Original article

Pulmonary Embolism: Diagnostic Approach, Clinical Findings, and the Alarming Rise in Incidence – A Critical Review

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ABSTRACT

Background: Pulmonary embolism (PE) is a potentially life-threatening condition resulting from the obstruction of pulmonary arteries, most commonly by thrombi originating from the deep veins of the lower limbs. In recent years, a notable rise in PE incidence has been observed globally, attributed to both improved detection and an increase in predisposing risk factors.

Objective: To provide a comprehensive overview of the evolving epidemiology, diagnostic approach, clinical features, therapeutic options, and long-term outcomes of PE, with emphasis on the critical rise in incidence and implications for clinical practice.

Methods: A narrative review was conducted using recent peer-reviewed literature and guideline-based recommendations. Studies were selected from indexed databases focusing on diagnostic algorithms, imaging modalities, treatment outcomes, and epidemiological trends related to acute PE.

Results: PE incidence is increasing globally, driven by aging populations, cancer survivorship, and postoperative complications. Clinical presentation varies widely, often mimicking other cardiopulmonary conditions, making early diagnosis challenging. Risk stratification tools such as the Wells score, revised Geneva score, and Pulmonary Embolism Severity Index (PESI) are critical in guiding the use of D-dimer testing and imaging. Computed tomography pulmonary angiography (CTPA) remains the diagnostic gold standard. Treatment strategies are guided by risk categories—ranging from anticoagulation alone in low-risk cases to thrombolysis or surgical embolectomy in high-risk cases. Long-term complications such as chronic thromboembolic pulmonary hypertension (CTEPH) and post-PE syndrome significantly impact quality of life, underscoring the importance of follow-up and rehabilitation.

Conclusion: The increasing incidence and variable presentation of PE demand heightened clinical vigilance. Early risk-adapted diagnosis and intervention are pivotal in reducing mortality and morbidity. Long-term monitoring and individualized therapy are essential for improving patient outcomes. Future strategies should emphasize prevention, early detection, and research into novel diagnostic and therapeutic tools.

Keywords:
Pulmonary embolism, Venous thromboembolism, Anticoagulation, Post-PE syndrome

INTRODUCTION

Pulmonary embolism (PE) is a critical and potentially fatal cardiovascular condition characterized by the obstruction of pulmonary arteries, most commonly due to thrombi originating from the deep veins of the lower extremities. It constitutes a major clinical emergency, ranking as the third most common cause of cardiovascular death after myocardial infarction and stroke[1]. Despite increased awareness and diagnostic advances, PE continues to be underdiagnosed due to its diverse and often non-specific clinical presentations[2].

In recent years, the global incidence of PE has shown a noticeable upward trend. While part of this rise can be attributed to the increased utilization of advanced imaging techniques such as computed tomography pulmonary angiography (CTPA), other contributors include aging populations, sedentary lifestyles, obesity, malignancy, and notably, the hypercoagulable state associated with COVID-19 infections[3,4]. Studies have demonstrated that patients hospitalized with COVID-19 are at a significantly increased risk of venous thromboembolism, including PE, due to endothelial dysfunction, systemic inflammation, and prolonged immobilization[5].

This trend burdens healthcare systems, necessitating better strategies for early detection and risk-adapted management. A comprehensive understanding of clinical predictors, diagnostic modalities, and risk assessment tools is imperative to reduce diagnostic delays and improve outcomes. Moreover, the recent epidemiological changes call for a re-evaluation of current guidelines and prevention protocols in both inpatient and outpatient settings.

This article critically reviews the current diagnostic approach to PE, outlines key clinical features, and examines the alarming rise in incidence, especially in the post-COVID era. The objective is to provide a consolidated update for clinicians and researchers to enhance early detection and management of this life-threatening condition.

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Epidemiological Trends and Rising Incidence of Pulmonary Embolism

Pulmonary embolism (PE) has long been recognized as a significant cause of cardiovascular morbidity and mortality, but recent decades have witnessed a striking rise in its reported incidence. In the United States alone, PE affects an estimated 60 to 70 per 100,000 individuals annually, with some studies reporting even higher rates in specific subgroups[6]. While improved diagnostic sensitivity plays a partial role, the increase cannot be solely attributed to enhanced detection; there is growing concern that the actual burden of disease is rising due to evolving risk factors and societal trends[7].

Improved Detection or True Increase

The widespread availability and utilization of computed tomography pulmonary angiography (CTPA) since the early 2000s have dramatically improved the detection of PE, especially smaller, sub-segmental emboli that were previously undiagnosed[8]. Studies have shown that the incidence of PE more than doubled between 1998 and 2006, coinciding with the introduction of multi-detector CT scanners[9]. However, this diagnostic shift also introduced concerns of over-diagnosis - identifying clinically insignificant emboli that may not require treatment[10].

Nevertheless, hospitalizations and outpatient diagnoses for PE have also increased, accompanied by growing rates of anticoagulant use and healthcare resource utilization, suggesting that a true epidemiological shift is underway[11].

Contributing Factors to Rising Incidence

Several demographic, behavioral, and clinical variables have contributed to the rising incidence of PE:

Aging Population: Age is one of the most important risk factors for PE, with incidence doubling with each subsequent decade after 50 years[12].

Obesity and Sedentary Lifestyle: The global obesity epidemic and increasing sedentary behavior have led to a surge in venous thromboembolism (VTE) events, including PE[13]. Obesity is an independent risk factor, possibly due to increased inflammatory markers, endothelial dysfunction, and impaired venous return[14].

Cancer: With improved cancer detection and survival, more patients are living longer with malignancy, which is a well-established prothrombotic state. Both solid and hematologic malignancies significantly elevate PE risk, especially in those receiving chemotherapy or undergoing surgery[15].

Surgical and Hospital Admissions: Despite widespread use of prophylactic anticoagulation, postoperative PE remains a notable complication, particularly following orthopedic, oncologic, and abdominal procedures[16].

Hormonal Therapies and Pregnancy: Estrogen-based therapies and pregnancy/postpartum states are well-known risk factors, and increased use of hormone replacement therapy and assisted reproductive technologies may be contributing to incidence trends[17].

COVID-19 Pandemic: A paradigm-shifting event in recent PE epidemiology has been the COVID-19 pandemic. SARS-CoV-2 infection induces endothelial injury, cytokine storm, and a hypercoagulable state, leading to increased incidence of PE, especially in hospitalized and ICU patients[18]. Autopsy studies and clinical reports have consistently documented high rates of thrombotic complications among COVID-19 patients, prompting new anticoagulation protocols[19].

Global Variations in Incidence

PE incidence varies significantly across regions, influenced by diagnostic resources, population demographics, and reporting systems. Developed countries with greater access to imaging report higher rates, while low- and middle-income countries often face under-diagnosis due to lack of resources and awareness[20]. Moreover, regional differences in risk factors like obesity, smoking, and healthcare access further contribute to incidence variability.

Mortality and Recurrent PE

While PE-related mortality has declined slightly over time due to earlier detection and treatment, it remains alarmingly high, especially in untreated or misdiagnosed cases. Massive PE, characterized by hemodynamic instability, carries a mortality rate exceeding 25%[21]. Recurrent PE is also common in patients without appropriate secondary prophylaxis, further underlining the importance of effective initial management and follow-up care[22].

Clinical Presentation and Risk Factors

The clinical presentation of pulmonary embolism (PE) is notoriously variable, ranging from asymptomatic cases to sudden cardiovascular collapse and death. This variability contributes to the diagnostic challenge and underscores the importance of clinical suspicion, especially in high-risk patients[23]. The classic triad of dyspnea, pleuritic chest pain, and hemoptysis is rarely seen in combination, and most patients present with nonspecific symptoms that mimic other cardiopulmonary conditions[24].

Common Clinical Manifestations

The most frequently reported symptoms and signs of PE include[25]:

- Dyspnea (73%) – Often of sudden onset and unexplained
- Pleuritic chest pain (44%)
- Tachypnea (54%) – The most common physical sign
- Tachycardia (24–30%)
- Cough (34%)

- Hemoptysis (rare, ~13%)
- Syncope – Often associated with massive PE and right ventricular dysfunction
- Signs of deep vein thrombosis (DVT) – Leg swelling or tenderness in 15–25% of cases

Despite these common features, atypical presentations are not uncommon, particularly in the elderly, pregnant patients, or those with comorbidities such as chronic obstructive pulmonary disease (COPD), heart failure, or malignancy[26]. In such populations, PE may masquerade as pneumonia, exacerbation of asthma or COPD, or acute coronary syndrome.

Severity-Based Classification

PE is stratified into three clinical categories based on hemodynamic stability and right ventricular function, which also guide management strategies[27]:

Massive PE: Characterized by sustained hypotension (SBP <90 mmHg), shock, or cardiac arrest. Mortality exceeds 25%.

Submassive PE: Hemodynamically stable but with right ventricular dysfunction or elevated cardiac biomarkers.

Low-risk PE: No hemodynamic compromise or right ventricular involvement.

This classification helps clinicians decide the urgency and intensity of interventions, including systemic thrombolysis or catheter-based therapy[28].

Risk Factors

Pulmonary embolism results from a combination of venous stasis, endothelial injury, and hypercoagulability—collectively known as Virchow's triad[29].

Numerous acquired and inherited risk factors contribute to this pathogenesis:

1. Acquired Risk Factors:

Recent surgery or trauma: Especially orthopedic or abdominal procedures increase risk significantly[30].

Prolonged immobilization: Includes hospitalization, long-haul travel, or sedentary lifestyle[31].

Cancer: Particularly adenocarcinomas (e.g., pancreas, lung, gastrointestinal tract)[32].

Pregnancy and postpartum period: Risk is highest during the first six weeks after delivery[33].

Estrogen therapy: Oral contraceptives and hormone replacement therapy increase thrombotic risk[34].

COVID-19 infection: A powerful prothrombotic stimulus due to cytokine storm, endothelial dysfunction, and immobilization[35].

2. Inherited Thrombophilias:

- Factor V Leiden mutation
- Prothrombin G20210A mutation
- Protein C, Protein S, or antithrombin III deficiency
- Hyperhomocysteinemia

These conditions predispose individuals to both unprovoked and recurrent thromboembolic events, particularly in younger patients without obvious risk factors[36].

3. Recurrent and Idiopathic PE:

Approximately 20–30% of patients with PE have no identifiable provoking factor. These unprovoked or idiopathic PEs warrant further evaluation for occult malignancy or thrombophilia and require long-term anticoagulation due to high recurrence risk[37].

4. Special Populations

Elderly: Diagnosis is frequently delayed or missed in older adults, where dyspnea or hypoxia is often attributed to underlying cardiac or pulmonary disease. Moreover, age itself is a strong independent risk factor for PE[38].

Pregnant Women: PE is a leading cause of maternal mortality worldwide. The diagnostic dilemma is heightened by overlapping symptoms with normal pregnancy, and the use of imaging is often limited by fetal safety concerns[39].

Hospitalized and ICU Patients: High rates of VTE are seen in critically ill or post-operative patients, necessitating routine prophylaxis protocols. Despite this, underutilization of prophylactic anticoagulation remains a global issue[40].

Diagnostic Approach to Pulmonary Embolism

Given the often nonspecific clinical manifestations of pulmonary embolism (PE), timely and accurate diagnosis remains one of the most challenging aspects of its management. The cornerstone of an effective diagnostic strategy lies in the integration of clinical prediction rules, biochemical markers, and imaging modalities, tailored to the patient's risk profile[41]. Inappropriate use of diagnostic tests may result in overdiagnosis, overtreatment, or missed diagnoses, all of which carry significant consequences[42].

1. Clinical Prediction Rules

Validated clinical probability scoring systems serve as essential tools to estimate the pretest probability of PE and guide further diagnostic steps:

a. Wells Score

The Wells criteria are the most widely used and stratify patients into low, intermediate, or high probability groups based on factors such as signs of DVT, previous PE/DVT, heart rate, immobilization, and clinical suspicion[43]. Simplified Wells Score Interpretation:

- ≤4 points: PE unlikely
- >4 points: PE likely

Patients in the "PE unlikely" category with a negative D-dimer can often avoid imaging, significantly reducing unnecessary radiation and cost[44].

b. Revised Geneva Score

An alternative, entirely objective tool, the revised Geneva score, uses age, heart rate, recent surgery, and hemoptysis among others. It is especially useful in settings where subjective clinical judgment may vary[45].

2. D-dimer Assay

D-dimer, a fibrin degradation product, is a sensitive marker for ongoing thrombosis. Elevated levels indicate thrombus formation and degradation, though the test lacks specificity[46]. It is most valuable in low or intermediate-risk patients, where a normal D-dimer level (<500 ng/mL) can effectively exclude PE without imaging[47].

In patients over 50 years, an age-adjusted cutoff improves specificity without compromising sensitivity:

Adjusted D-dimer threshold = Age (in years) × 10 ng/mL for patients >50 years[48].

However, D-dimer levels can also be elevated in various other conditions (e.g., infection, trauma, cancer, pregnancy), limiting its standalone utility[49].

3. Imaging Modalities

Imaging is the definitive step in confirming or excluding PE in moderate- to high-risk patients or those with positive D-dimer tests.

a. Computed Tomography Pulmonary Angiography (CTPA)

CTPA is the gold standard for PE diagnosis due to its high sensitivity and specificity, rapid availability, and ability to visualize alternative diagnoses[50]. It can detect emboli down to sub-segmental arteries and assess right ventricular strain, which has prognostic implications[51].

Limitations:

- Requires contrast — contraindicated in renal impairment or contrast allergy
- Radiation exposure — relevant for pregnant or young patients

b. Ventilation–Perfusion (V/Q) Scan

A V/Q scan evaluates mismatch between ventilation and perfusion in lung segments. It is especially useful in pregnant women, young individuals, and those with renal dysfunction[52].

- Normal scan: Excludes PE
- High-probability scan: Strongly supports PE diagnosis in appropriate clinical context

V/Q scans have lower sensitivity than CTPA in patients with abnormal chest radiographs or underlying lung disease[53].

c. Compression Ultrasonography

Given that most PEs originate from DVTs, bilateral lower limb venous ultrasonography can aid diagnosis, especially when imaging is delayed or contraindicated. A positive DVT in a symptomatic patient can justify empirical anticoagulation[54].

4. Role of Echocardiography and Biomarkers

a. Transthoracic Echocardiography (TTE)

While not diagnostic for PE, TTE is crucial in hemodynamically unstable patients. It can reveal right ventricular dilation, hypokinesis, and elevated pulmonary artery pressures — signs of massive or submassive PE[55].

b. Cardiac Biomarkers

Troponin and brain natriuretic peptide (BNP) levels may be elevated in PE with right heart strain, serving as prognostic markers[56].

Elevated biomarkers, in conjunction with imaging, help risk-stratify and identify candidates for thrombolysis[57].

5. Diagnostic Algorithm (Overview)

Assess clinical probability using Wells or Geneva score.

- If PE is unlikely → D-dimer:
- If negative → rule out PE
- If positive → proceed to CTPA
- If PE is likely or patient is high risk → CTPA directly
- If CTPA contraindicated → V/Q scan or leg ultrasound
- In unstable patients → Echocardiography for RV strain; start empiric treatment if needed

This stepwise approach ensures efficient diagnosis while minimizing unnecessary testing and exposure[58].

Management of Pulmonary Embolism

The management of pulmonary embolism is a nuanced process that varies based on clinical severity, hemodynamic stability, and comorbidities. The primary goals are to prevent clot progression, reduce cardiopulmonary strain, and prevent recurrence or death. Treatment decisions range from anticoagulation to thrombolysis, interventional procedures, and in some cases, supportive care or surgical embolectomy.

1. Risk Stratification and Initial Management

Effective PE management begins with risk stratification, which categorizes patients into:

- High-risk (massive PE): Hemodynamic instability (SBP <90 mmHg or shock)
- Intermediate-risk (submassive PE): Right ventricular (RV) dysfunction or elevated biomarkers without shock
- Low-risk PE: Hemodynamically stable, no RV dysfunction or elevated troponin[59]

Initial supportive measures include:

- Oxygen therapy
- Hemodynamic support (IV fluids, vasopressors if necessary)

- Monitoring in ICU or telemetry for high/intermediate-risk cases[60]

2. Anticoagulation: Mainstay of Therapy

Anticoagulation prevents further thrombus propagation and allows endogenous fibrinolysis to occur. It should be initiated as soon as PE is suspected, provided there's no major bleeding risk[61].

a. Initial Anticoagulants

- Low Molecular Weight Heparin (LMWH): Preferred in cancer and pregnancy
- Unfractionated Heparin (UFH): Preferred if rapid reversal is anticipated
- Fondaparinux: Synthetic factor Xa inhibitor with predictable kinetics[62]

b. Direct Oral Anticoagulants (DOACs)

Rivaroxaban, apixaban, dabigatran, and edoxaban are increasingly favored due to oral administration, predictable pharmacokinetics, and no need for routine INR monitoring[63]. Studies show comparable efficacy and improved safety profiles versus warfarin[64].

Rivaroxaban: 15 mg BID for 21 days → 20 mg OD

Apixaban: 10 mg BID for 7 days → 5 mg BID

Dabigatran/Edoxaban: Require 5–10 days of parenteral anticoagulation first[65]

c. Warfarin

Used less frequently today; requires INR monitoring and bridging with heparin for at least 5 days[66].

3. Thrombolytic Therapy

Systemic thrombolysis is reserved for high-risk PE with shock or persistent hypotension, as it rapidly reduces clot burden and RV afterload[67].

- Agents: Alteplase 100 mg over 2 hours (or adjusted for body weight)
- Benefits: Reduced mortality and hemodynamic deterioration
- Risks: Major bleeding, especially intracranial hemorrhage (~2%)68

Intermediate-risk PE: Controversial. Routine use of thrombolysis is not recommended, but may be considered in select cases with RV dysfunction and worsening symptoms[69].

4. Catheter-Directed Therapies (CDT)

In patients with contraindications to systemic thrombolysis or refractory shock, catheter-based thrombolysis or thrombectomy may be performed:

- Ultrasound-assisted thrombolysis (USAT)
- Mechanical thrombectomy
- Local delivery of lower-dose thrombolytics

These methods reduce bleeding risk while preserving efficacy, especially in experienced centers[70].

5. Surgical Embolectomy

Reserved for:

- Massive PE with contraindication to thrombolysis
- Failure of thrombolysis or CDT
- Large proximal thrombi (e.g., saddle PE) causing obstruction

Though invasive, surgical embolectomy has improved outcomes when performed early and in high-volume centers[71].

6. Inferior Vena Cava (IVC) Filters

IVC filters do not treat PE but may prevent recurrent embolism in:

- Patients with absolute contraindications to anticoagulation
- Recurrent PE despite anticoagulation

Their use should be temporary and retrievable filters are preferred. Long-term placement is associated with increased DVT risk[72].

Duration of Anticoagulation

Clinical Scenario	Duration
PE provoked by surgery	3 months
PE provoked by transient risk factor	3–6 months
Unprovoked PE	≥3 months, possibly lifelong
PE in cancer	At least 6 months, ongoing
Recurrent PE or thrombophilia	Long-term/lifelong

Long-term decisions should balance bleeding risk vs recurrence risk, using tools like HAS-BLED or VTE-BLEED scores[73].

Management in Special Populations

a. Pregnancy

LMWH is the treatment of choice; DOACs and warfarin are contraindicated. Diagnosis often relies on V/Q scan over CTPA to reduce fetal radiation[74].

b. Cancer-associated PE

LMWH was previously preferred, but newer studies favor DOACs (e.g., apixaban, edoxaban) due to ease of use and non-inferior efficacy[75].

c. Elderly and Renal Impairment

Dose adjustments and bleeding risk assessments are crucial. DOACs may accumulate in renal impairment; monitor renal function regularly[76].

Prognosis and Long-Term Outcomes

Despite therapeutic advances, pulmonary embolism (PE) remains a potentially fatal condition. The prognosis depends largely on early recognition, appropriate risk stratification, and timely intervention. Even after acute management, long-term complications such as chronic thromboembolic pulmonary hypertension (CTEPH) and recurrent venous thromboembolism (VTE) significantly affect morbidity.

1. Short-Term Prognosis

a. Mortality

- Acute PE has an overall 30-day mortality of 5–15%, with higher rates in high-risk (massive) PE[77].

- In hemodynamically unstable PE, mortality may exceed 30–50% without thrombolytic or surgical intervention[78].

b. Prognostic Indicators

- RV dysfunction, elevated troponins, and BNP levels are associated with poor outcomes[79].
- Risk stratification tools like PESI (Pulmonary Embolism Severity Index) and sPESI help predict short-term mortality and guide treatment intensity[80].

2. Recurrence of VTE

- Approximately 25–30% of patients experience recurrent VTE within 10 years[81].
- Risk is highest in patients with unprovoked PE, thrombophilia, cancer, or non-adherence to anticoagulation.
- Prolonged or indefinite anticoagulation is considered in high-risk groups[82].

3. Post-PE Syndrome

A subset of patients experience persistent dyspnea, exercise intolerance, and reduced quality of life, even without objective cardiopulmonary abnormalities. This condition is referred to as post-PE syndrome, affecting 30–50% of survivors[83].

Causes include deconditioning, mild residual pulmonary hypertension, and psychological sequel such as anxiety or PTSD.

4. Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

CTEPH is a serious long-term complication characterized by persistent obstruction of pulmonary arteries, leading to pulmonary hypertension and right heart failure. It occurs in about 3–4% of patients after acute PE[84].

Suspected in patients with dyspnea >3 months post-PE despite anticoagulation and confirmed by:

- Ventilation-perfusion (V/Q) scan: Shows mismatched perfusion defects
- Right heart catheterization
- Pulmonary angiography or CT-PA for surgical planning

Pulmonary endarterectomy (PEA) is the treatment of choice in eligible patients, with >90% survival at 5 years in expert centers[86].

Medical therapy (e.g., riociguat) or balloon pulmonary angioplasty is considered in inoperable cases[87].

5. Quality of Life and Functional Recovery

Even after successful treatment, many patients experience:

- Fatigue
- Reduced exercise tolerance
- Emotional distress, especially fear of recurrence

Rehabilitation programs focusing on physical conditioning, psychological support, and education can significantly improve outcomes[88].

6. Follow-Up Recommendations

- 3-month review: Reassess for symptoms, RV function, anticoagulation adherence
- 6–12 months: Evaluate for post-PE syndrome or CTEPH if symptoms persist
- D-dimer testing and thrombophilia workup (if indicated) may help determine duration of anticoagulation[89]

Conclusion

Pulmonary embolism (PE) remains a critical and increasingly prevalent cardiovascular emergency, posing significant diagnostic and therapeutic challenges. The rising global incidence, in part due to improved imaging, aging populations, and heightened awareness, necessitates a proactive clinical approach. Despite advances in risk stratification tools, non-invasive imaging, and anticoagulant therapies, PE continues to cause considerable morbidity and mortality, especially when diagnosis or treatment is delayed.

A thorough understanding of clinical presentation, risk factors, and pathophysiology is vital for timely identification. The use of validated diagnostic algorithms, biomarkers, and clinical probability scores can significantly improve diagnostic accuracy while reducing unnecessary imaging. Treatment must be tailored based on risk stratification, encompassing anticoagulation, thrombolysis, or interventional procedures, alongside consideration for comorbidities and bleeding risk.

Long-term follow-up is essential to detect and manage complications such as CTEPH, post-PE syndrome, and recurrent VTE. Additionally, patient education, lifestyle modification, and rehabilitation play critical roles in improving outcomes and quality of life.

Given the notable burden of disease, continuous efforts are needed to refine diagnostic strategies, personalize therapeutic interventions, and ensure comprehensive follow-up. Integrating emerging technologies, biomarker profiling, and real-world risk assessment tools could further enhance outcomes in the evolving landscape of PE care.

Limitations: This review presents a comprehensive synthesis of the diagnostic and therapeutic landscape of pulmonary embolism; however, several limitations should be acknowledged. First, as a narrative review, it is subject to selection bias in the inclusion of studies and may lack the systematic rigor of meta-analyses. The heterogeneity of data from different healthcare settings, populations, and diagnostic protocols limits the generalizability of findings. Additionally, rapidly evolving evidence, especially in the context of COVID-19-associated thrombosis, means that newer data may have emerged since the time of writing. The review also does not delve

deeply into pediatric PE, pregnancy-associated PE, or genetic thrombophilias, which represent unique subgroups with specific diagnostic and management considerations. Furthermore, while clinical prediction rules and imaging modalities are discussed, real-world adherence to these protocols and resource limitations in low-income settings are not addressed in depth. Finally, although long-term outcomes such as chronic thromboembolic pulmonary hypertension (CTEPH) and post-PE syndrome are highlighted, data on their incidence, predictors, and optimal management remain incomplete and warrant further prospective research.

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