</sup> 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.<sup>64,65</sup> In validation studies of translations of the



**Fig. 1** Flow chart for patient self-report of the Post-VTE Functional Status scale. Image courtesy: Boon et al.<sup>62</sup>

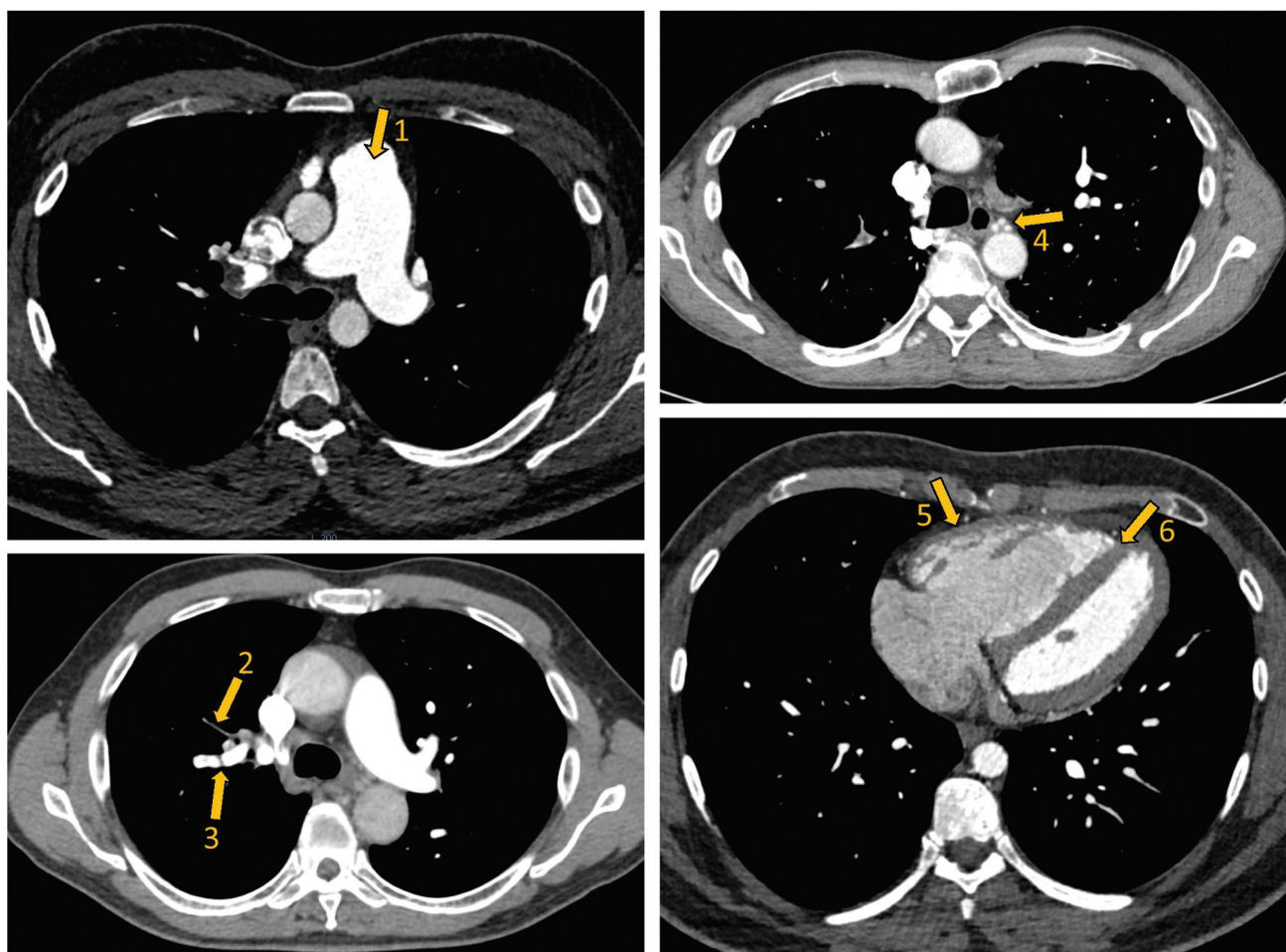
PCFS scale into Turkish language, Mexican-Spanish, and Chilean-Spanish, and a cross-cultural adaptation study of the PCFS scale for the Chilean population, the scale had good psychometric properties in terms of reliability and was found to be a valid instrument.<sup>66-69</sup> To assess pain severity, PROMIS Short Forms for pain can be applied.<sup>70</sup> 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.<sup>71-73</sup> The Checklist Individual Strength with fatigue severity subscale is an adequate tool to measure fatigue.<sup>74</sup>

### 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.<sup>23,75,76</sup> 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).<sup>77-81</sup> 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.<sup>7,23,82</sup> A low probability of PH (peak tricuspid regurgitation of  $\leq 2.8$  m/s and no “PH signs”) on transthoracic echocardiogram (TTE) rules out CTEPH.<sup>7,30</sup> 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.

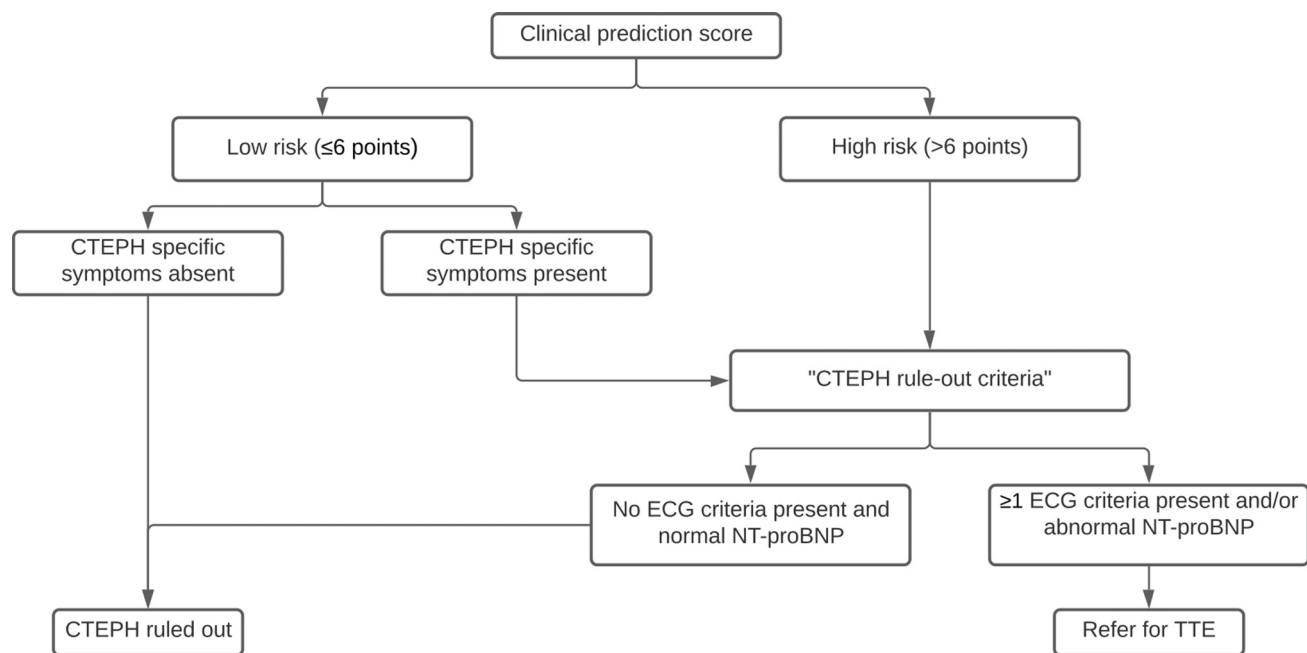
A noninvasive screening algorithm consisting of a clinical prediction score and the so-called “CTEPH rule-out criteria”



1. Dilated pulmonary trunk
2. Arterial retraction
3. Intravascular web

4. Dilated bronchial arteries
5. RV wall hypertrophy
6. Flattening of the interventricular septum

**Fig. 2** Chronic thromboembolic pulmonary hypertension signs on CTPA. Image courtesy: Boon et al.<sup>79</sup>



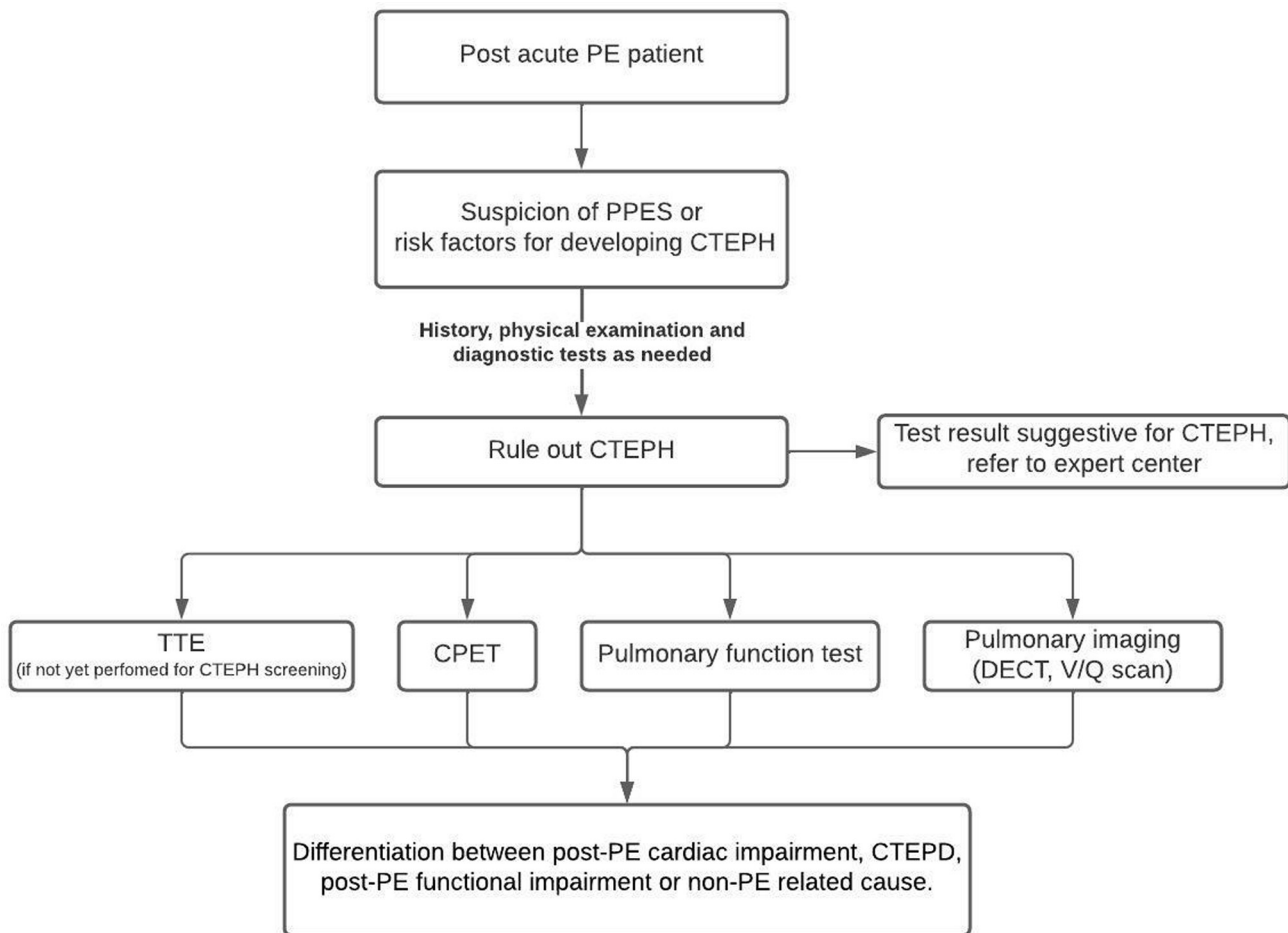
**Fig. 3** Noninvasive early exclusion of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: the InShape II algorithm.<sup>87</sup> The ECG criteria of RV pressure overload: (1) rSR' or rSr' pattern in lead V1, (2) R:S > 1 in lead V1 with R > 0.5 mV, and (3) QRS axis > 90°. 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.<sup>83</sup> The clinical prediction score can identify post-PE patients with a higher pretest probability of developing CTEPH.<sup>84</sup> 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).<sup>85</sup> Application of the CTEPH rule-out criteria to rule out CTEPH without further testing was deemed safe in retrospective studies.<sup>85,86</sup> 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.<sup>87</sup> 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%.<sup>87</sup>

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).<sup>88</sup> 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.<sup>89</sup> With the recognition of the pathological limiting factor, potential therapeutic targets can be identified and prognostic information is provided.<sup>89</sup> 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.<sup>8,43,44,90,91</sup> 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.<sup>90</sup> Mostly, CPET may play a role in detecting CTEPH without PH<sup>92,93</sup> 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.<sup>43,44</sup> 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.<sup>23</sup> 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.<sup>7,23</sup> Single-photon emission computed tomography (SPECT) V/Q has shown to be superior to planar V/Q scanning.<sup>23</sup> 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.<sup>23,94</sup> 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 persis-

tent perfusion defects do not report related symptoms.<sup>95</sup> 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.<sup>43</sup> 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).<sup>7,23,30</sup> PEA results in improved hemodynamic and exercise tolerance and is associated with low early mortality when performed in expert centers.<sup>23,96,97</sup> 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.<sup>23,30</sup> 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.<sup>98,99</sup> Inoperable

**Table 1** PH medication studies for treatment of CTEPH

Study	Year	Study type	Patients	Intervention	Outcome
CHEST-1 <sup>132</sup>	2013	RCT	Inoperable CTEPH of residual PH after PEA ( <i>n</i> = 261)	Riociguat	<ul style="list-style-type: none"> <li>PVR mean difference of <math>-226 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5}</math> for riociguat group and <math>+23 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5}</math> for the control group (mean difference: <math>-246 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5}</math>; 95% CI: <math>-303</math> to <math>-190</math>)</li> <li>6MWT mean difference of <math>+39 \text{ m}</math> for riociguat group and <math>-6 \text{ m}</math> for placebo group (mean difference: <math>46 \text{ m}</math>; 95% CI: <math>25</math>–<math>67</math>)</li> </ul>
Reichenberger et al <sup>133</sup>	2007	Open label uncontrolled trial	Inoperable CTEPH ( <i>n</i> = 104)	Sildenafil	<ul style="list-style-type: none"> <li>Decrease in PVR of <math>104 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5}</math></li> <li>Increase in 6MWT of <math>+51 \text{ m}</math></li> </ul>
BENEFIT <sup>134</sup>	2008	RCT	Inoperable CTEPH of residual PH after PEA ( <i>n</i> = 157)	Bosentan	<ul style="list-style-type: none"> <li>PVR mean difference of <math>-146 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5}</math> for bosentan group and <math>+30 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5}</math> for the control group (mean treatment effect: <math>-24.1\%</math>; 95% CI: <math>-31.5</math> to <math>-16.0\%</math>)</li> <li>6MWT mean difference of <math>+2.9 \text{ m}</math> for bosentan group and <math>+0.8 \text{ m}</math> for placebo group (mean difference: <math>2.2 \text{ m}</math>; 95% CI: <math>22.5</math>–<math>26.8</math>)</li> </ul>
MERIT-1 <sup>135</sup>	2017	RCT	Inoperable CTEPH ( <i>n</i> = 80)	Macitentan	<ul style="list-style-type: none"> <li>PVR mean difference of <math>-206 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5}</math> for macitentan group and <math>-86 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5}</math> for placebo group (geometric PVR ratio: <math>0.84</math>; 95% CI: <math>0.70</math>–<math>0.99</math>)</li> <li>6MWT mean difference of <math>+35 \text{ m}</math> for macitentan group and <math>+1 \text{ m}</math> for placebo group (mean difference: <math>34 \text{ m}</math>; 95% CI: <math>2.9</math>–<math>65.2</math>)</li> </ul>

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.<sup>23,30</sup>

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.<sup>23</sup> CTEPD patients without PH might also benefit from these treatments, but efficacy has only been evaluated in noncontrolled cohort studies with small patient populations.<sup>35,36</sup> 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.<sup>23</sup>

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.<sup>100–107</sup> 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.<sup>105,107</sup> 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  $\text{VO}_{2\text{max}}$ , 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.<sup>106</sup> 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.<sup>104</sup> 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 <sup>100</sup>	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	<ul style="list-style-type: none"> <li>No AE in either group</li> <li>Mean difference of exercise per week of 133 min in favor of intervention group</li> <li>VO<sub>2max</sub> improved significantly for the intervention group (26.1 to 29.8 mL O<sub>2</sub>/kg)</li> </ul>
Noack et al <sup>101</sup>	2015	Retrospective cohort study	Post-acute PE patients referred for rehabilitation; timing unknown (n = 422)	3-week inpatient rehabilitation course	-	<ul style="list-style-type: none"> <li>57 AEs occurred, all nonrelated to the rehabilitation course</li> </ul>
Amoury et al <sup>102</sup>	2018	Prospective cohort study	Post-acute PE patients; timing unknown (n = 70)	3-week inpatient rehabilitation course	-	<ul style="list-style-type: none"> <li>No patients died during rehabilitation; 4 patients (5.7%) died during the 12-month follow-up period</li> <li>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%)</li> </ul>
Cires-Drouet et al <sup>103</sup>	2020	Prospective cohort study	PE <28 days before enrolment (n = 23)	3-month aerobic exercise training	-	<ul style="list-style-type: none"> <li>No AE during the exercise period</li> <li>1 death, 1 DVT, and 5 readmissions due to non-exercise-related reasons</li> <li>VO<sub>2max</sub> improved significantly (+3.9 mL O<sub>2</sub>/kg)</li> </ul>
Rolving et al <sup>104</sup>	2020	RCT	PE 2–3 weeks before enrolment (n = 140)	8-week home-based exercise program	Usual care with brief nurse consultation	<ul style="list-style-type: none"> <li>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 PE-emb-QoL score, respectively)</li> </ul>
Nopp et al <sup>105</sup>	2020	Retrospective cohort study	Acute PE median of 19 weeks before starting rehabilitation (n = 22)	6-week outpatient pulmonary rehabilitation	-	<ul style="list-style-type: none"> <li>Mean improvement of 6MWT of 49.4 m</li> <li>Improvement of self-reported health (78% of the patients reported much better or better health status)</li> </ul>
Ghram et al <sup>106</sup>	2021	RCT	Acute PE 3–4 weeks before baseline measurements (n = 24)	8-week high-intensity interval training	Usual care	<ul style="list-style-type: none"> <li>Improvement of estimated VO<sub>2max</sub> (22.9 to 37.7 mL O<sub>2</sub>/kg; p &lt; 0.05), RV/LV ratio (1.1 to 0.8; p = 0.005), and health-related QoL in the intervention group</li> <li>No significant improvement estimated VO<sub>2max</sub> (28.6 to 33.3 mL O<sub>2</sub>/kg; p = 0.08), RV/LV ratio (0.8 to 0.8; p = 0.33), and health-related QoL for the control group</li> </ul>
Boon et al <sup>107</sup>	2021	Prospective cohort study	Patients with persistent moderate-to-severe dyspnea 3 months after acute PE (n = 27)	12-week outpatient rehabilitation program	-	<ul style="list-style-type: none"> <li>Significant improvement in training intensity (+20 watt), PE-specific QoL (+3.9 points on PE-emb-QoL score), fatigue (+16 points on Checklist Individual Strength scale), and functional status (67% of patients had improvement of ≥1 PVFS scale grade)</li> </ul>

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.”<sup>108–116</sup> 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.<sup>117–123</sup> 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.<sup>124–126</sup> 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.<sup>124,127</sup> This can lead to endothelial dysfunction, which is one of the hallmarks of CTEPH.<sup>22</sup> 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.<sup>128</sup> 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).<sup>129,130</sup> 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.<sup>131</sup>

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  $\text{VO}_2$  at anaerobic threshold of 32% of predicted,  $\text{Vd/Vt}$  that appropriately decreased during exercise (until 0.25 at peak of exercise),  $\text{VE/VCO}_2$  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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