REGULAR ARTICLE

# Postpulmonary Embolism Follow-Up and Epidemiology of Chronic Thromboembolic Pulmonary Hypertension

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The follow-up of patients with acute pulmonary embolism is an essential component of their comprehensive care. This manuscript will discuss the critical components involved in the outpatient follow-up of pulmonary embolism, including the development of post hospitalization follow-up clinics, assessment of functional capacity and residual right ventricular function, anticoagulation, recurrence risk of venous thromboembolism, and retrieval of inferior vena cava filters. In addition to these listed topics, the epidemiology of chronic thromboembolic pulmonary hypertension will be discussed, including the spectrum of postpulmonary embolism syndrome (PPES), risk factors for the development of chronic thromboembolic pulmonary hypertension, and the incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism.

## INTRODUCTION

The follow-up of patients with acute pulmonary embolism (PE) is an essential component of their comprehensive care. This manuscript will discuss post-PE follow-up recommendations as well as the epidemiology of chronic thromboembolic pulmonary hypertension (CTEPH). While there is a good collection of data to call upon for the epidemiology of CTEPH, there is little primary data on the outpatient follow-up of acute PE, and more research is needed in this area. PE is a disease process that leads to significant morbidity and mortality, with the 30-day mortality rate for massive PE ranging from 12% to 34%.[1,2] While the treatment of acute PE is an important and necessary consideration, it is crucial to concomitantly address the outpatient follow-up of patients after their acute PE, especially given that the recurrence rate for venous thromboembolism (VTE) events is up to 30%, with the highest recurrence rate occurring immediately after the initial event.[3] In patients with submassive PE, the mortality risk persists after the index hospitalization to the posthospitalization time period.[1] Furthermore, the outpatient follow-up of acute PE should include monitoring for the development of post-PE syndrome (PPES), which is a spectrum of disease that includes chronic thromboembolic disease (CTED) and CTEPH. Between 0.1% and 9.1% of patients go on to develop CTEPH after an episode of acute PE.[4-11] The European Society of Cardiology and the PERT (PE response team) Consortium have published consensus guidelines on the follow-up of patients with PE, which will be expanded upon in this manuscript (Figure 1).[12-14]

## OUTPATIENT FOLLOW-UP OF PE

### *Timing and Logistics of Post-PE Follow-Up*

The outpatient follow-up of patients diagnosed with acute PE begins during the index hospitalization, when transitions of care are set up for outpatient follow-up. Recently, several medical centers have developed dedicated outpatient post-PE clinics, as an extension of the inpatient PERT that evaluates acute PE patients during inpatient hospitalization. The primary aim of an outpatient, post-PE follow-up clinic is to monitor for recurrent, persistent, or progressive symptoms after PE and determine an appropriate plan for anticoagulation (Figure 2). Furthermore, these clinics

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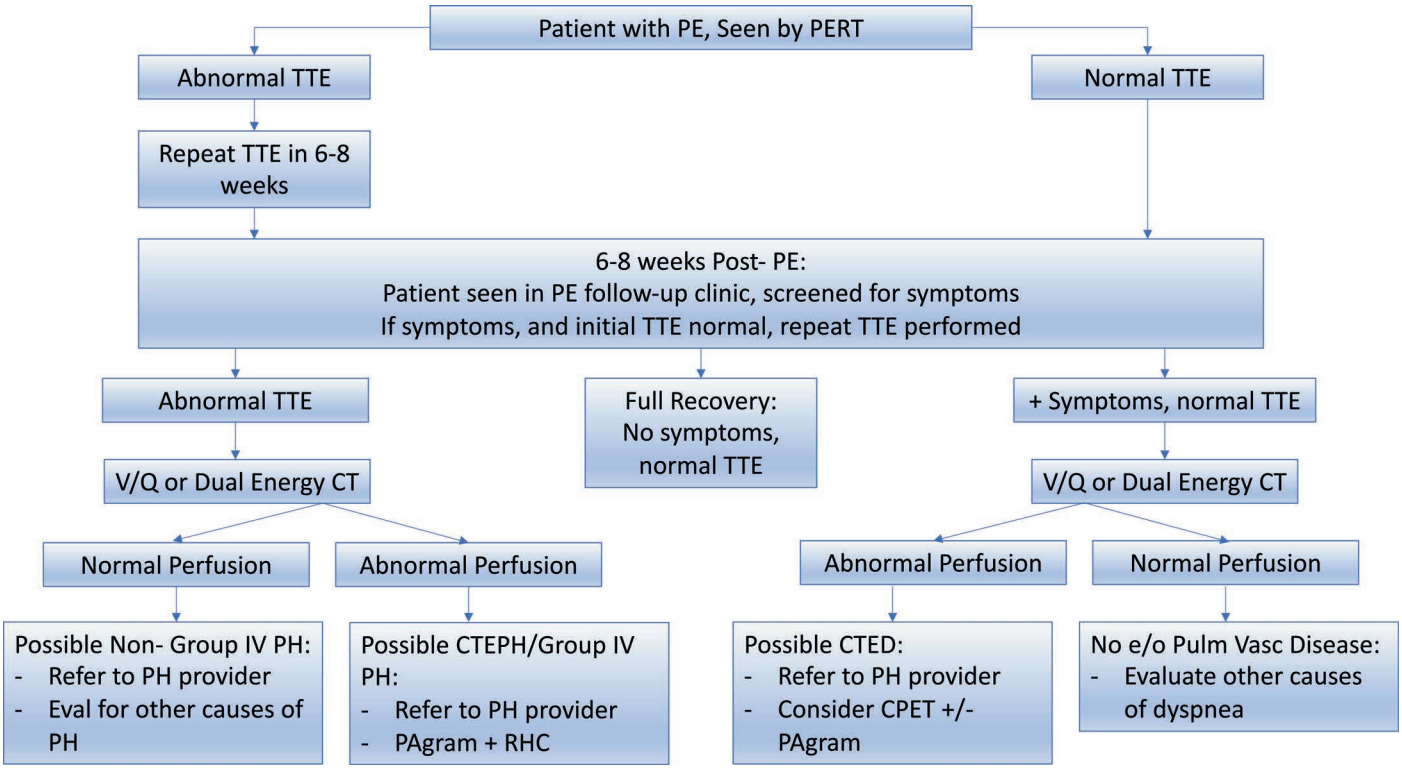


**Figure 1:** Post-PE follow-up algorithm. PE indicates pulmonary embolism; PERT, PE Response Team; TTE, transthoracic echo; V/Q, ventilation perfusion scan; CT, computed tomography; PH, pulmonary hypertension; Pulm Vasc, pulmonary vascular disease; PAgram, pulmonary angiogram; RHC, right heart catheterization; CPET, cardiopulmonary exercise test.

address possible underlying factors contributing to the development of the PE, including workup of acquired thrombophilia in appropriate situations and age-appropriate cancer screening. Lastly, these clinics facilitate the appropriate removal of temporary inferior vena cava (IVC) filters, and perhaps most importantly, monitor for and identify PPES, including CTED and CTEPH.[15] These post-PE clinics are run by a variety of specialties, including pulmonary, pulmonary vascular disease, cardiology, hematology, or interventional radiology. Oftentimes, the inpatient PERT will refer patients to the post-PE clinic upon discharge.

The initial follow-up visit in the post-PE clinic occurs 2 to 12 weeks after hospital discharge, depending on the patient's clinical course while in the hospital.[12,14] Patients with more severe PE, such as massive PE requiring embolectomy, extracorporeal membrane oxygenation support, systemic thrombolysis, or patients with a high bleeding risk are seen in follow-up sooner than patients with an uncomplicated low or intermediate-risk PE. Patients who

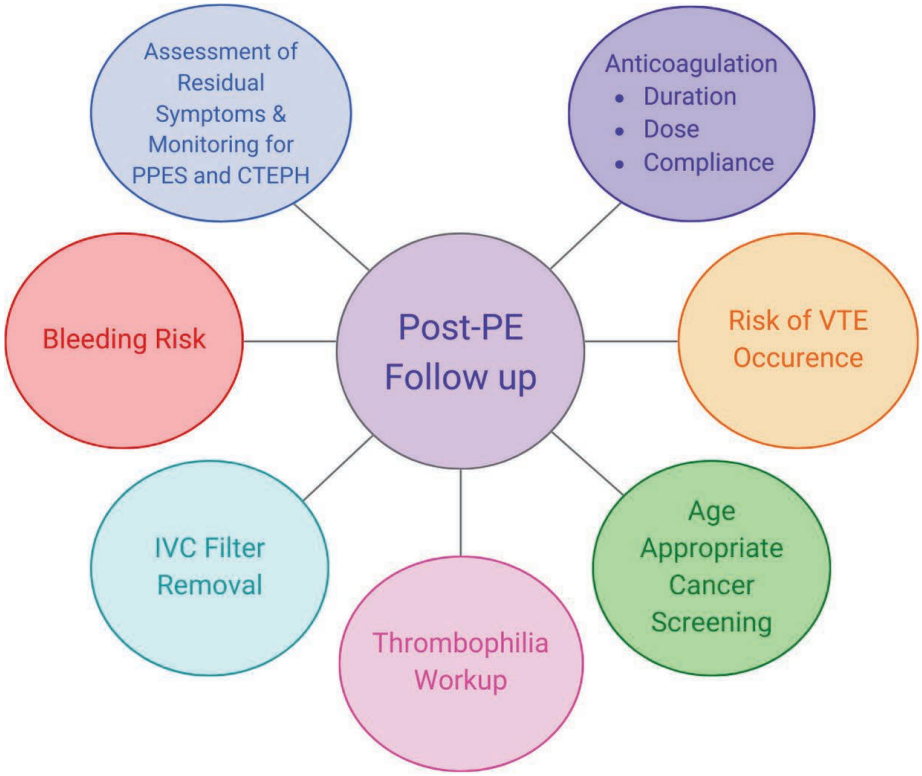


**Figure 2:** Post-PE follow-up: Components of post-PE care. PE indicates pulmonary embolism; PPES, post-PE syndrome; CTEPH, chronic thromboembolic pulmonary hypertension; VTE, venous thromboembolism; IVC, inferior vena cava.

had evidence of right ventricular (RV) dysfunction at the time of PE diagnosis, either on transthoracic echocardiogram or computed tomography angiogram of the chest, undergo a follow-up transthoracic echocardiogram to evaluate for resolution of RV dysfunction 6 to 8 weeks after their acute PE event. Guidelines do not recommend the universal screening of all post-PE patients with echocardiography, however the first post-PE clinic visit provider should review initial computed tomography imaging from hospitalization to determine if the initial presentation was due to a diagnosis of CTEPH, rather than acute PE. This determination is based on the findings of elevated pulmonary artery systolic pressure on transthoracic echocardiogram and the presence of computed tomography findings consistent with CTEPH, such as the presence of eccentric clot, arterial bands or webs, bronchial artery collaterals, distal tapering of pulmonary vessels, stenotic lesions or poststenotic dilation of pulmonary artery, complete occlusion or pouch defects, and a pattern of mosaicism indicating differential perfusion to the lungs.[5,16-18] Persistent RV dysfunction 6 to 8 weeks after acute PE in conjunction with persistent or worsening functional deficits prompts further workup of PPES.

The initial visit with the post-PE clinic mainly addresses plans for anticoagulation, including specific agent and supply, planned duration of therapy, and appropriate monitoring of anticoagulation. In certain populations of patients, the post-PE clinic provider will address any recommended age-appropriate cancer screening and will consider a limited thrombophilia workup in the appropriate clinical setting.[13]

A second visit to the post-PE clinic occurs at the 3-mont or 6-month mark after acute PE, depending on the planned duration of therapeutic anticoagulation. In patients with strongly provoking factors who can stop anticoagulation after 3 months, the second post-PE clinic visit occurs at 3 months after PE diagnosis. For patients who require either 6 months of therapeutic anticoagulation or indefinite anticoagulation, the second visit to the post-PE clinic occurs at the 6-month mark, when any indicated changes in dose of anticoagulation can be prescribed.

The second visit to the post-PE clinic also assesses for any residual respiratory symptoms or functional limitations, as a first step in monitoring for the PPES. Patients who present to post-PE clinic with persistent or progressive pulmonary symptoms, including dyspnea at rest or exertion, presyncope or syncope, chest pain, or exercise intolerance should be evaluated for PPES, which can range from a mild chronic condition to the most severe form, CTEPH.[19] The ELOPE cohort study demonstrated that 46.5% of PE patients had residual exercise limitation, defined as a persistent percent-predicted peak $Vo_2$ of <80%, 1 year after PE event. This functional limitation did not correlate with the presence of residual clot on either chest computed tomography angiogram or ventilation perfusion scan.[20]

The results of this study demonstrated that residual limitation in functional capacity after acute PE is frequently because of underlying patient comorbidities, such as obesity or heart failure with preserved ejection fraction, rather than because of an underlying diagnosis of CTED or CTEPH.

The PPES is described as a spectrum of disease, with the mildest form presenting as residual symptoms of dyspnea or exercise intolerance after 3 to 6 months from the acute PE event. It is important to further characterize exercise limitation in this group of patients, which can be done with formal cardiopulmonary exercise testing.[19,21] Patients with persistent pulmonary symptoms and residual unmatched lobar or segmental perfusion deficits on ventilation perfusion imaging after 3 months of therapeutic anticoagulation who do not have evidence of pulmonary hypertension are characterized as CTED. Finally, patients with residual pulmonary symptoms and residual unmatched lobar or segmental perfusion deficits on ventilation perfusion imaging after 3 months of therapeutic anticoagulation who have evidence of pulmonary hypertension on right heart catheterization are diagnosed with CTEPH.[19,22] Pulmonary hypertension is defined as a mean pulmonary artery pressure >20 mm Hg, a pulmonary capillary wedge pressure of ≤ 15 mm Hg, and a pulmonary vascular resistance of ≥ 3 Wood units on right heart catheterization.[22,23]

### *Duration of Anticoagulation*

Duration of anticoagulation is a major topic addressed at every visit to the post-PE clinic and is a crucial portion of post-PE follow-up, as it has major implications for recurrence risk, which is highest in the months after acute PE and after anticoagulation is stopped.[24] At least 3 to 6 months of anticoagulation should be prescribed to every patient with acute PE.[25]

### *Recurrence Risk of VTE*

Once this initial period of therapeutic anticoagulation is complete, an assessment of VTE recurrence risk should be the determining factor of whether it is appropriate to stop anticoagulation.[26] The case-fatality rate for death from recurrent PE is between 4% and 9%, and data from the International Cooperative Pulmonary Embolism Registry suggests that 7.9% of patients experience recurrent PE within 3 months of their index event, with the mortality rate of recurrent PE reaching 33.7% at 14 days after recurrence and as high as 46.8% at 30 days after recurrence.[26,27] In determining recurrence risk, the provider must assess the presence or absence of provoking factors, which may be transient or persistent, that contributed to the development of the acute PE. VTE in the setting of nonsurgical predisposing factors, such as minor surgery, hormone replacement therapy/oral contraceptive pill use, or short hospital admission have a lower risk of VTE recurrence, between 3% and 8% per year. Patients with active cancer, a history of prior VTE without provoking factors, or antiphospholipid antibody syndrome have the highest rate of VTE recurrence.[3,12] Postoperative VTE has a very low risk of recurrence, whereas malignancy-associated VTE has the highest risk of recurrence.[28] Patients with major transient or reversible provoking factors, such as the postoperative state or recent trauma, can stop anticoagulation after 3 to 6 months of therapy.[12] Practitioners should consider continuation of anticoagulation, either at therapeutic or prophylactic dosing,

in patients with persistent provoking factors, weak provoking factors, or for patients without any identifiable provoking factors.[12,29-32] More in-depth guidelines for duration of anticoagulation after PE are reviewed elsewhere and are outside the scope of this manuscript.

*Prediction Tools for VTE Recurrence*

Several models have been developed to aid in the prediction of VTE recurrence. The Vienna prediction model can be used in patients with a first episode of unprovoked PE to calculate the 1-year and 5-year recurrence risk of VTE event. These tools can be especially helpful when used in shared decision making discussions to help decide the best duration of anticoagulation for each patient.[33,34] The DASH prediction score is another prediction tool and can also be used to assess VTE recurrence risk in patients with unprovoked VTE.[35]

*Presence of Residual Deep Vein Thrombus*

Another consideration during the second post-PE clinic visit at 3 to 6 months after the VTE event is the presence of residual or chronic deep vein thrombosis (DVT). Repeat lower extremity venous duplex ultrasound is obtained in patients who presented with DVT and PE at diagnosis. If these patients have evidence of residual or chronic DVT, anticoagulation should be continued given increased risk of PE recurrence with residual DVT.[36]

*Bleeding Risk*

The strategy for anticoagulation addressed in the post-PE follow-up assessment should include an assessment of bleeding risk. There are several bleeding risk calculators that can be used when assessing bleeding risk among this patient population. HAS-BLED, ATRIA, and HEMORR2HAGES-score are all studied in patients with atrial fibrillation, but they can also be applied in the setting of VTE.[37-39] Additionally, the RIETE score was developed as a bleeding risk assessment specifically for VTE patients.[40]

*IVC Filter Retrieval*

The timely retrieval of temporary IVC filters is an important consideration in the follow-up of post-PE patients. These filters should be removed as soon as the patient is tolerating therapeutic anticoagulation, generally within 2 to 4 weeks after implantation.[12,41] IVC filter removal should be addressed systematically at regular intervals in cases where expeditious removal is not feasible. The long-term presence of IVC filters places patients at risk for further venous stasis and development of DVT, with the most extreme example being phlegmasia cerulea dolens. Thus, the use of these filters has fallen out of favor given increased long-term risk for clot formation.

## EPIDEMIOLOGY OF CTEPH

*The Post-PE Syndrome*

As discussed above, CTEPH is the most severe diagnosis on a spectrum of long-term complications that can arise after the diagnosis of acute PE.[19,21,42,43] It is unknown whether this spectrum of disease exists as a progressive continuum versus a group of related disease processes after acute PE. While the incidence of CTEPH after acute PE episode is between 0.1% and 9.1%, multiple studies have reported that up to 50% of patients experience residual pulmonary symptoms or exercise/functional limitations after acute PE, thus bringing about the entity of the PPES, which includes CTEPH, CTED, post-PE cardiac impairment and post-PE functional impairment.[4-11,43] Boon et al recently published a thorough review of the prevalence of PPES and broke down the spectrum of disease into these 4 categories. The PPES is reported in as many as 40% to 60% of PE survivors.[43,44] The epidemiology of CTEPH, specifically, will be discussed in this manuscript.

*Chronic Thromboembolic Pulmonary Hypertension*

It is well known that acute PE is a predisposing factor for the development of CTEPH.[4,5,45,46] Approximately 75% of patients diagnosed with CTEPH have a known prior history of PE, and approximately 50% of patients diagnosed with CTEPH have a history of DVT.[45] The timely diagnosis of CTEPH is of crucial importance to the well-being of these patients because CTEPH is a severe, progressive, and life-threatening disease that can be successfully treated and potentially cured if identified appropriately.[10,47] Multiple studies have been conducted to assess the incidence of CTEPH after acute PE, with considerable variability in study design, including screening protocols and inclusion criteria. Overall, the cumulative incidence of CTEPH after acute PE is between 0.1% and 9.1%.[4-11,43] More clinically relevant is the systematic review and meta-analysis by Ende-Verhaar et al that determined that the overall incidence of CTEPH was 0.56%, and increased to 3.2% in survivors of PE and 2.8% in survivors without major comorbidities.[18] This meta-analysis included low bias studies that used right heart catheterization to establish the diagnosis of CTEPH, thus providing the current best estimate of CTEPH incidence.

It is posited that studies that used echocardiography without right heart catheterization to diagnose pulmonary hypertension resulted in a higher incidence than studies that assessed hemodynamics invasively. Another study that required a stepwise approach to the diagnosis of CTEPH, estimated a 2-year cumulative incidence of 0.79%.[48] When discussing incidence of CTEPH, it is also important to note that the initial presentation of CTEPH is often misclassified as acute PE during index hospitalization. Guerin et al evaluated signs of CTEPH at initial presentation, which occurred at a rate of 4.8% and encompassed all 7 of 108 patients who were diagnosed with CTEPH in the study.[5]

*Factors in Delayed Diagnosis of CTEPH*

The diagnosis of CTEPH after PE is often delayed due to the nonspecific nature of clinical presentation and diagnostic misclassification, with a median delay of more than 1 year.[42] Furthermore, the clinical symptoms of CTEPH after acute PE often lags due to a well-described honeymoon period before the onset of symptoms from pulmonary hypertension.[49] In the study by Hsu et al, 4% of patients with acute PE were eventually diagnosed with CTEPH, with a median time from PE event to CTEPH diagnosis of 36 months.[4] This highlights the importance of a high index of suspicion for CTEPH

in patients with either a history of VTE or in patients who present with dyspnea on exertion of unclear origin.

### *Risk Factors for the Development of CTEPH*

It is important to be aware of the risk factors that are associated with the development of CTEPH after acute PE. Several studies have evaluated possible risk factors for the development of CTEPH. Klok et al followed patients after acute PE and identified 6 factors that were independently associated with the diagnosis of CTEPH: unprovoked PE, known hypothyroidism, symptom onset >14 days prior to the diagnosis of PE, the presence of RV dysfunction on computed tomography or echocardiogram, a known history of diabetes mellitus, and thrombolytic therapy or embolectomy.[50] Of these factors, unprovoked PE had an odds ratio of 20 and onset of symptoms >14 days before diagnosis had an odds ratio of 7.9. Using these factors, Klok et al developed a CTEPH prediction score, which categorizes patients into a risk category for the development of CTEPH.[50]

Another study showed that older age, multiple previous VTE events, proximal PE, higher levels of BNP and higher pulmonary artery systolic pressures were risk factors for the diagnosis of CTEPH after acute PE.[5]

Additionally, Bonderman et al discuss that specific medical diagnoses, including splenectomy, ventriculoatrial shunt, inflammatory bowel disease, and osteomyelitis are risk factors for the development of CTEPH in comparison to the development of pulmonary arterial hypertension.

## CONCLUSION

The follow-up of patients after acute PE is of critical importance in their comprehensive care. Purposeful follow-up after PE allows for assessment of RV function, determination of an appropriate anticoagulation dose and duration and monitoring for PPES, including CTEPH. Given the high incidence of PPES in the absence of CTEPH, it is imperative to monitor for this spectrum of disease. Finally, in reviewing the epidemiology of CTEPH, a high index of suspicion should be maintained for CTEPH both at initial hospitalization and in the follow-up of acute PE given frequent delays in the diagnosis and treatment of CTEPH.

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