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HAEMODYNAMIC CLASSIFICATION OF PULMONARY EMBOLISM AND ITS LONG-TERM PROGNOSTIC ROLE

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INDEX

Definition **1**

Introduction **2**

Epidemiology *2*

Predisposing risk factors *3*

Natural History *8*

Pathophysiology *12*

Chronic thromboembolic pulmonary hypertension *16*

Clinical classification of pulmonary embolism severity *19*

Diagnosis **23**

Clinical presentation *23*

D-dimer testing *28*

Compression venous ultrasonography (CUS) *29*

Chest X-ray *29*

Electrocardiography *31*

Lung scintigraphy *31*

Computed tomographic pulmonary angiography *32*

Pulmonary angiography *33*

Echocardiography *34*

Diagnostic strategies *35*

Prognostic assessment **38**

Prognostic registers *40*

Main prognostic indicators *42*

Prognostic assessment strategy *47*

Therapy **49**

Haemodynamic and respiratory support *50*

Anticoagulation *51*

Venous filters *53*

Thrombolytic treatment *54*

Surgical embolectomy *55*

Percutaneous catheter-directed treatment *56*

Therapeutic strategy *57*

Invasive haemodynamic assessment 58

The importance of invasive haemodynamic assessment in the acute phase 58

The importance of invasive haemodynamic assessment in the post acute phase 60

Research purpose 64

Study protocol 64

Patient population 65

Invasive haemodynamics using right heart catheterization 65

Statistical analysis 65

Results 67

Long term follow-up 68

Right heart catheterization at 6-months follow-up 71

Discussion 73

Bibliography 83

Definition

Pulmonary embolism (PE) together with **deep vein thrombosis (DVT)** are known as **venous thromboembolism (VTE).** PE is the obstruction of one or more pulmonary arteries by material (most commonly thrombus) that travels to the lungs from another site in the body, most often from deep veins of the lower extremities or pelvis. However, PE may also result from non-thrombotic material such as fat, tumor, or air.

Introduction

Epidemiology

Venous thromboembolism (VTE) is the **third most common cardiovascular disease** worldwide, after acute myocardial infarction and stroke, with approximately **10 million cases occurring globally each year** (1). The incidence of VTE in North America and Europe is approximately 1.5 cases per 1000 person-years. About two thirds of cases are DVT, and the rest are PE with or without DVT. Very few studies have been carried out on the Italian population: in Italy, regional studies have estimated approximately **42 new PE episodes per 100,000 individuals per year in northern Italy and 18.9 per 100,000 in southern Italy.** These differences may reflect true population-level variation, differences in diagnostic rates, or both. The annual incidence in Western populations is approximately 1–2 cases per 1,000 person-years, and in Western countries the incidence of PE specifically is estimated at 60–120 cases per 100,000 population per year (2,3). Rates of VTE are lower in Asian populations, and data from low-income countries remain sparse. In general, since previous autopsy studies have shown that many embolic events are **currently unrecognized**, an underestimation of the true incidence of PE should always be considered (2,4).

The incidence of pulmonary embolism is obviously influenced by the nature of the population surveyed. Incidence increases **exponentially with age**, reaching up to 1 case per 100 persons per year among those older than 80 years (1).

PE is one of the leading causes of mortality, morbidity and hospitalization in Europe. It frequently isn't the sole cause of death, as it commonly **coexists with cancer, sepsis, or other serious conditions** (5). In the United States, PE contributes to approximately 200,000 deaths per year, making it one of the leading causes of cardiovascular mortality. The age-standardized mortality rate for PE in the US is approximately 4 deaths per 100,000 population annually(2).

VTE is a chronic disease with a high recurrence burden. Approximately **30% of all patients with VTE experience a recurrence within 10 years** (1). Among patients with unprovoked or weakly provoked first PE, the risk of recurrent VTE is approximately 10% at 1 year and 36% at 10 years after stopping anticoagulation, with a corresponding risk of fatal PE of 0.4% at 1 year and 1.5% at 10 years; **these risks are higher in men than in women**. Beyond recurrence, survivors of acute PE face significant long-term morbidity. Approximately half of patients diagnosed with PE have functional and exercise limitations one year later, a condition termed *post-pulmonary embolism syndrome* (5). In addition to recurrent VTE, patients who survive acute PE are at increased risk of arterial cardiovascular disease, cancer, and chronically

reduced quality of life owing to lasting functional limitations (3,6).

Predisposing risk factors

There are multiple risk factors that may increase the clinical probability of developing VTE, as Table 1 shows.

The likelihood of pulmonary embolism increases with the number of predisposing factors for venous thromboembolism. Therefore, evaluating their presence is useful both for estimating clinical probability and for guiding decisions on primary prevention.

Provoking risk factors	Non-provoking risk factors	Genetic risk factors
Cancer	Age > 60 years	Antithrombin-deficiency
Surgery	Sex	Antithrombin-resistance
Trauma	Ethnicity	Protein C deficiency
Acute infection	Oral contraceptive	Protein S deficiency
Immobilization	Hormone therapy	Factor V-Leiden (G1691A)
Pregnancy	BMI	Factor II-Mutation (G20210A)
Post-partum period		Elevated FVIII level
Long distance travel		Dysfibrinogenemia
Hospitalization		Blood group Non-O
Catheterization		Loci for VTE susceptibility: *TSPAN15, SLC44A2*

Table 1: Risk Factors for VTE (7)

VTE results from the interplay between **patient-related risk factors**, which are typically permanent, and **setting-related risk factors**, which are usually temporary. Temporary risk factors increase the risk of pulmonary embolism only for a limited period, after which the risk returns to baseline. In contrast, permanent risk factors lead to a persistently elevated risk of VTE over time (8).

VTE is defined as “provoked” when it occurs in the presence of a recent (within 6 weeks to 3 months before diagnosis) and transient (reversible) risk factor. It is considered “unprovoked” when it develops in patients without a preceding major clinical risk factor and who are not on hormonal therapy (such as oral contraceptives or hormone replacement therapy), and do not have active cancer, thrombophilia, or a family history of VTE. These latter conditions are regarded as persistent underlying risks. In patients diagnosed with unprovoked DVT or PE who are not already known to have cancer, further evaluation for occult malignancy should be considered (9).

The commonly accepted risk factors for venous thromboembolism (VTE) fall into one or more of Virchow’s triad categories: **hypercoagulability, stasis of blood flow, and vascular endothelial damage**; and since PE is one of the manifestations of VTE, we can say that this triad

is also involved in the pathogenesis of PE itself.

The type of risk factors or their absence have important consequences on the duration of **anticoagulant therapy**; this can be modulated based on an unprovoked PE or the presence of persistent and non-modifiable risk factors.

Following the **American Society of Hematology (ASH) 2023 guidelines,** it is possible to divide risk factors into **hereditary** or **acquired**. Approximately 50–60% of the variance in VTE incidence is attributed to genetic effects (10).

Inherited (Heritable) Risk Factors:

- Factor V Leiden (FVL): Present in 3–7% of Europeans; heterozygosity increases VTE risk ~3–7-fold, homozygosity ~15–80-fold. FVL is found in ~20% of initial DVT episodes but only ~8% of isolated PE (the "Leiden paradox") (1,11)
- Prothrombin G20210A mutation: Prevalence 1–2% in Europeans; OR ~2.6 for isolated PE (1,12)
- Antithrombin deficiency: Rare (~0.02–0.2%); strongest thrombotic risk among natural anticoagulant deficiencies (1,13)
- Protein C deficiency: Prevalence ~0.2–0.5%; impairs inactivation of factors Va and VIIIa (1,13)
- Protein S deficiency: Prevalence ~0.1–1%; cofactor for activated protein C (1,13)
- Non-O blood group: Present in ~55% of the population; associated with higher factor VIII and von Willebrand factor levels

Figure 1, below, illustrates how inherited thrombophilias disrupt normal coagulation control mechanisms, leading to excessive thrombin activity.

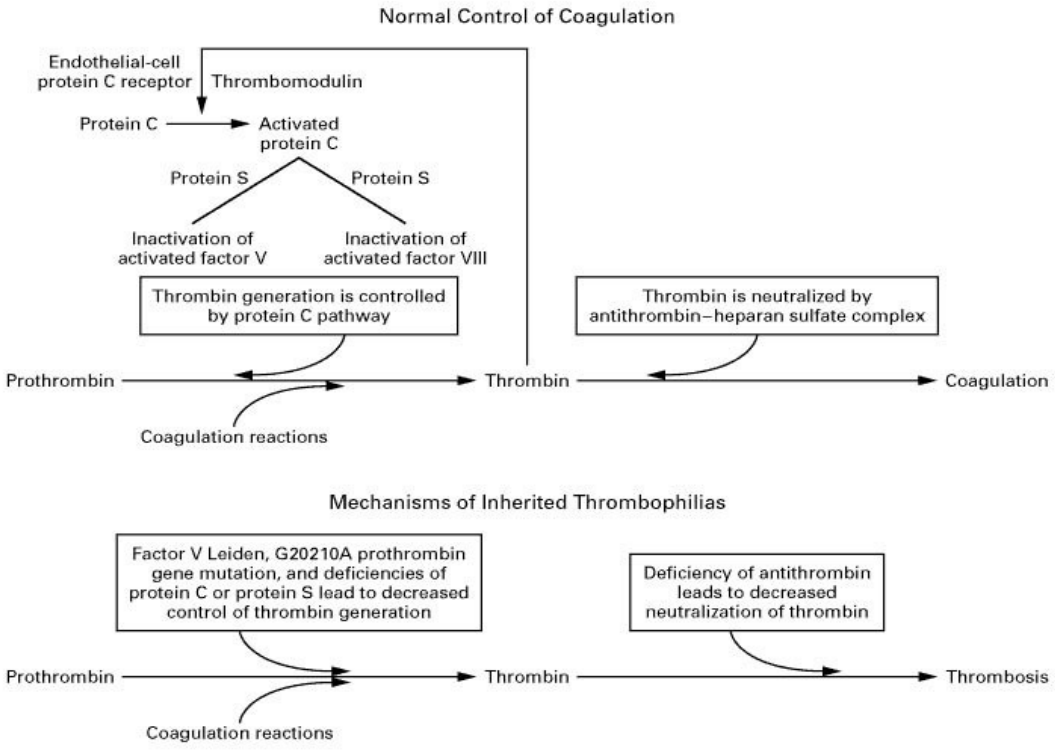

Figure 1: Major Mechanisms Involved in the Normal Control of Coagulation and Inherited Thrombophilias(14).

Acquired risk factors can be subdivided into **transient (provoking)** and **persistent** categories, per the CHEST and ISTH classification:(3,15)

Transient acquired risk factors (major):

- Surgery with general anesthesia >30 min
- Hospitalization/bed confinement ≥3 days
- Major trauma or fracture
- Cesarean section

Transient acquired risk factors (minor):

- Minor surgery (<30 min), short hospitalization (<3 days)
- Estrogen therapy (oral contraceptives, HRT, tamoxifen)
- Pregnancy and puerperium
- Leg injury with reduced mobility ≥3 days

- Prolonged travel (>4 hours)
- Acute infection, including **COVID-19** (15)

Persistent acquired risk factors:

- **Active cancer** (~20% of all VTE)
- Antiphospholipid syndrome
- Chronic inflammatory disorders (e.g., IBD, autoimmune diseases)
- Congestive heart failure
- Obesity
- Polycythemia, sickle cell disease
- Central venous catheters/pacemakers (1,3,16–18)

Other demographic/lifestyle factors: Older age (>65), male sex (in older adults), female sex (in younger adults <50), smoking, hypertension, metabolic syndrome, and air pollution (18,19)

It is also possible to divide them based on their modifiability:

- Among the main **modifiable risk factors** for VTE there are: obesity, metabolic syndrome, cigarette smoking, hypertension, abnormal lipid profile;
- Among the main **non-modifiable risk factors** there are: advanced age, arterial disease, congestive heart failure, recent surgery, trauma, immobility, chronic inflammation (e.g., inflammatory bowel disease), pregnancy, oral contraceptive pills, postmenopausal hormone replacement therapy, hypercoagulable states and personal or family history of venous thromboembolism.
-

From the analysis of the main risk factors it emerges that:

- Surgery and trauma: VTE risk increases acutely following surgery. Specifically, patients undergoing orthopedic or oncologic surgery have a particularly high risk for VTE following the procedure (20). Secondary tissue damage from surgery or trauma may lead to the release of inflammatory cytokines, which impair fibrinolysis and down regulate endogenous anticoagulants all of which contribute to an increased risk for VTE;
- Cancer: active cancer is a major risk factor for VTE. Patients with cancer have twice the

incidence of DVT and PE compared to patients without cancer. The incidence differs according to the type of cancer, is comparable in elderly and younger patients. The highest incidence of VTE is observed during the first year after cancer diagnosis and shortly after initiation of treatment (21);

- Prolonged immobility: Some of the more commonly causes of immobility are joint fixation, hospitalization, and prolonged travel. Among patients with joint fixation, the incidence of VTE increase approximately twice, compared to control, after 72 hours of immobility (22). About long-haul travel there is a dose-response relationship between travel duration and VTE risk; however, the absolute risk of VTE for any traveler is relatively low (23). The greatest risk of VTE from limb immobility comes from recently hospitalized patients;
- Estrogen use and pregnancy: VTE is associated with estrogen-containing oral contraceptives, pregnancy, and postmenopausal hormone replacement therapy. Oral contraceptives increase the risk of VTE by 3-4 times (24). Postmenopausal hormone replacement therapy increases the risk of VTE 2 to 3-fold (25). VTE risk during pregnancy begins in the first trimester and continues into the postpartum period where within 2 weeks of delivery approximately 70% of pregnancy related VTE occurs (26);
- Indwelling catheters: vessel wall damage is the major contributing factor to formation of VTE related to an indwelling catheter. Catheter might prompt the fibrin and coagulation factors to attach to the vessel wall and propagate (27);
- Age: With advancing age, circulating anticoagulant production declines more rapidly than procoagulant factor production, resulting in a progressively more prothrombotic state in the elderly;
- Venous insufficiency: is common in the elderly as a result of venous dilation and venous valvular dysfunction. Venous dilation promotes venous stasis, and the resulting pooling and stagnation of blood increases the risk of clot formation;
- Obesity: there is a linear relationship between body mass index (BMI) and VTE. Severe obesity (BMI > 35) predisposed individuals to a VTE risk 6 times that of normal weight (BMI < 25) cohorts (28);
- Rheumatologic Disease: patients with inflammatory rheumatologic condition have an increased risk for VTE compared to unaffected patients (29);
- Arterial Cardiovascular Disease and Risk Factors: There may be overlapping pathophysiological mechanisms involved in the development of both arterial and venous

disease. Established cardiovascular risk factors, such as smoking, hypertension, and obesity, may also increase the risk of idiopathic pulmonary embolism.

- Previous VTE: one of the strongest risk factors for VTE is a history of prior VTE, even in patients who are actively being treated with anticoagulation (30).

Natural History

The limits of establishing the natural history of pulmonary embolism lie in the difficulty of accurately fixing the incidence and estimating the number of deaths per year (in which the death is due to pulmonary embolism and not for other concomitant pathologies).

Approximately half of all deaths caused by pulmonary embolism are attributable to **massive pulmonary embolism**. In the United States, the annual mortality from pulmonary embolism is estimated at about 200,000 cases, meaning that nearly 100,000 deaths are due to massive PE. About 67% of total deaths occur within the first hour after symptom onset, leaving insufficient time for diagnosis and initiation of appropriate therapy. Consequently, around 133,000 deaths occur in patients who survive for more than one hour, mainly because the condition remains undiagnosed and untreated.

The natural history of pulmonary embolism differs significantly between patients who receive adequate treatment and those who do not.

Dalen et al., in 1975, have estimated that the total number of symptomatic episodes of pulmonary embolism per year were 630,000. Figure 2 schematically represents collected data.(31)

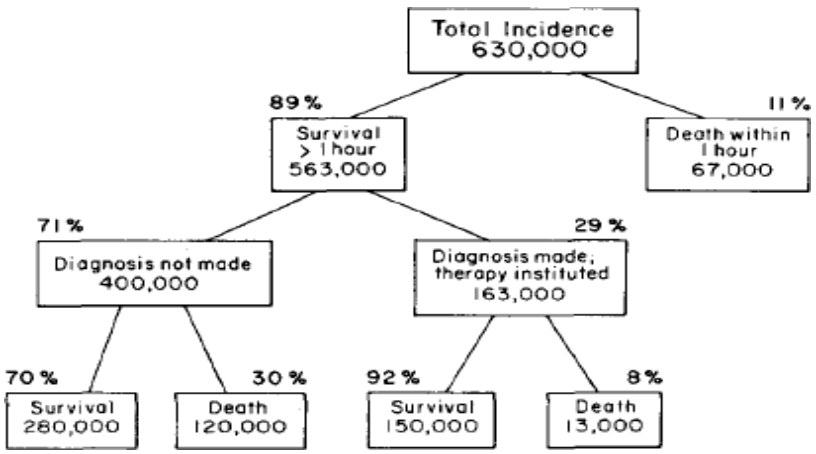

Figure 2: Incidence of pulmonary embolism per year in the USA.

Out of approximately 630,000 cases of pulmonary embolism, about 11% of patients die within the first hour after symptom onset, making diagnosis and treatment impossible. Post-mortem examinations in these early deaths frequently reveal the presence of massive pulmonary embolism.

The clinical course of the remaining patients with acute pulmonary embolism who survive beyond the first hour (around 563,000 individuals) largely depends on whether the condition is **recognized and treated promptly**. Diagnosis is missed in nearly 400,000 patients (71%), and among these untreated individuals, about 30% (120,000 cases) die because appropriate therapy is not administered. Therefore, the **mortality rate of symptomatic pulmonary embolism in the absence of treatment is estimated to be around 30%.**

The prognosis of patients who survive an acute pulmonary embolism without treatment remains uncertain, as they are at increased risk of major complications, including recurrent venous thrombosis, pulmonary hypertension, cor pulmonale, arterial cardiovascular events, and death related to comorbidities. Conversely, some patients may **spontaneously lyse the thrombus** and, in the absence of recurrence, remain asymptomatic.

Among patients who receive treatment, outcomes depend on both the therapeutic approach and the severity of the disease. **Among treated patients, mortality is approximately 5–8%.**

In summary, most of the deaths (more than 90%) occur in patients who are not treated because the diagnosis is not made (32). Whereas, less than 10% of deaths occur in patients undergoing treatment (33). Improved treatment will have little impact on the number of deaths due to pulmonary embolism. Improved diagnosis and more prevention of DVT present the greatest opportunities to prevent fatal pulmonary embolism (34).

The acute course of patients with pulmonary embolism who live long enough for the diagnosis to be established and therapy to prevent further pulmonary embolism instituted may be summarized as follows:

- Death due to pulmonary embolism is uncommon if treatment to prevent further pulmonary embolism is instituted;
- The acute prognosis is largely determined by the presence of associated disease, particularly heart disease;
- Evidence of partial resolution of pulmonary embolic obstruction can be detected by lung scan and angiogram within days of the embolic episode;
- Complete resolution of major pulmonary embolism may occur as early as 14 days after

embolism, but usually requires a longer period of time;

- The haemodynamic correlates of pulmonary embolism resolve as the degree of pulmonary vascular obstruction resolves.

The favorable prognosis of patients who survive the initial haemodynamic consequences of massive pulmonary embolism is related to the fact that pulmonary vascular obstruction begins to decrease almost immediately after the embolic event. Resolution of the obstruction occurs through two main mechanisms: **in vivo fibrinolysis** and **mechanical changes**, namely alterations in clot position. Even slight displacement of a thrombus may convert a completely obstructed artery into a partially obstructed one.

Regarding **the long-term prognosis** of acute pulmonary embolism, outcomes—similarly to the acute phase—**depend largely on whether the embolic episode is promptly recognized and appropriately treated** in order to prevent recurrent pulmonary embolism.

The long-term clinical course of patients who survive an episode of acute pulmonary embolism may be summarized as follows:

- Further resolution of pulmonary embolic obstruction occurs in the first 3 months after acute pulmonary embolism;
- Complete haemodynamic and angiographic resolution occurs in most patients;
- Chronic cor pulmonale is an exceedingly rare complication of treated acute pulmonary embolism, but it may occur in patients who have repeated episodes of pulmonary embolism that are undetected and untreated;
- With appropriate therapy, that is, long-term anticoagulation or IVC interruption in patients who are chronically predisposed to pulmonary embolism, recurrent, symptomatic pulmonary embolism is rare;
- With appropriate therapy, the long-term prognosis of patients with pulmonary embolism is excellent and limited only by associated diseases.

In 5-10% of patients, the clinical manifestations of PE are **shock** and/or **hypotension** (configuring the high-risk PE framework), while 50% of cases occur without shock but with signs of **right ventricular dysfunction** or myocardial laboratory, that lay down for a **negative prognosis** (35). Approximately 10% of pulmonary embolisms are rapidly fatal, while an additional 5% result in death at a later stage, despite appropriate diagnosis and treatment. Around 50% of diagnosed

pulmonary embolisms are associated with right ventricular dysfunction, a condition linked to a fivefold increase in in-hospital mortality. Following treatment, about 50% of pulmonary emboli resolve within the first month, and pulmonary perfusion eventually returns to a normal state in nearly two thirds of patients. However, approximately 5% of treated patients develop **pulmonary hypertension due to incomplete thrombus resolution**. After completion of therapy, the risk of recurrent thrombosis remains higher—approximately 10% per patient-year—in patients without reversible risk factors, in individuals with cancer, and in those with prothrombotic biochemical abnormalities, such as antiphospholipid antibodies or homozygous factor V Leiden mutation (33).

The risk for recurrent VTE is estimated at 20 to 25% after 5 years in unselected cohorts, and higher than 25% in those without a clear provoking cause (36). Recurrence is also increased in those with associated congenital or acquired risk factors (37).

Moreover, recurrence is more frequent after multiple VTE and after unprovoked VTE as opposed to a single event and to the presence of a temporary risk factor (38) and is higher in women who continue hormone intake after a first episode, patients who suffered PE or proximal vein thrombosis compared to distal (calf) vein thrombosis (8).

The natural course of a thrombus is gradual resolution over time. Nevertheless, residual thrombus is still detected on lung scintigraphy one year after the initial event in approximately 15–30% of patients. Persistent thrombotic material may lead to sustained elevation of pulmonary vascular resistance (PVR) and increased right ventricular (RV) pressure overload, resulting in physiologic consequences associated with **functional limitation and reduced quality of life.**

Patients who survive PE may develop a long-term complication known as *post-PE syndrome*, which is associated with an increased risk of recurrent PE. Post-PE syndrome is characterized by dyspnoea, exercise intolerance, and reduced quality of life; resulting from persistently elevated pulmonary vascular resistance and RV pressure overload. These changes can impair cardiac function and alter pulmonary arterial flow and gas exchange (39).

This syndrome includes two chronic conditions: **chronic thromboembolic disease (CTED)**, which is characterized by persistent perfusion defects caused by residual thromboembolic material in the pulmonary arteries without the presence of pulmonary hypertension; and **chronic thromboembolic pulmonary hypertension (CTEPH)**, the more severe form. CTEPH is estimated to occur in approximately 0.1% to 8.8% of patients who survive an acute pulmonary embolism (40).

In the last few years several risk scores have been developed to predict the risk of recurrent VTE

and PE after stopping anticoagulant treatment, including the DASH score (based on D-dimer level, Age, Sex, Hormones), the Vienna prediction rule and the HERDOO2 rule (based on VTE clinical signs, such as Hyperpigmentation, Oedema or Redness in either leg, and other parameters such as D-dimer level ≥250 μg/L; BMI ≥30, obesity; and age ≥65 years, older age).

About the first one, it appears to predict recurrence risk in patients with a first unprovoked VTE and may be useful to decide whether anticoagulant therapy should be continued indefinitely or stopped after an initial treatment period of at least 3 months (41).

The last one is the only rule which has been validated prospectively but it is not reliable when applied to women > 50 years old (42).

Furthermore, a recent study suggests that mean platelet volume (MPV) and platelet distribution width (PDW) may serve as potential predictive markers for assessing the risk of recurrence and mortality in pulmonary embolism. In particular, it was shown that MPV and PDW values were significantly higher in patients who experienced recurrent PE compared with those without recurrence (43). However, further studies are needed to confirm and validate these findings.

Pathophysiology

Venous stasis, hypercoagulability, and localized vessel wall injury—collectively known as Rudolf Virchow's triad—represent the primary factors contributing to VTE. Thrombosis develops when an **imbalance** occurs **between the coagulation process and the body's natural anticoagulant or fibrinolytic systems**. Venous thrombi consist mainly of fibrin, red blood cells, and platelets. They typically form in areas of vessel injury or blood stasis, such as venous sinuses or valve cusps. While some small DVTs may resolve spontaneously through lysis, others can extend into proximal veins. If a DVT detaches, it follows the normal venous circulation through the vena cava to the right chambers of the heart and eventually reaches the pulmonary arteries, where it becomes lodged as a pulmonary embolism.

There are both respiratory and haemodynamic consequences associated with pulmonary embolism:

- Haemodynamic consequences due to **acute right-sided heart failure**;
- Respiratory consequences due to **alteration of ventilation / perfusion and interference in gaseous exchanges**.

The clinical manifestations of PE depend upon four main factors:

- The extent of occlusion of the vascular tree and the size of the emboli;
- Patient's pre-existing cardiopulmonary condition;
- Chemical vasoconstriction due to the release of serotonin and thromboxane from platelets that adhere to the embolus, as well as to fibropeptide B, which is a product of fibrinogen breakdown;
- The reflex vasoconstriction that is likely to occur as a consequence of pulmonary artery dilatation.

Effect of PE on gas exchange

The obstruction of blood flow in embolized arteries leads to the formation of **dead space** in the affected areas of the lung. An increase in dead space directly influences arterial carbon dioxide pressure (PCO2), which is determined by carbon dioxide production (VCO2) and alveolar minute ventilation (Vc).

In most patients, the total minute ventilatory volume (VE)—which includes both alveolar ventilation and dead space ventilation—increases. This increase exceeds the level necessary for CO2 elimination, leading to **hypocapnia**.

In contrast, patients with massive acute PE or underlying respiratory disease may develop rapid respiratory muscle fatigue, resulting in elevated PCO2 levels (**hypercapnia**).

A certain degree of **hypoxaemia**, although generally mild, is observed in most patients with PE. Approximately 63% of patients present with a partial arterial oxygen pressure (PO2) below 70 mmHg. The remaining patients maintain normal PO2 levels due to **hyperventilation**, which may increase VE to two or three times the normal value.

Four mechanisms have been determined to contribute to PE hypoxaemia:

- Arteriovenous communications develop both in the lungs and in the heart: in the pulmonary circulation, newly opened vessels bypass the capillary network in an **attempt to lower**

pulmonary pressure; at the cardiac level, increased right atrial pressure caused by PE may lead to a **right-to-left shunt through a patent foramen ovale**.

- Ventilation–perfusion (V/Q) mismatch represents the principal mechanism responsible for hypoxaemia. Histamine release induces bronchospasm, whereas serotonin promotes vasospasm, creating areas with preserved perfusion but impaired ventilation (functional shunt) alongside regions with adequate ventilation but reduced perfusion.
- A marked PE is often associated with reduced cardiac output, which lowers mixed venous oxygen saturation. This reduction further aggravates hypoxaemia already caused by V/Q imbalance.
- In massive PE, diminished oxygen perfusion may also contribute to hypoxaemia. Blood flow is redirected through the unaffected lung regions in greater quantities, reducing the time available for adequate oxygenation. Although gas exchange abnormalities are important in the pathophysiology and diagnosis of PE, hypoxaemia generally improves with supplemental oxygen therapy. Consequently, the severity of PE depends mainly on its haemodynamic impact on pulmonary and systemic circulation rather than on impaired gas exchange itself (44).

In summary, **respiratory failure** in pulmonary embolism is primarily related to **haemodynamic impairment.** Reduced cardiac output leads to desaturation of the mixed venous blood returning to the lungs. In addition, hypoperfusion of the pulmonary regions supplied by the obstructed vessels, together with compensatory hyperperfusion of the unaffected capillary bed, results in ventilation–perfusion mismatch, thereby contributing to hypoxaemia. The compensatory increase in respiratory rate subsequently causes a reduction in PCO_2 levels.

Effect of PE on pulmonary circulation

Since the lungs are linked to the right heart, so everything that happens in the lung immediately affects the right side of the heart, haemodynamic consequences on the pulmonary circulation generally occur when the obstruction involves more than 30–50% of the total cross-sectional area of the

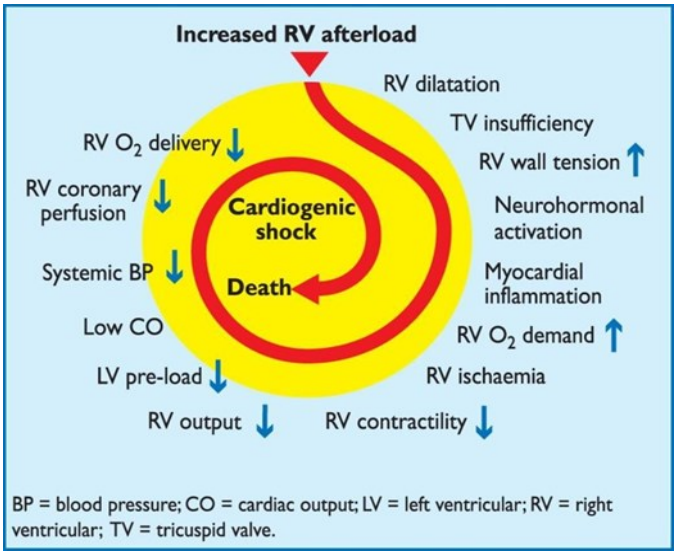

Figure 3: *Key factors contributing to haemodynamic collapse in acute pulmonary embolism*

pulmonary arterial tree. Up to this threshold, the pulmonary vascular bed is able to compensate through mechanisms such as **vasodilation and vascular recruitment**, thereby maintaining relatively stable pulmonary pressures without major pathological alterations.

Depending on its size, the thrombus may lodge at different levels of the pulmonary arterial tree: larger emboli typically obstruct the bifurcation of the pulmonary artery or the lobar arteries, whereas smaller emboli tend to occlude distal vessels of smaller calibre. Pulmonary infarction develops in only about 10% of cases.

The reduction in the cross-sectional area of the pulmonary vascular bed leads to an increase in pulmonary vascular resistance, mainly as a consequence of the mechanical obstruction caused by the embolus; thereby increasing RV afterload. In addition, reactive vasoconstriction of the pulmonary arterioles, triggered by hypoxia and by the release of serotonin and thromboxane A2 from platelets within the thrombus, further contributes to the rise in RV afterload.

When this pressure overload develops acutely, the right ventricle, which has a relatively thin muscular wall, becomes unable to adapt adequately and undergoes dilation. RV dilation alters myocardial contractility through the Frank–Starling mechanism: the increase in RV pressure and volume raises wall tension and stretches myocardial fibres.

In pulmonary embolism, the sudden elevation in pulmonary vascular resistance therefore produces an acute increase in RV afterload, leading to **progressive right ventricular dilation and dysfunction**. If the afterload becomes excessive and the right ventricle can no longer maintain an adequate ejection fraction, **cardiac arrest may occur**.

As a consequence of RV dilation, several important haemodynamic alterations may occur.

One of the earliest manifestations is the onset of **tricuspid regurgitation**. The tricuspid valve is particularly susceptible to dilation because its leaflets are thin and its annulus is mainly composed of loose connective tissue, unlike the mitral valve, whose annulus is supported by denser connective tissue. The severity of tricuspid insufficiency is directly related to the degree of RV dilation.

At the same time, abnormal stretching of the RV wall and activation of systemic pressure receptors stimulate the **neurohumoral response: activation of the sympathetic–adrenergic system** induces systemic vasoconstriction together with positive inotropic and chronotropic effects. Initially, these compensatory mechanisms increase pulmonary arterial pressure, improve blood flow through the

partially obstructed pulmonary circulation, and temporarily preserve systemic blood pressure. Nevertheless, these adaptive responses are often insufficient to maintain adequate RV function over time, even in the absence of recurrent embolic events.

Neurohumoral activation is also associated with **myocardial inflammation**. Histological studies in patients who died within 48 hours after acute pulmonary embolism demonstrated massive inflammatory infiltrates in the right ventricular myocardium, possibly related to the high levels of circulating epinephrine. This inflammatory process may contribute to the **secondary haemodynamic deterioration** that can occur 24–48 hours after the acute event, although recurrent pulmonary embolism may also account for some of these cases.

As the dilated right ventricle requires an increased oxygen supply, a mismatch between oxygen demand and delivery may develop. This imbalance damages cardiomyocytes and progressively reduces myocardial contractility, ultimately leading to RV failure.

In addition, the enlarged and dysfunctional right ventricle adversely affects left ventricular (LV) function. **Interventricular septal displacement** impairs LV filling, while the reduction in pulmonary blood flow decreases LV preload. Consequently, LV cardiac output and systemic arterial pressure fall. The resulting reduction in coronary perfusion further increases the risk of **myocardial ischaemia**. In severe cases, the abrupt decline in cardiac output may lead to hypotension, syncope, and sudden death. When pulmonary arterial pressure exceeds approximately 40 mmHg, the right ventricle may progress to acute failure.

Altogether, these mechanisms can culminate in **cardiogenic shock** and **death** if the pulmonary arterial obstruction caused by thromboemboli is not promptly relieved.

Chronic thromboembolic pulmonary hypertension

The chronic thromboembolic pulmonary hypertension (CTEPH) is a debilitating disease which is caused by the chronic obstruction of major pulmonary arteries. The prevalence of CTEPH is unknown and the median age of patients suffering from CTEPH is 63 years. It is also considered as a **long-term complication of PE**.

Pathophysiology

Chronic Thromboembolic Pulmonary Hypertension is mainly a consequence of pulmonary thromboembolism, and nearly 80% of affected patients have a documented history of venous thromboembolism (VTE). The development of CTEPH may result from inadequate anticoagulant therapy, a large thrombotic burden, persistence of residual thrombi, or recurrent thromboembolic events.

The risk factors associated with CTEPH differ substantially from those typically linked to VTE and can be classified into **plasmatic** and **non-plasmatic factors**, as summarised in Table 2.

	Risk factors
Plasmatic	Lupus anticoagulant antibodies or antiphospholipid antibodies Elevated levels of anticoagulation factor VIII Hypercoagulation 'Sticky' red blood cells high platelet counts 'uncleavable' fibrinogen
Non-plasmatic	Remodelling pulmonary arteries after PE Splenectomy Ventriculoatrial shunt Inflammatory bowel disease Chronic osteomyelitis

Table 2: Risk factor for CTEPH (8).

Plasmatic risk factors associated with Chronic Thromboembolic Pulmonary Hypertension include the presence of lupus anticoagulant or antiphospholipid antibodies, as well as elevated plasma levels of coagulation factor VIII.

Following pulmonary embolism, pulmonary vascular remodelling may occur and contribute to the progression toward CTEPH. In addition, conditions such as hypercoagulability, increased erythrocyte adhesiveness, thrombocytosis, and the presence of fibrinogen resistant to fibrinolysis, may further promote obliteration of the pulmonary arterial bed.

Non-plasmatic risk factors include splenectomy, ventriculoatrial shunts used in the treatment of hydrocephalus, inflammatory bowel disease, and chronic osteomyelitis.

The pathophysiology of CTEPH also involves the development of **pulmonary microvascular disease**, which may contribute to the incomplete effectiveness or failure of pulmonary endarterectomy. This microvascular involvement may result from high-flow or high-pressure states within non-obstructed pulmonary vessels, as well as from mechanisms related to hypoxia, infection, or chronic inflammation.

Clinical presentation and diagnosis

Clinical signs and symptoms of Chronic Thromboembolic Pulmonary Hypertension are often non-specific or may even be absent during the early stages of the disease. When present, the clinical picture may resemble that of acute pulmonary embolism or Idiopathic Pulmonary Arterial Hypertension (iPAH). Nevertheless, some differences in presentation can help distinguish the two conditions: syncope is more frequently observed in iPAH, whereas ooedema and haemoptysis are more commonly associated with CTEPH.

The lack of specific clinical findings makes the differential diagnosis particularly challenging. The diagnosis of CTEPH is established after at least three months of effective anticoagulant therapy and is based on the following criteria:

- mean pulmonary arterial pressure ≥ 25 mmHg with pulmonary arterial wedge pressure ≤ 15 mmHg;
- at least one segmental perfusion defect identified on ventilation–perfusion lung scanning, or evidence of pulmonary arterial obstruction detected by multidetector CT (MDCT) angiography or conventional pulmonary cineangiography.

Treatment

The treatment of choice for Chronic Thromboembolic Pulmonary Hypertension is **pulmonary endarterectomy (PEA).** In experienced European centres, the perioperative mortality is reported to be below 4.7%. The procedure is carried out under conditions of **deep hypothermia** with **circulatory arrest**, a technique that differs from that used in the management of acute pulmonary embolism.

Assessment of operability is complex and cannot be fully standardised. It depends on several factors, including the patient's clinical suitability (advanced age is not considered an absolute contraindication), the expertise of the surgical team, and the availability of specialised resources.

Patients who are not candidates for surgery, or who present with persistent or residual pulmonary hypertension after PEA, generally have a poor prognosis.

Medical management includes **lifelong anticoagulation**, **diuretics**, and **oxygen** therapy. In cases where concomitant pulmonary microvascular disease is present, pharmacological agents approved for pulmonary arterial hypertension may be used, such as *Riociguat*.

Clinical classification of pulmonary embolism severity

The 2026 AHA/ACC/ACCP/ACEP/CHEST/SCAI/SHM/SIR/SVM/SVN Guideline introduces a new 5-category classification system (Categories A through E) with subcategories, replacing the older "massive/submassive/low-risk" terminology to provide more granular severity stratification of acute pulmonary embolism (45)

The categories are described, in this case, as follows:

Category A — Asymptomatic / Incidental PE

- A1: Incidentally discovered PE on imaging performed for another indication (e.g., cancer staging CT). Patients can safely be discharged home without hospitalization (45).

Category B — Symptomatic, Low Risk

- Low risk by validated severity indices: PESI ≤85, sPESI 1, or Hestia 1 (45).
- B1: Subsegmental PE (single or multiple) — triage and anticoagulation decisions may differ based on clot location and presence of DVT.
- B2: Segmental or more proximal PE without RV dysfunction.
- Early hospital discharge is generally recommended (45).

Category C — Symptomatic, Elevated Risk (Haemodynamically Stable)

- Elevated severity index: PESI >85, sPESI ≥1, or Hestia ≥1 (45).

- C1: No biomarker elevation and no RV dysfunction.
- C2: Elevated biomarkers (troponin, BNP) OR RV dysfunction on imaging.
- C3: Elevated biomarkers AND RV dysfunction.
- A respiratory modifier (R) can be appended (e.g., C1R) when hypoxemia, tachypnea, or supplemental oxygen requirement is present (45).
- Hospitalization is recommended (45).

Category D — Pre-Cardiopulmonary Failure

- Normotensive shock states or approaching need for ventilatory support (45).
- D1: Transient or recurrent hypotension (including relative hypotension) that is short-lived or responds to volume expansion, without signs of end-organ dysfunction.
- D2: Cardiovascular compromise beyond D1 criteria.
- D3: Respiratory compromise approaching ventilatory failure.
- Hospitalization is recommended; advanced therapies (systemic thrombolysis, catheter-based thrombolysis, mechanical thrombectomy, surgical embolectomy) can be considered for D1–D2 (45) .

Category E — Cardiopulmonary Failure

- Persistent hypotension, cardiogenic shock, or cardiac arrest (45).
- E1: Persistent hypotension requiring vasopressors with end-organ hypoperfusion.
- Advanced therapies are reasonable for E1 (45).
- Hospitalization with intensive care is required.

Evolution from prior classification systems

This new AHA/ACC schema represents a significant departure from the prior 3-tier (massive/submassive/low-risk) AHA 2011 classification and the 4-tier (high-risk/intermediate-high/intermediate-low/low-risk) 2019 ESC/ERS system (46,47).

The prior ESC system defined high-risk PE as SBP <90 mmHg, a drop >40 mmHg for >15 minutes, or need for vasopressors; intermediate-high risk required both RV dysfunction on imaging and elevated troponin; intermediate-low risk required only one of these; and low risk required neither (48).

The following figure illustrates the prior AHA and ESC classification systems side by side for comparison:

Guidelines	Category	Hemodynamic Status	PE Severity Index (PESI) (or Simplified PESI)	Evidence of RV Dysfunction
American Heart Association (AHA, 2011)	Massive	Unstable	High	Typically Abnormal RV on Imaging, Elevated Troponin, OR Both
	Submassive	Stable	High	May Have Abnormal RV on Imaging OR Elevated Troponin OR Both
	Low Risk	Stable	Typically Low	None
European Society of Cardiology (ESC, 2019)	High Risk	Unstable	High	Typically Abnormal RV on Imaging, Elevated Troponin, OR Both
	Intermediate-High Risk	Stable	High	Abnormal RV on Imaging, AND Elevated Troponin
	Intermediate-Low Risk	Stable	High	May Have Abnormal RV on Imaging OR Elevated Troponin But Not Both
	Low Risk	Stable	Low	None

Figure 4: Risk categories for patients presenting acute PE (49).

The 2026 guideline addresses several recognized limitations of these older systems: the heterogeneity within the "submassive" or "intermediate-risk" category, the lack of recognition of incidental PE, and the absence of a distinct category for patients in a pre-failure state who have not yet developed frank haemodynamic collapse (45,50) The new Category D specifically fills this gap, capturing patients with transient hypotension or impending respiratory failure who may benefit from escalated monitoring and consideration of advanced therapies before overt cardiopulmonary failure occurs.

Key innovations of this classification compared to prior systems (45)

- Recognizes asymptomatic/incidental PE as a distinct category (A).
- Introduces a pre-cardiopulmonary failure category (D) to capture patients at imminent risk of decompensation who were previously grouped with intermediate-risk PE.
- Adds a respiratory modifier (R) to identify patients with prominent respiratory compromise independent of haemodynamic status.
- Patients may transition between categories over time, emphasizing the dynamic nature of PE severity.
- Validated risk scores (PESI, sPESI, Hestia) are integrated to distinguish Category B from Category C (45).

Treatment implications by category

- Categories A and B: Anticoagulation; outpatient management is appropriate for most patients (45).
- Category C: Hospitalization with anticoagulation; close monitoring for clinical deterioration, particularly in C3 patients (45).
- Categories D and E: Hospitalization with consideration of advanced reperfusion therapies. PE response teams (PERTs) are recommended to improve timeliness of care.

Diagnosis

Signs and symptoms alert the clinician to suspect pulmonary embolism and to perform an assessment based on clinical probability (pre-test category); after this, a variety of diagnostic tests are available to help clarify the diagnosis.

The 2026 AHA/ACC/ACCP/ACEP/CHEST/SCAI/SHM/SIR/SVM/SVN Guideline recommends a stepwise diagnostic algorithm integrating clinical pretest probability assessment, D-dimer testing, and imaging to diagnose acute PE (45).

Patients with low and intermediate probability may undergo an initial diagnostic evaluation with the D-dimer test. If this is high, imaging is the next step.

Clinical presentation

Sometimes, it can be asymptomatic and that is the reason why PE can be an unknown event or discovered during diagnostic work-up for other disease.

Moreover, the signs and symptoms of pulmonary embolism are not specific and the lack of sensitivity of the clinical diagnosis depends on this, especially in those patients at intermediate risk (34).

The most common symptoms of PE are **pleuritic chest pain** and **dyspnea** (occurring in over 90% of patients with PE) (51); haemoptysis, syncope, and shock are less common (45). Syncope and arterial hypotension (shock), although rare symptoms, they are a indicator of an important **haemodynamic impairment** (52). Physical examination findings such as tachycardia, hypotension, tachypnea, hypoxemia, jugular venous distension, an accentuated P2, and leg swelling suggestive of DVT should be assessed (45).

Dyspnoea severity is related to the PE localization: severe and acute dyspnoea occurs in central PE, mild dyspnoea in peripheral PE.

In central PE, chest pain may have a typical angina character, possibly reflecting RV ischaemia and requiring differential diagnosis with acute coronary syndrome (ACS) or aortic dissection.

All these signs and symptoms, although important in raising clinical suspicion of PE, are neither specific nor sensitive and may not always be present; therefore, they cannot reliably confirm or exclude the presence of acute PE.

Assessment of clinical probability

Although common tests and individual signs and symptoms have limited diagnostic accuracy, in terms of sensitivity and specificity, their combined assessment allows patients with suspected PE to be stratified into different clinical or pre-test probability categories. Moreover, the post-test probability of PE depends not only on the diagnostic performance of the test employed, but also on the patient's pre-test probability.

Several clinical prediction rules have been developed for the assessment of suspected PE. Among these, the most widely used is the ***Wells score*** (Table 3) (53), which is simple and based on readily obtainable clinical information. However, the inclusion of the subjective criterion "alternative diagnosis less likely than PE" may reduce inter-observer reproducibility. A simplified version of the Wells score has also been developed and validated (54). Another validated clinical prediction model is the ***Geneva score*** (Table 4) (55), which relies exclusively on clinical variables; a simplified version of this score has likewise been proposed and validated (56).

The AHA/ACC 2026 Guideline for the Evaluation and Management of Acute Pulmonary Embolism also includes the ***PERC*** (*Pulmonary Embolism Rule-Out Criteria*): a further diagnostic scoring system among the recommended assessment tools; however, the first two scores are still the most widely adopted in clinical practice (45).

Both Wells and Geneva score take into consideration parameters such as: heart rate, surgical interventions or immobilization in the last month, signs and/or symptoms of peripheral venous thrombosis, possible presence of neoplasia, previous PE or DVT and haemoptysis. The probability of pulmonary embolism emerges from the sum of the scores assigned to each of these parameters.

It is possible to classify patients, regardless of the score used, in three clinical probability categories of PE in which the prevalence of PE increases with increasing clinical probability: in the low probability category the percentage of patients with PE is approximately 10%, 30% in the intermediate probability and 65% in the high probability one.

It is also possible a two-level classification, PE likely or PE unlikely, and in this case the proportion of patients diagnosed with PE in the "PE unlikely" category is about 12% (57).

Items	Clinical decision rule points	
Wells rule	**Original version**	**Simplified version**
Previous PE or DVT	1.5	1
Heart rate ≥ 100 b.p.m.	1.5	1
Surgery or immobilization	1.5	1
Haemoptysis	1	1
Active cancer	1	1
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Clinical probability		
Three-level score		
Low	0-1	N/A
Intermediate	2-6	N/A
High	≥ 7	N/A
Two-level score		
PE unlikely	0-4	0-1
PE likely	≥ 5	≥ 2
Revised Geneva score	**Original version**	**Simplified version**
Previous PE or DVT	3	1
Heart rate **75-94 b.p.m.** **≥ 95 b.p.m.**	3 5	1 2
Surgery or fracture within the past month	2	1
Haemoptysis	2	1
Active cancer	2	1
Unilateral lower limb pain	3	1
Pain on lower limb deep venous palpation and unilateral ooedema	4	1
Age > 65 years	1	1
Clinical probability		
Three-level score		
Low	0-3	0-1
Intermediate	4-10	2-4
High	≥ 11	≥ 5
Two-level score		
PE unlikely	0-5	0-2
PE likely	≥ 6	≥ 3

Table 3 and 4: Clinical prediction rules for PE *(8)*.

The following figure (Figure 5) illustrates the relationship between the Simplified Revised Geneva Score and PE prevalence across risk categories:

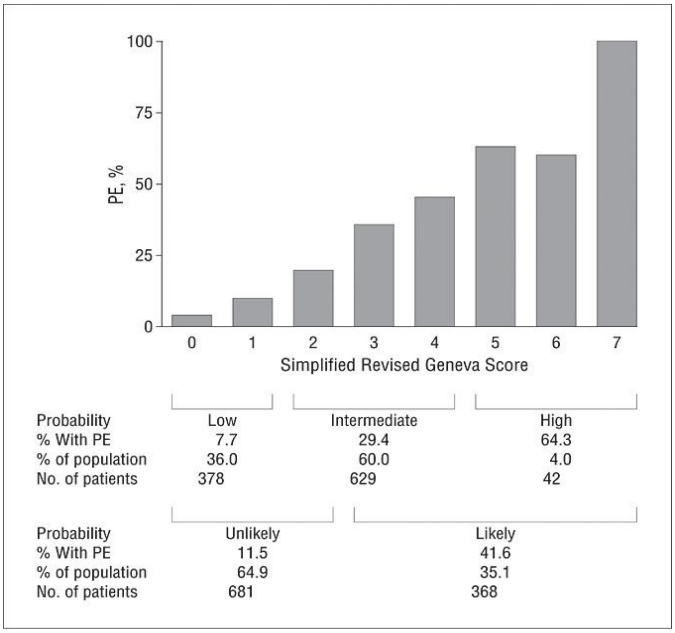

Figure 5: Prevalence of pulmonary embolism (PE) according to the Simplified Revised Geneva Score.

Wells score can be applied when symptoms have been present for **<30 days** and it has some limitations: it cannnot be used when there is suspicion of an upper limb DVT origin of embolus; when patient has received anticoagulants for more than 72 hours; when patient has been asymptomatic for 72 hours prior to presentation; and in case of pregnancy.

Importantly, clinical decision rules cannot safely exclude PE alone and must be used in conjunction with **D-dimer testing or imaging** (1). Recent studies suggested that the combined use of **lung and venous ultrasound** improves the diagnostic accuracy of the Wells score alone. This approach may reduce the need for computed tomography pulmonary angiography (CTPA), thereby representing a **safer and more cost-effective strategy** for patient management (58). A Wells score ≤ 4 indicates that pulmonary embolism is unlikely, although it does not completely exclude the diagnosis. In such cases, additional diagnostic information, including D-dimer testing, is required. However, elevated D-dimer levels are more frequently associated with false-positive rather than true-positive results.

Observation such as this led to the development and validation of the *Charlotte rule* and the previous cited PERC rule (59). This score is used in emergency department; is based on clinical criteria defining patients with a greater than 40% probability of PE, and categorizes them as either "*safe*" or "*unsafe*" for D-dimer testing.

When PE is considered unlikely, then it is possible to apply the PERC rule. In this case, PERC rule considers:

- Age (<50);
- Pulse rate (<100bpm);

- SaO2 (≥ 95%);
- No haemoptysis;
- No oestrogen use;
- No surgery/trauma requiring hospitalization within four weeks;
- No prior venous thromboembolism;
- No unilateral leg swelling (60).

When PERC score is >0, then a D-dimer measurement is recommended (using enzyme-linked immunosorbent assay, ELISA-type). The PERC rule may allow exclusion of PE without any further testing in patients with very low clinical probability in low-prevalence settings (3,61).

Ultimately, standard diagnostic strategies for PE follow a **three-step Bayesian approach** (4,45):

1. **Estimate clinical probability** using Wells or Revised Geneva score
2. **D-dimer testing** in patients with low or intermediate probability — a normal D-dimer (threshold 500 ng/mL, or age-adjusted: age × 10 ng/mL for patients >50 years) safely excludes PE with a 97–100% negative predictive value (4,45)
3. **Imaging,** if D-dimer is elevated or clinical probability is high. Patients with high pretest probability should proceed directly to imaging without D-dimer testing (4,45)**.**

Figure 6, below, summarizes this diagnostic algorithm:

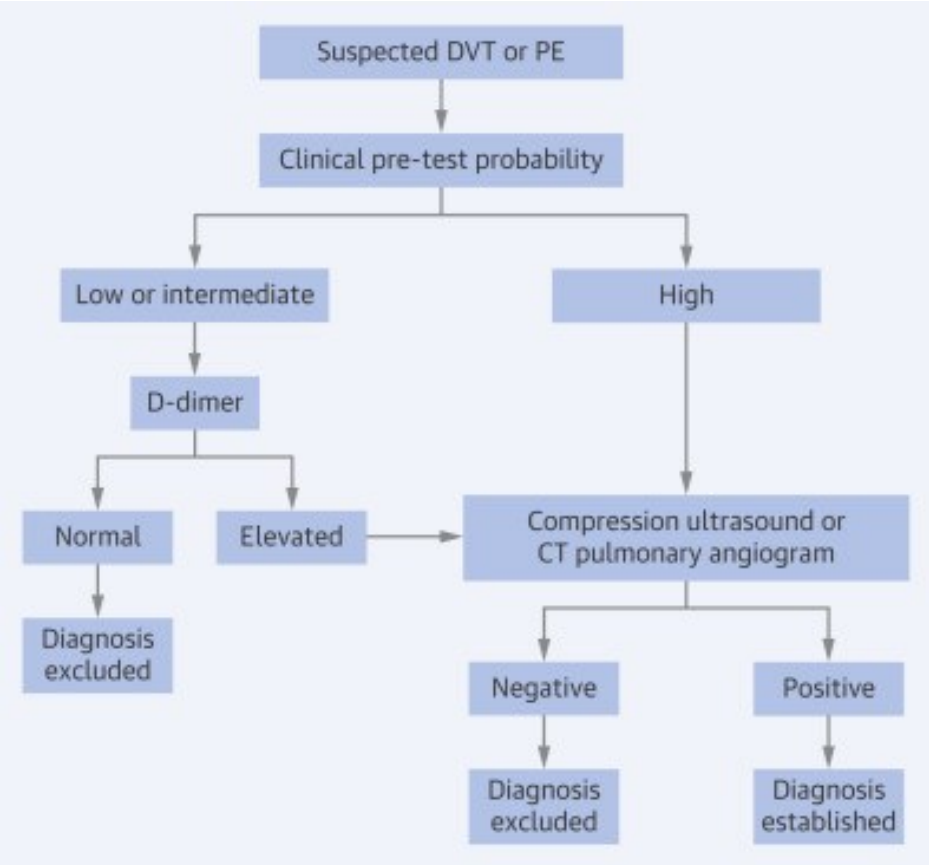

Figure 6: algorithm for Diagnosis of DVT or PE Using D-Dimer (62).

Blood gas analysis

Both hypoxaemia (a typical finding in acute PE, especially in patients with massive acute PE) and hypocapnia (due to hyperventilation) are often present. Nevertheless, more than 40% of patients have normal arterial oxygen saturation and 20% have normal alveolar-arterial oxygen gradient (62).

D-dimer testing

Plasma D-dimer is a degradation product of fibrin. In the presence of an acute thrombotic event, the plasma levels increase due to the concomitant activation of the coagulation and the consequent fibrinolysis (not enough to prevent the PE, but able to break some fibrin clots reducing them to D-dimers).

It is a protein that may be elevated in several conditions, including infections, inflammatory states, neoplastic diseases, necrosis, and aortic dissection. Consequently, its positive predictive value (PPV) is low, as **elevated blood levels are not specific for PE**; therefore, further diagnostic investigations are required to confirm the diagnosis.

Conversely, D-dimer has a **high negative predictive value** (NPV), making it particularly useful for excluding PE in patients with low or intermediate clinical probability. When the two-level clinical probability assessment model is applied, a negative D-dimer test safely excludes PE in patients classified as "PE unlikely."

In cases of suspected PE, the specificity of this test (the ability to correctly identify healthy subjects), decreases with advancing age, up to ≤10% in the over 80s (63). To improve the performance of the D-dimer measurement, age-adjusted cut-offs are used. The use of these cut-offs increases the number of patients in whom the PE can be excluded without further false-negative results (64).

Compression venous ultrasonography (CUS)

In approximately 90% of patients, PE originates from a deep vein thrombosis (DVT) of the lower limbs (65). The standard diagnostic method for DVT is compressive venous ultrasound (CUS), which identifies a non-compressible vein suggestive of the presence of a thrombus. Using this technique, DVT has been detected in 30–50% of patients with PE (66).

However, at least half of the patients with PE do not show signs of DVT, so a normal CUS does not rule out the presence of PE. Therefore, in case of high or moderate clinical suspicion of PE, patients without evidence of DVT should also undergo further evaluation.

Chest X-ray

The chest radiograph is abnormal in approximately 80–84% of patients with acute PE, but findings are neither sensitive nor specific for the diagnosis (67,68). The primary value of chest X-ray in suspected PE is to exclude alternative diagnoses (pneumonia, pneumothorax, heart failure) and to aid in V/Q scan interpretation (69–71).

The most commonly recognized clinical signs:

- **Westermark sign** — focal oligemia (decreased vascular markings) distal to an occluded pulmonary artery, suggesting massive central embolic occlusion (69,72,73).
- **Hampton hump** — a peripheral, pleural-based, wedge-shaped opacity (usually above the diaphragm) indicating pulmonary infarction; uncommon but relatively specific when present (69,71)..
- **Fleischner sign (Palla sign)** — prominent or enlarged central pulmonary artery, reflecting acute pulmonary hypertension or distension by thrombus (68,73). It has a low sensitivity but a high specificity and is usually seen in the acute setting.
- **"Sausage-like" descending pulmonary artery** — an enlarged descending pulmonary artery that tapers rapidly after the enlarged portion (69,73,74).

The following figure (Figure 7) demonstrates both Hampton hump (wedge-shaped opacity at the left lung base) and Westermark sign (increased lucency with decreased vascular markings in the right upper lung field) in a patient with confirmed PE.

Atelectasis and/or parenchymal opacities are the most common radiographic abnormalities in PE, found in up to 68% of patients without pre-existing cardiopulmonary disease, but these findings occur at similar rates in patients without PE (68,75). **Cardiomegaly** on chest X-ray has only 48% sensitivity and 63% specificity for echocardiographic right ventricular hypokinesis, and **pulmonary artery enlargement** has 38% sensitivity and 76% specificity for the same finding (67).

A normal chest radiograph does not allow exclusion of PE — approximately 12–24% of patients with confirmed PE, has normal films (68,76).

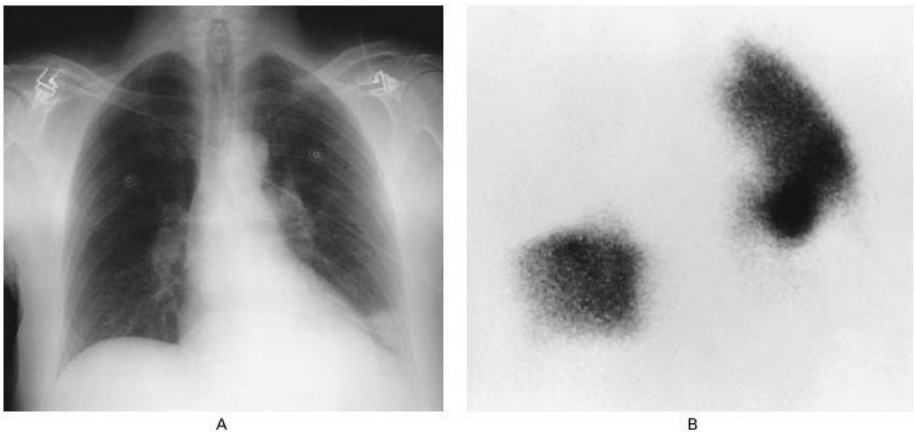

Figure 7: Hampton hump and Westermark sign in a patient with confirmed PE (77).

Electrocardiography

The ECG in acute PE is **insensitive for diagnosis**, but valuable for raising clinical suspicion and, more importantly, for **risk stratification and prognostication**. Notably, 20–25% of patients with PE (including those with large clot burden) have entirely normal ECGs (78).

The most frequent abnormalities, which can be investigated by an ECG, are (79):

- Tachycardia;
- Atrial arrhythmias, due to right atrium dilatation (fibrillation, flutter, atrial tachycardia);
- Low voltage;
- Q waves in leads III and aVF;
- Pulmonary P waves (due to acute right atrium dilatation);
- Right-axis deviation;
- Non-specific ST segment and T wave changes (including ST elevation and depression);
- QT prolongation;
- Inversion of the T waves in V1-V4 and in the inferior leads (II, III, aVF), this pattern is due to the dilatation of the right ventricle, which is caused by high pulmonary pressures;
- QR pattern in V1;
- S1Q3T3 pattern: deep S wave in lead I, Q wave in lead III, inverted T wave in lead III;
- Incomplete or complete right bundle-branch block (RBBB).

These alterations are correlated with a worse short-term prognosis in acute PE.

Lung scintigraphy

Ventilation-perfusion scintigraphy (V/Q scan) is an established diagnostic test for suspected PE. The technique involves the intravenous administration of technetium-labelled albumin particles, allowing the assessment of pulmonary perfusion. In the presence of an occlusion within a branch of the pulmonary artery, these particles are unable to reach the peripheral capillary bed, resulting in the visualization of a non-perfused area on imaging. Perfusion imaging is combined with ventilation imaging, obtained using various radiolabelled inhaled gases, such as xenon or

krypton. Ventilation imaging increases diagnostic specificity by identifying hypoventilated regions associated with non-embolic perfusion defects secondary to reactive vasoconstriction. In contrast, in patients with PE, ventilation remains preserved within hypoperfused areas, producing the characteristic ventilation-perfusion "mismatch." (80).

The results of lung scintigraphy are generally divided into three categories: normal findings, which effectively exclude PE; high-probability findings, which are considered diagnostic in most cases; and non-diagnostic results (81). A high-probability ventilation-perfusion scan provides strong evidence supporting the diagnosis of PE. Nevertheless, in patients with a low clinical probability of PE, additional diagnostic investigations may still be required, as the PPV of a high-probability V/Q scan is lower in this subgroup.

Recent studies suggest the use of tomographic mode in single photon emission computed tomography (SPECT) imaging. Combined with or without low-dose CT may reduce the frequency of non-diagnostic scans (82).

Computed tomographic pulmonary angiography

With the advent of multi-detector computed tomographic (MDCT) angiography, characterized by improved spatial and temporal resolution together with better arterial opacification, computed tomographic pulmonary angiography (CTPA) has become the imaging modality of choice for evaluating the pulmonary vasculature in patients with suspected PE.

A negative CT scan has a negative predictive value (NPV) of approximately 90% in patients with a low or intermediate clinical probability of PE according to the Wells criteria; whereas the NPV decreases to about 60% in patients with a high clinical probability. Conversely, a positive CT scan shows a PPV greater than 90% in patients with intermediate or high clinical probability, but only around 58% in those with a low probability of PE. Therefore, a negative MDCT finding is considered sufficient to exclude PE in patients with low clinical probability.

In patients with a high clinical suspicion of PE, a negative CT result may not be sufficient to safely exclude the diagnosis, and additional investigations, such as ventilation-perfusion scintigraphy or pulmonary angiography, should be considered. On the other hand, the identification of embolic defects on MDCT involving segmental or more proximal pulmonary arterial branches is considered strong evidence of PE in patients with an intermediate or high clinical probability.

CT imaging can also identify the presence of concomitant pulmonary or cardiac diseases and may help explain clinical conditions that mimic PE, including pneumonia, atelectasis, pneumothorax, aortic disorders, and pleural or pericardial effusions. In addition, CT provides detailed visualization of the cardiac chambers, which is particularly useful for risk stratification. In fact, patients with PE associated with right ventricular dilatation have a short-term mortality rate approximately five times higher than those with normal right ventricular dimensions.

The diagnostic criteria for acute pulmonary embolism include the following (83):

- Arterial occlusion with failure to enhance the entire lumen, due to a large filling defect; the artery may be enlarged compared with adjacent patent vessels;
- A partial filling defect surrounded by contrast material, producing the "*polo mint*" sign on images acquired perpendicular to the long axis of a vessel and the "*railway track*" sign on longitudinal images of the vessel;
- A peripheral intraluminal filling defect that forms acute angles with the arterial wall;
- Other signs, such as peripheral wedge-shaped areas of hyperattenuation (which may represent pulmonary infarcts) and the presence of linear bands. These findings are not specific for acute PE, therefore, to confirm the diagnosis, a ventilation-perfusion scintigraphy or a conventional pulmonary angiography may be performed.

Pulmonary angiography

Pulmonary angiography is an invasive diagnostic technique that enables visualization of small thrombi, measuring approximately 1–2 mm, within the subsegmental branches of the pulmonary arteries. The diagnosis of PE is established by identifying an intraluminal filling defect visible in at least two different projections. For many years, pulmonary angiography was considered the "gold standard" for confirming or excluding PE; however, its use has markedly declined because computed tomographic angiography provides comparable diagnostic accuracy with a much less invasive approach (84).

Currently, pulmonary angiography may still be useful in cases where non-invasive imaging findings are inconclusive or when catheter-directed treatment of acute PE is planned. Whenever angiography is performed, haemodynamic measurements should also be obtained in order to evaluate the severity of the embolic event.

Echocardiography

Echocardiographic findings suggestive of PE can be classified into **direct** and **indirect criteria**. Direct signs include the visualization of thromboemboli within the main pulmonary artery branches (although this finding is uncommon), or within the right atrium. Indirect criteria are mainly related to the increase in pulmonary arterial pressure. The resulting pressure overload leads to right ventricular dilatation, which is assessed in comparison with the size of the left ventricle. In particular, an end-diastolic right-to-left ventricular diameter ratio greater than 0.7 is considered significant.

A characteristic echocardiographic finding in pulmonary embolism is ***McConnell's sign***, which refers to a regional pattern of right ventricular dysfunction characterized by akinesia of the mid free wall with preserved or hypercontractile apical motion. In addition to this specific sign, right ventricular function can also be evaluated by measuring tricuspid annular plane systolic excursion (TAPSE).

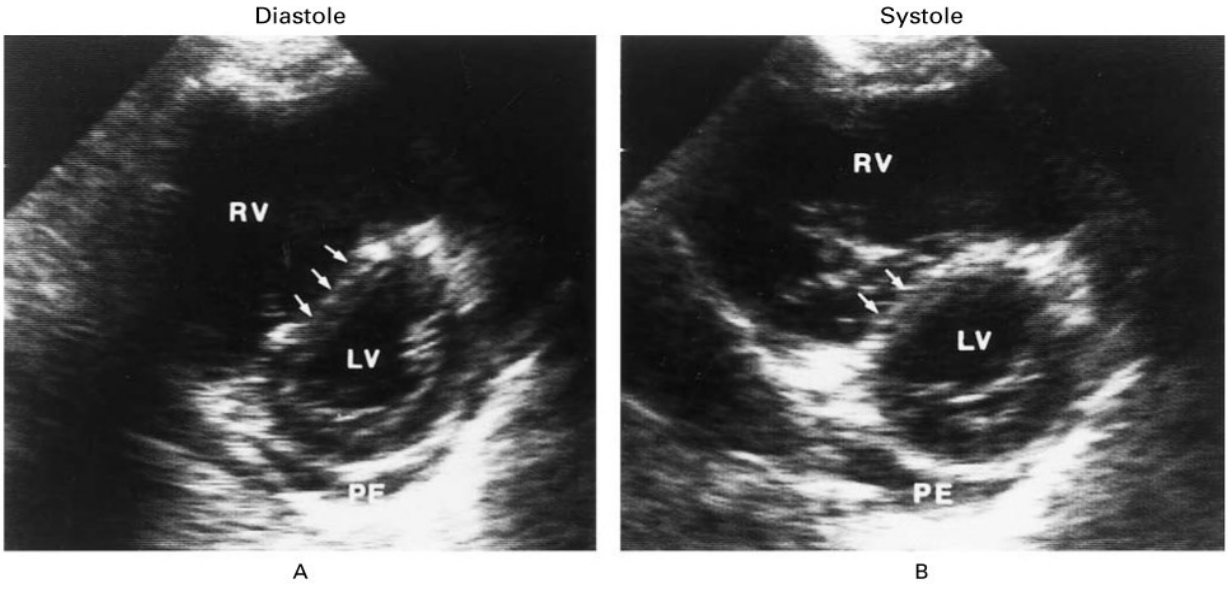

Figure 8: *Typical Findings of Transthoracic Echocardiography in Patients with Massive PE (71).*

Echocardiography is a low specificity test because signs of overload or dysfunction of the right ventricle may also be due to concomitant cardiac or respiratory disease in the absence of acute PE (85). Moreover, considering the low NPV, a negative test does not allow to exclude a PE (86).

In patients with suspected high-risk PE presenting with shock or hypotension, the absence of echocardiographic signs of right ventricular overload or dysfunction makes PE an unlikely cause of haemodynamic instability. Moreover, echocardiography plays an important role in the differential diagnosis of shock, as it can help identify alternative conditions such as cardiac tamponade, acute

valvular insufficiency, acute myocardial infarction, aortic dissection, and hypovolaemia. Conversely, in haemodynamically compromised patients with suspected PE, the presence of right ventricular pressure overload or dysfunction is highly suggestive of the diagnosis.

In low-risk PE, the primary role of echocardiography is to support prognostic stratification by identifying possible right ventricular dilatation and dysfunction. However, these isolated echocardiographic findings have limited PPV, which explains the need to integrate more advanced cardiac imaging techniques together with **laboratory biomarkers** such as **pro-BNP, troponin I, and troponin T** in order to achieve a more accurate risk assessment.

Diagnostic strategies

There are different diagnostic algorithms based on a suspected high-risk PE, with shock or hypotension (Figure 9), or a not high-risk PE, without shock or hypotension (Figure 10).

A suspected high-risk PE should be considered in the differential diagnosis alongside conditions such as acute valvular insufficiency, cardiogenic shock, aortic dissection, and pericardial tamponade. In this clinical setting, the most useful initial investigation is bedside transthoracic echocardiography, which may demonstrate signs of acute pulmonary hypertension and right ventricular dysfunction if PE is responsible for the haemodynamic instability. In patients who are severely unstable, echocardiographic evidence of right ventricular dysfunction alone is sufficient to justify immediate reperfusion therapy without the need for further diagnostic testing.

Once the patient has been stabilised with supportive therapy, definitive confirmation of the diagnosis should be pursued. In this context, computed tomography (CT) should be the preferred imaging modality, while conventional pulmonary angiography should generally be avoided due to the increased mortality risk in haemodynamically unstable patients (87) and the higher likelihood of bleeding complications, particularly if subsequent thrombolytic therapy is required (88).

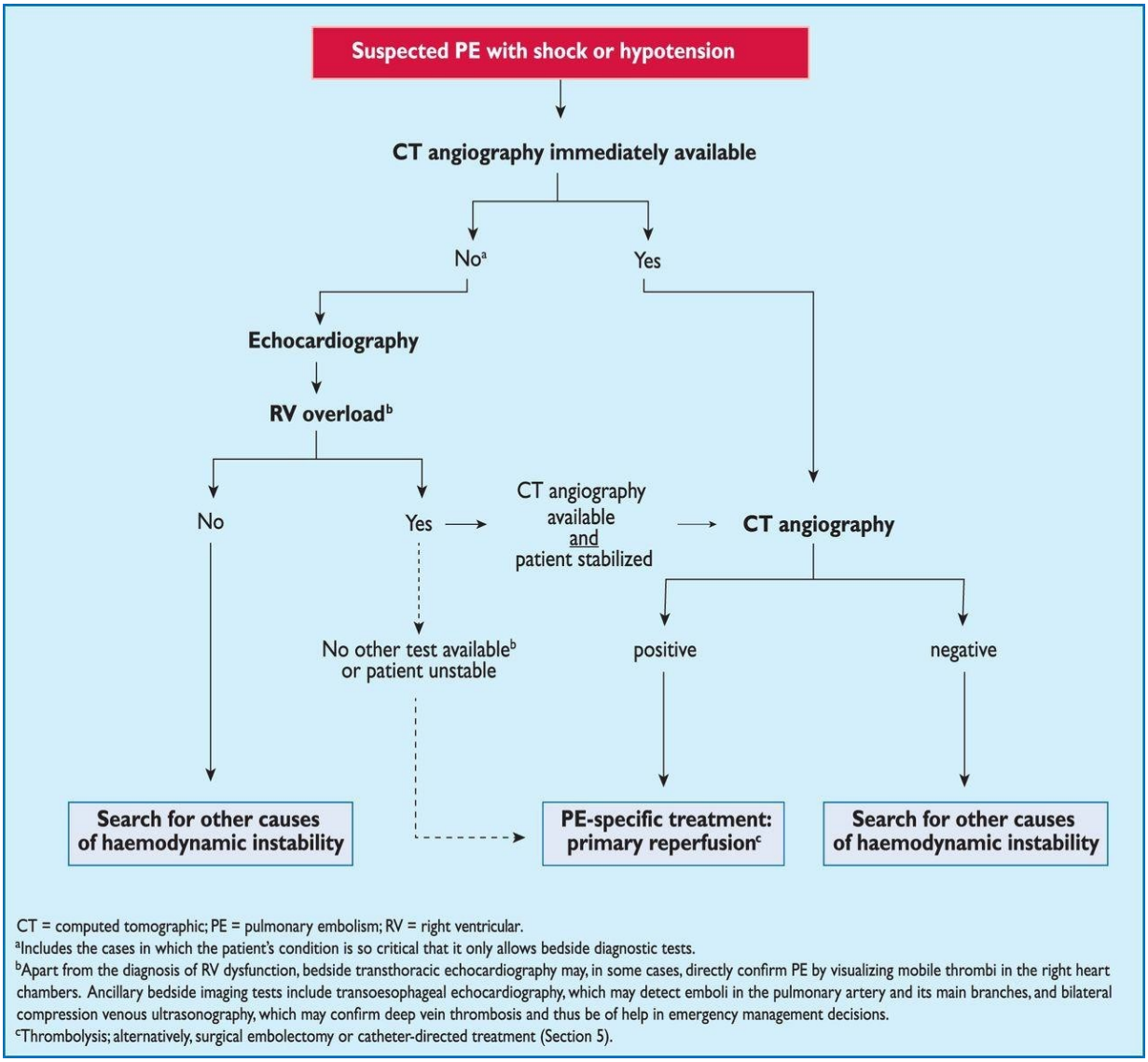

Figure 9: *Diagnostic Algorithm for patients with suspected high-risk pulmonary embolism (8).*

Conversely, in suspected low-risk PE, the recommended initial strategy combines clinical probability assessment with plasma D-dimer testing. D-dimer measurement is not reliable in patients with high clinical probability because of its low negative predictive value in this setting (89). Since CT angiography has become the main imaging modality for suspected PE, it is generally considered a second-line test in patients with elevated D-dimer and a first-line examination in those with high clinical probability. CT pulmonary angiography has largely replaced ventilation-perfusion scintigraphy, which is now performed less frequently, partly due to the relatively high rate of non-diagnostic results (90). Nevertheless, scintigraphy remains a useful alternative in patients with elevated D-dimer who have contraindications to CT, such as renal impairment or iodinated contrast allergy.

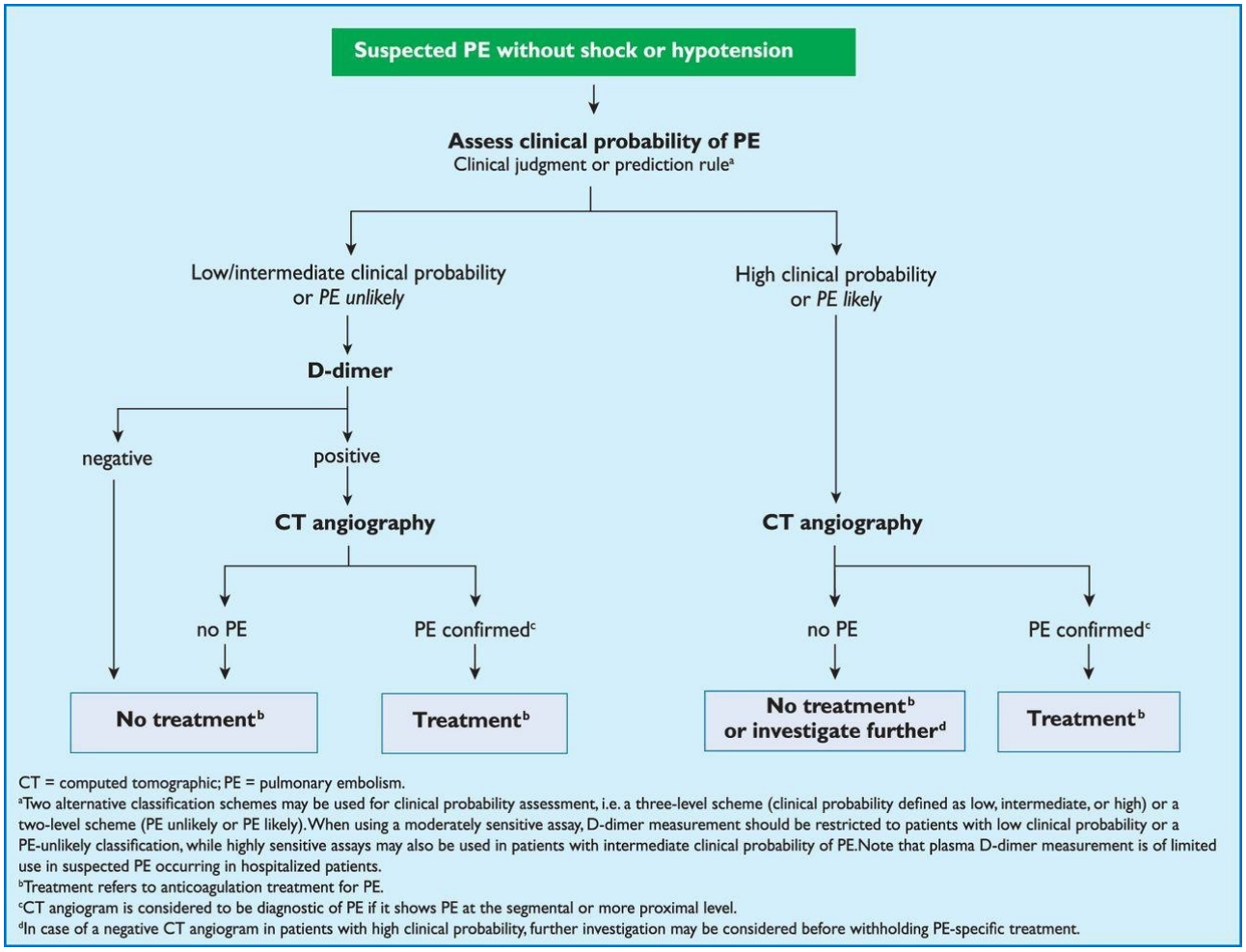

Figure 10: diagnostic algorithm for patients with suspected not high-risk pulmonary embolism (8).

Prognostic assessment

The prognosis depends on the degree of obstruction and haemodynamic effects of PE.

Approximately 80% of patients with PE present with normal systemic arterial pressure at diagnosis, and among these normotensive patients, echocardiographic signs of RV dysfunction are found in about 27% to 55% of cases. This finding has a relevant impact on prognosis. In fact, normotensive patients with RV impairment show an average short-term PE-related mortality of around 9.3%, whereas those with preserved RV function have a markedly lower mortality rate of approximately 0.4%. The presence of RV dysfunction therefore identifies a subgroup of normotensive patients at significantly increased risk of both recurrent PE and death. From a prognostic standpoint, these patients can be considered within a continuum ranging from individuals with normal blood pressure and normal RV function to those presenting with hypotension, shock, or even cardiac arrest (91).

At discharge, a comprehensive prognostic stratification is essential; with consideration of the extent of the embolic burden, the presence or persistence of DVT, any haemodynamic compromise and/or right ventricular dilatation, as well as possible underlying thrombophilia or associated comorbid conditions. These factors help guide and individualise the therapeutic strategy, including the duration of treatment, with the aim of preventing recurrence, minimising bleeding risk, and ensuring early detection of progression towards pulmonary hypertension.

The most widely validated clinical score for prognostic assessment in patients with PE is the Pulmonary Embolism Severity Index (PESI), which is used to stratify patients according to their risk of early mortality (92). Due to the complexity of the original model, a simplified version, known as the sPESI, has also been developed and validated (93).

Both scores incorporate variables that are directly related to the embolic event, such as heart rate, systolic blood pressure, respiratory rate, and oxygen saturation, as well as parameters reflecting the patient's baseline clinical status, including age, sex, and comorbidities.

Parameter	Original version (PESI)	Simplified version (sPESI)
Age	Age in years	1 point (if age>80 years)
Male sex	+10 points	-
Cancer	+30 points	1 point
Chronic heart failure	+10 points	1 point
Chronic pulmonary disease	+10 points	
Pulse rate ≥110 b.p.m.	+20 points	1 point
Systolic blood pressure <100 mmHg	+30 points	1 point
Respiratory rate>30 breaths per minute	+20 points	-
Temperature <36°C	+20 points	-
Altered mental status	+60 points	-
Arterial oxyhaemoglobin saturation <90%	+20 points	1 point
	Risk stratification	
	Class I: ≤65 points Very low 30-day mortality risk (0-1.6%)	**0 point**: 30-day mortality risk 1.0% (95%CI 0.0%-2.1%)
	Class II: 66-85 points Low mortality risk (1.7-3.5%)	
	Class III: 86-105 points Moderate mortality risk (3.2-7.1%)	**≥1 point**: 30-day mortality risk 10.9% (95% CI 8.5%-13.2%)
	Class IV: 106-125 points High mortality risk (4.0-11.4%)	
	Class V: >125 points Very high mortality risk (10.0-24.5%)	

Table 4: Original and simplified PESI (8)

Prognostic registers

The main prospective registers that take into account the prognostic factors of patients with PE, and, more generally, with VTE are: the ICOPER (International Cooperative Pulmonary Embolism Registry) (94) and the IPER (Italian Pulmonary Embolism Registry) (95), which included patients exclusively with PE; the RIETE (Registro Informatizado de Enfermedad TromboEmbólica) (96) and the MASTER (Multicenter Advanced Study for a Thromboembolism Registry) (97) who considered patients with DVT, PE or both.

International Cooperative Pulmonary Embolism Registry (ICOPER)

The primary aim of the registry was to **evaluate all-cause mortality at 3 months** in patients diagnosed with PE, whether symptomatic or asymptomatic, provided that the diagnosis was established within 31 days from symptom onset.

The overall mortality was 17.5% attributable to the following causes:

- 45.1% PE;
- 17.6% cancer;
- 11.8% sudden death;
- 11.8% respiratory failure;
- 2.5% hemorrhage;
- 2.5% stroke;
- 1.3% acute coronary syndrome;
- 7.3% other causes.

The proportion of PE recurrences at 3 months was 7.9%.

It was demonstrated that several factors were significantly associated with an increased risk of mortality. In particular, these included: age over 70 years, the presence of malignancy, concomitant COPD, heart failure, systolic blood pressure below 90 mmHg, respiratory rate greater than 20 breaths per minute, and right ventricular hypokinesis detected on echocardiography. Notably, the presence of right ventricular hypokinesis was associated with a twofold increase in 3-month mortality risk.

Italian Pulmonary Embolism Registry (IPER)

The registry included patients with PE of different degrees of severity, with the aim of describing the clinical characteristics and outcomes of these patients during both hospitalization and follow-up; as well as the diagnostic strategies, prognostic stratification, and therapeutic approaches adopted. Among the patients enrolled in the study, 6.8% died during the in-hospital phase. Of those who survived hospitalization, an additional 12.8% died within 12 months after discharge. The factors significantly associated with increased mortality included older age, with risk progressively increasing by decade, the presence of cancer either previously known or diagnosed during hospitalization, and underweight status (defined as a BMI lower than 20 kg/m^2).

When comparing provoked and unprovoked PE, mortality rates were reported to be 16.1% and 3%, respectively. In addition, deaths related to malignancy accounted for 53.2% of cases in the provoked PE group, whereas no cancer-related deaths were observed among patients with unprovoked PE. Conversely, deaths due to atherosclerotic events were more frequent in patients with idiopathic PE, accounting for 60% of cases, compared with 6.3% in those with provoked PE.

Overall, the study showed that short-term mortality is mainly associated with the degree of **haemodynamic instability** at presentation, whereas long-term prognosis appears to be less dependent on the severity of the acute event itself and more closely related to the underlying condition responsible for the embolism. In particular, patients with a known malignancy or a neoplasm diagnosed during hospitalization had the most unfavourable outcomes.

Registro Informatizado de Enfermedad TromboEmbólica (RIETE)

This registry includes patients with VTE, including both DVT and/or PE cases. Its main objective is to collect and analyse data regarding the management of these patients in order to **optimize treatment strategies**. In addition, follow-up (FU) data are evaluated to identify prognostic indicators and improve long-term patient outcomes.

The registry enrols patients with symptomatic VTE confirmed through objective diagnostic tests, including venography and venous Doppler ultrasound for DVT, as well as pulmonary angiography, lung scintigraphy, or CT pulmonary angiography for PE. A minimum FU period of three months was required, although no upper limit was established for the duration of subsequent FU.

The study showed that patients presenting with at least one exclusion criterion for antithrombotic therapy had higher rates of both fatal PE and major bleeding compared with patients without such criteria. Moreover, the risk of fatal bleeding was found to increase with advancing age.

Among the enrolled patients, approximately 20% had active cancer. In this subgroup, the risk of fatal PE and fatal haemorrhage during the first three months was significantly higher than in patients without malignancy, with rates of 2.6% and 1%, respectively, compared with 1.4% and 0.3% in non-cancer patients.

Renal failure, metastatic disease, recent major bleeding, and recent immobilization were identified as independent risk factors associated with an increased incidence of both fatal PE and fatal haemorrhage. In contrast, obese patients did not show a higher rate of recurrent embolic events, while they appeared to have significantly lower mortality compared with patients of normal weight.

Multicenter Advanced Study for a Thromboembolism Registry (MASTER)

The study included patients with confirmed VTE who were followed for 24 months in order to **evaluate the clinical course** of the disease over time. Nearly all patients received anticoagulant therapy for at least six months. During the FU period, the overall mortality rate was 4.55%.

The independent prognostic factors, significantly associated with mortality, included: malignancy (hazard ratio [HR] 7.2), prolonged heparin therapy (HR 2.5), in-hospital treatment of VTE (HR 2.0, likely reflecting the poorer clinical status of hospitalized patients compared with those managed as outpatients), and iliocaval thrombosis (HR 1.7). Conversely, the use of elastic compression stockings was associated with reduced mortality (HR 0.6). No significant differences in mortality were observed between patients presenting with PE and those with DVT.

Regarding recurrence, 3.63% of patients experienced at least one recurrent VTE event. The initial clinical presentation was the strongest predictor of the type of recurrence; specifically, patients initially presenting with PE were more likely to develop recurrent PE rather than DVT. Male sex and the presence of cancer were identified as major risk factors for recurrence, whereas transient risk factors were associated with a lower incidence of recurrent VTE. Mortality was substantially higher among patients with recurrent VTE, reaching 16.5%, compared with 4.2% in patients without recurrence.

Main prognostic indicators

Biomarkers

Measurement of plasma D-dimer is useful for distinguishing patients at low risk of recurrence, defined as less than 5% per year, in whom anticoagulant therapy may be safely discontinued,

from those at higher risk who may benefit from prolonged anticoagulation. An elevated D-dimer level one month after discontinuation of anticoagulant treatment is associated with a significantly increased risk of recurrence (98). In addition, D-dimer values below 1500 ng/mL have been shown to provide a 99% negative predictive value for excluding all-cause mortality at three months (99). Serial D-dimer assessment during the first three months after withdrawal of anticoagulant therapy can further identify patients at low risk of relapse. In this subgroup, the incidence of recurrent events after treatment discontinuation is approximately 3% per patient per year (100).

Right ventricular dysfunction leads to increased myocardial wall stress and stretching of cardiac fibers, resulting in the release of brain natriuretic peptide (BNP). In patients with acute PE, plasma levels of BNP and the N-terminal fragment of proBNP (NT-proBNP) correlate with the severity of right ventricular dysfunction and haemodynamic impairment (101). An NT-proBNP plasma concentration above 600 pg/mL is considered the threshold for identifying patients at higher risk (102). Although elevated BNP and NT-proBNP levels are associated with a poorer prognosis, their PPV remains limited. Conversely, low concentrations of these biomarkers have a high NPV and are therefore considered reliable indicators of a favourable prognosis (103).

Elevated levels of troponin have been associated with a poorer prognosis in patients with PE, including an increased risk of mortality even among haemodynamically stable individuals (104); whilst the combined assessment of troponin and NT-proBNP provides a more precise prognostic stratification in patients with normotensive PE. Patients presenting with elevated levels of both biomarkers showed a PE-related mortality exceeding 30% at 40 days. In contrast, patients with isolated elevation of NT-proBNP had an intermediate mortality risk of approximately 4%, whereas low levels of both biomarkers were associated with a favourable short-term prognosis (105).

The combination of elevated troponin with echocardiographic RV dysfunction identifies a subgroup at particularly high risk for adverse outcomes among haemodynamically stable patients (106).

Electrocardiogram

Electrocardiographic findings suggestive of acute RV overload, including T-wave inversion in leads V1–V4, a QR pattern in V1, the classic S1Q3T3 pattern, and complete or incomplete right bundle branch block, may support the diagnosis of PE; however, these signs have limited sensitivity (107).

Clinical parameters

Shock and hypotension carry major prognostic significance in acute PE and are considered the principal indicators of high early mortality risk. A post hoc analysis of the ICOPER study demonstrated that patients with systolic blood pressure below 90 mmHg had a 90-day all-cause mortality rate of 52.4%, compared with 14.7% among normotensive patients (108).

Additional clinical factors associated with an increased risk of fatal PE include immobilization due to neurological disease, age greater than 75 years, and the presence of cancer (109). Furthermore, the coexistence of DVT has been identified as an independent predictor of mortality within the first three months following diagnosis (110).

Echocardiography

The 2026 AHA/ACC Guideline recommends echocardiography for risk stratification of patients with acute symptomatic PE and an elevated clinical severity score (AHA/ACC PE Categories C–D), as RV dysfunction on echocardiography is a strong independent predictor of adverse outcomes (45).

It is recommended that all patients diagnosed with non-high-risk PE undergo echocardiographic evaluation. This assessment is useful for accurate prognostic stratification, allowing distinction between low-risk patients without evidence of cardiac dysfunction and intermediate-risk patients in whom RV dysfunction is present.

Patients with echocardiographic abnormalities at discharge should be monitored remotely. Instead, it is superfluous to monitor with echocardiography patients who have right heart cavities and pulmonary pressure normal to discharge.

In the large multicenter RIETE registry (15,375 patients), RV hypokinesis was associated with a 4-fold increased odds of PE-related mortality (OR 3.11; 95% CI, 1.85–5.21) (45).

The timing of FU evaluation depends mainly on the patient's symptoms at discharge. When echocardiographic abnormalities are associated with dyspnoea during mild or moderate exertion, both clinical and echocardiographic reassessment should be performed within three months after discharge. In asymptomatic patients, follow-up may instead be scheduled between three and six months. Subsequent evaluations and any additional investigations should then be planned according to the patient's symptoms and the severity of pulmonary hypertension.

Right heart catheterization is currently considered the only universally accepted method for accurately measuring pulmonary arterial pressure. Nevertheless, this procedure is performed in a limited number of patients, while echocardiography remains the most widely used tool for an initial, although less precise, estimation of pulmonary artery pressures because of its non-invasive nature. In patients presenting with symptomatic dyspnoea, extensive perfusion defects on pulmonary scintigraphy, and an RV–RA gradient greater than 32 mmHg on echocardiography, right heart catheterization should always be considered. The aim is to obtain an accurate assessment of pulmonary arterial pressure and vascular resistance, particularly when evaluating the patient for possible pulmonary endarterectomy (PEA).

Computed tomographic angiography

CT angiography allows to evaluate the relationship between the diameters of the right and left ventricle (as an indicator of the right ventricular dysfunction) and the severity of the pulmonary artery obstruction. The RV/LV diameter ratio on CTPA is the single most robust and well-validated CT prognostic parameter in acute PE, while thrombus burden (obstruction index) has surprisingly limited prognostic value according to the 2026 AHA/ACC guidelines (45,111). CTPA provides prognostic information through assessment of RV dysfunction, vascular obstruction, and ancillary signs of right heart strain.

An increased end-diastolic RV/LV diameter ratio, using a threshold value of 1.0, as well as a degree of vascular obstruction greater than 40%, are considered unfavourable prognostic indicators. Conversely, an RV/LV diameter ratio ≤1.0 is generally associated with an uncomplicated clinical course. On the other hand, no significant prognostic value has been demonstrated for either the pulmonary artery-to-ascending aorta diameter ratio or the morphology of the interventricular septum assessed by CT imaging (112).

CTPA-derived RV dysfunction is incorporated into the Category C subcategories (C1–C3) alongside biomarker elevation to guide management decisions (45). Importantly, anatomic

characterization of thrombus burden, while not useful for risk stratification, can be helpful in assessing the feasibility and safety of catheter-directed or surgical therapies in patients selected for advanced treatment (45).

The following figure illustrates the measurement technique for the RV/LV diameter ratio on axial CTPA, showing RV dilation with interventricular septal bowing to the left:

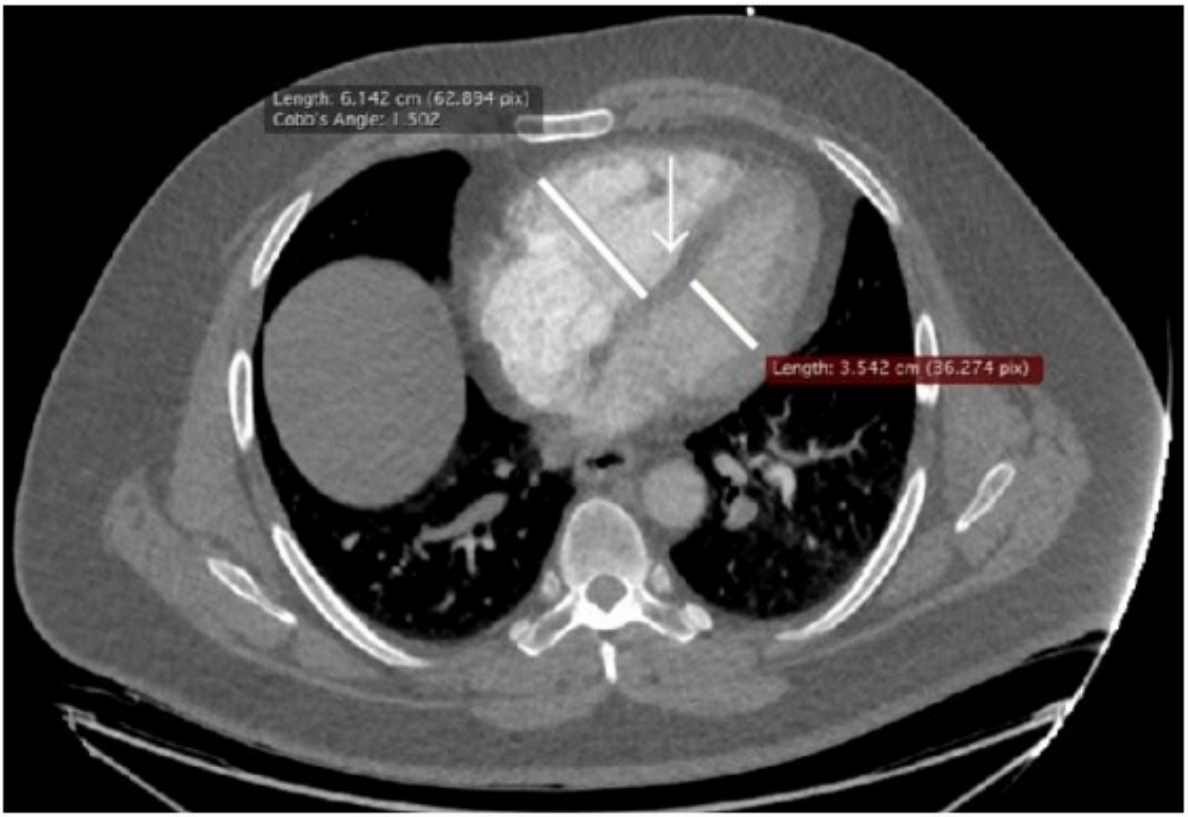

Figure 11: CT of a 75-year-old man with RV dysfunction showing increased right-to-left diameter ratio (113).

Lung Scintigraphy

This method allows assessment of pulmonary perfusion. In patients with intermediate- or high-risk PE, ventilation–perfusion (V/Q) scintigraphy also has relevant prognostic value. In particular, a residual vascular obstruction of ≥35% of the pulmonary vascular bed is considered a strong predictor of clinical events at 6 months, including death, recurrent PE, and heart failure in patients with intermediate to high risk. This prognostic impact is further reinforced by clinical factors such as active cancer, renal failure, or persistent echocardiographic signs of right ventricular dysfunction (114).

Lung scintigraphy is recommended approximately three months after the acute event in patients who present persistent symptoms or in whom right ventricular dysfunction or signs of pulmonary hypertension are still detected. Discontinuation of anticoagulant therapy may be considered if the scintigraphic examination shows complete normalization of pulmonary perfusion and no other indications for continued treatment are present. However, anticoagulation should be maintained in specific situations, such as idiopathic PE, active cancer, or thrombophilia.

Right Heart Catheterization

Right heart catheterization enables direct measurement of right ventricular filling pressures and cardiac output. However, at present, its routine use is not recommended for risk stratification in patients with acute PE.

In patients who develop clinical signs of pulmonary hypertension during FU and in whom CTEPH is suspected based on non-invasive investigations such as echocardiography, ventilation–perfusion scintigraphy, or CT angiography, further evaluation with right heart catheterization combined with selective pulmonary digital subtraction angiography is recommended (115). This combined approach provides essential prognostic information and is considered the gold standard both for confirming the diagnosis of CTEPH and for assessing surgical operability (116).

Prognostic assessment strategy

The 2026 AHA/ACC Guideline recommends a stepwise, integrated approach to prognostic assessment in acute PE, combining clinical risk scores, cardiac biomarkers, and right ventricular (RV) imaging (45).

At the time of clinical suspicion of PE, patients presenting with shock or hypotension must be promptly recognized as high-risk cases: these patients require an emergency diagnostic approach (as shown in figure 9) and, once PE has been confirmed, immediate reperfusion treatment should be initiated, preferably pharmacological, or alternatively surgical or catheter-based intervention.
In patients with acute symptomatic PE, a validated PE-specific risk score (PESI, sPESI, or Hestia) should be applied to identify those at low risk for short-term adverse outcomes (all-cause mortality, PE-related mortality, recurrent VTE, major bleeding. In haemodynamically stable patients, PESI

and sPESI can also identify patients at higher risk for adverse outcomes, though no score has consistently strong predictive ability for identifying which individual patients will deteriorate. Any validated PE-specific score may be chosen, as none demonstrates substantially superior performance (45).

Patients may transition among categories with reassessment: the first 24–72 hours represent a critical window for haemodynamic collapse (45).

The PESI/sPESI directly maps to the AHA/ACC PE Clinical Categories: PESI ≤85 (or sPESI = 1) corresponds to Category B (low risk), while PESI >85 (or sPESI ≥1) corresponds to Category C (elevated risk), which then triggers further subtratification with biomarkers and RV imaging (45). Patients who display evidence of both RV dysfunction (by echocardiography or CT-angiography) and elevated cardiac biomarker levels in the circulation (particularly a positive cardiac troponin test) should be classified into an intermediate-high-risk category. On the other hand, patients in whom the RV is normal on echocardiography or CT angiography and/or cardiac biomarker levels are also normal, belong to an intermediate-low-risk group.

Early mortality risk		Risk parameters and scores			
		Shock or hypotension	PESI class III–V or sPESI ≥1	Signs of RV dysfunction on an imaging test	Cardiac laboratory biomarkers
High		+	(+)	+	(+)
Intermediate	Intermediate–high	–	+	Both positive	
	Intermediate–low	–	+	Either one (or none) positive	
Low		–	–	Assessment optional; if assessed, both negative	

Table 5: Classification of patients with acute PE based on early mortality risk (8).

Therapy

The stratification of the risk in patients with PE allows identifying the best clinical intervention.

First, haemodynamic and respiratory support is recommended in all patients, regardless risk stratification when needed.

The 2026 AHA/ACC Guideline recommends a stepwise approach to PE therapy, with anticoagulation as the cornerstone for all patients and advanced therapies reserved for higher-risk categories (C3 through E) (45). Intravenous anticoagulant with unfractionated heparin (UFH) should be administered without delay. The treatment of choice is the primary reperfusion especially systemic thrombolysis. When thrombolysis is contraindicated or when it has already failed, surgical embolectomy is recommended in order to improve the haemodynamic status. Finally, if that treatment cannot be practise as well, the last alternative that should be considered is percutaneous catheter-directed treatment. Nevertheless, adequate experience with this method of intervention and appropriate resources are necessary.

Most cases of PE without haemodynamic instability require treatment with low molecular weight heparin (LMWH) or fondaparinux, which are considered the preferred therapeutic options in this clinical setting. The only contraindication is the presence of severe renal dysfunction.

Patients with low-risk PE (PESI I–II, sPESI 0, or negative Hestia criteria) may be treated as outpatients if adequate access to medications, follow-up, and home circumstances exist (45). In patients classified as intermediate-high risk (Category C3–D2) routine systemic thrombolysis is not recommended: in the PEITHO trial (1,006 patients), tenecteplase prevented cardiovascular collapse but increased major bleeding (6.3% vs 1.2%) and intracranial hemorrhage (~2%). If clinical signs of haemodynamic deterioration develop, despite anticoagulation, rescue thrombolysis is beneficial (45). For this reason, these patients should undergo close monitoring with biomarkers and imaging studies in order to detect early signs of RV dysfunction as promptly as possible. Initially, in the absence of evidence of RV dysfunction, anticoagulant therapy remains the recommended first-line treatment.

Patients who cannot achieve the use of anticoagulant drugs and those who objectively confirmed recurrent PE despite adequate anticoagulation treatment should receive venous filters. They may reduce PE-related mortality rates in acute phase despite an increase risk of recurrence of VTE.

Prophylactic measures are feasible and can significantly reduce the incidence of PE, although many risk factors cannot be modified. Nevertheless, the occurrence of PE may be lowered through

adequate control of hypertension, reduction of body mass index when necessary, and improvement of lifestyle habits.

Haemodynamic and respiratory support

Supportive therapy is crucial in patients with PE associated with right ventricular dysfunction. Current evidence suggests that aggressive volume expansion does not provide clinical benefit; however, a modest fluid challenge of approximately 500 mL may improve cardiac index in patients with PE who present with low cardiac output despite normal blood pressure (117).

Vasopressor therapy also plays an important role in the management of PE with RV dysfunction. Agents such as norepinephrine, dobutamine, dopamine, and epinephrine may be used to improve haemodynamic status. These drugs enhance RV function through their positive inotropic effects and by improving right coronary perfusion. Coronary perfusion is further supported by alpha-receptor-mediated peripheral vasoconstriction, which increases systemic blood pressure. Dobutamine and/or dopamine may be considered in patients with PE who have a low cardiac index despite preserved blood pressure, although these agents can worsen ventilation–perfusion mismatch (118). Epinephrine combines the beneficial inotropic effects of the previously mentioned drugs without inducing significant systemic vasodilation. In cases of persistently reduced cardiac output, the addition of dobutamine to norepinephrine may be indicated (119).

The main limitation of vasodilator therapy is its lack of specificity. Some studies have suggested that inhaled nitric oxide may improve both haemodynamic parameters and gas exchange in patients with PE (120). Similarly, levosimendan has been proposed as a potential agent for restoring ventricular–pulmonary arterial coupling (121). However, definitive evidence supporting the clinical benefit of these therapies is still lacking.

In cases of massive PE, extracorporeal membrane oxygenation (ECMO) may represent an effective supportive strategy for stabilizing patients with severe circulatory compromise. In the currently used venoarterial configuration, venous drainage is usually obtained through the common femoral vein, with the cannula positioned at the junction between the inferior vena cava and the right atrium, while the arterial cannula is inserted into the femoral artery. This configuration allows adequate circulatory support even in the presence of severe RV failure and shock (119).

Anticoagulation

Anticoagulation is recommended in all patients independently of the stratification risk they belong to. The use of anticoagulation prevents both early death and recurrent symptomatic or fatal VTE and should cover at least 3 months. Three different options can be followed:

- The conventional strategy which consists on parenteral therapy with Warfarin;
- The parenteral therapy with Dabigatran or Enoxaban (NOACs);
- The oral anticoagulation with Rivaroxaban or Apixaban.

Acute-phase treatment is based on the administration of parenteral anticoagulants, including unfractionated heparin (UFH), low molecular weight heparin (LMWH), or fondaparinux. This initial therapy is generally continued for 5–10 days and maintained until the international normalized ratio (INR) remains within the therapeutic range of 2.0–3.0 for two consecutive days (122). During this phase, parenteral anticoagulation should overlap with the initiation of vitamin K antagonists (VKAs). An alternative therapeutic approach involves the use of direct oral anticoagulants (DOACs), such as dabigatran, a direct thrombin inhibitor, or edoxaban, a factor Xa inhibitor. Oral treatment with rivaroxaban or apixaban, both direct factor Xa inhibitors, can be initiated either immediately or after a short course (1–2 days) of UFH, LMWH, or fondaparinux.

The selection between UFH, LMWH, or fondaparinux should be guided by the patient's comorbid conditions, bleeding risk, and the overall therapeutic strategy being adopted. LMWH is recommended over UFH for initial parenteral therapy due to reduced recurrent VTE risk, predictable pharmacokinetics, and lower incidence of heparin-induced thrombocytopenia (45). Fondaparinux is contraindicated in patients with severe renal insufficiency and it is associated with recurrent VTE and major bleeding rate like those with intravenous UFH. Moreover, no proven cases of heparin-induced thrombocytopenia (HIT) have been reported (123). Fondaparinux is a selective factor Xa inhibitor, that is administered once-daily injection at weight-adjusted dose and does not need monitoring (124).

UFH is recommended in patients with severe renal impairment (creatinine clearance <30 mL/min) or marked obesity, as well as in those in whom primary reperfusion therapy is being considered. When UFH is administered, the therapeutic goal is to maintain an activated partial thromboplastin time (aPTT) between 60 and 80 seconds. Treatment is typically initiated with a bolus dose of 80 IU/kg, followed by a continuous infusion of 18 IU/kg per hour. This approach is supported by the short half-life of UFH, the ease of monitoring its anticoagulant effect, and the possibility of rapid reversal with protamine (125).

If patients are suspected or proven heparin-induced thrombocytopenia, two parenteral direct thrombin inhibitors can be administrated: Argatroban and Bivalirudin (126).

DOACs are preferred over VKAs for long-term management, given comparable efficacy in preventing recurrent VTE, lower risk of major bleeding (especially intracranial hemorrhage), and greater convenience. Apixaban and rivaroxaban can be initiated as oral monotherapy; dabigatran and edoxaban require a short course of initial parenteral anticoagulation (45). Exceptions to DOACs use:

- VKAs are preferred in antiphospholipid syndrome;
- DOACs are contraindicated in pregnancy and breastfeeding;
- caution is warranted in severe renal impairment (CrCl $\leq$ 15 mL/min) and with potent CYP3A4/P-gp inhibitors or inducers (45).

In obesity, DOACs appear effective based on subgroup and observational data, though dose adjustments for LMWH may be reasonable in severely obese patients (45).

Duration of anticoagulation

The duration of anticoagulation depends on clinical presentation and the presence of comorbidities weighs on it. However, it should last at least three months. An indefinite treatment reduces the risk of recurrent VTE by about 90% but the annual major bleeding risk is increase of 1% or more (127).

Based on the different context:

- **Major transient risk factor** (e.g., surgery >30 min, prolonged immobilization): 3 months, then stop (annualized recurrence rate <1%/year) (45).
- **Unprovoked PE or no identifiable risk factor**: Extended-phase anticoagulation (beyond 3–6 months, without a planned stop date) is recommended, as the 10-year recurrence risk after stopping is ~36% (5,45).
- **Persistent risk factors** (active cancer, antiphospholipid syndrome, inflammatory bowel disease): Indefinite anticoagulation is recommended. VKAs are preferred over DOACs in antiphospholipid syndrome (45,61).
- **Minor transient risk factors** (estrogen therapy, minor surgery, pregnancy): Decision-making is more nuanced; extended anticoagulation may be considered based on individual bleeding risk and patient preference (5,61).

- For **extended-phase therapy**, reduced-dose apixaban (2.5 mg BID) or rivaroxaban (10 mg daily) may be considered after the initial 6 months of full-dose therapy (5,61).

After a first episode of PE, patients with cancer are at a higher risk of recurrence and are therefore candidates for extended or indefinite anticoagulant therapy, which does not necessarily imply lifelong treatment but rather should be tailored to the individual patient's characteristics and risk profile. Lifelong anticoagulation is generally recommended in patients who experience a second unprovoked episode of PE or VTE. The presence of permanent risk factor should be an indication to indefinite anticoagulation treatment after a first unprovoked VTE.

Long-term anticoagulant therapy may be associated with an increased risk of major bleeding. The main risk factors in this context include: age over 75 years, a history of gastrointestinal bleeding, previous stroke, chronic renal or hepatic disease, concomitant antiplatelet therapy, severe acute or chronic comorbidities, poor anticoagulation control, and inadequate monitoring of anticoagulant treatment.

The balance between the risk of recurrent VTE events and the bleeding risk is essential to establish the duration of anticoagulation in patients with unprovoked PE. They should be treated for at least 3 months with VKA. After this period further evaluation should follow.

Venous filters

The venous filter is typically positioned in the infrarenal segment of the inferior vena cava (IVC). One of the early complications is thrombosis at the insertion site, occurring in approximately 10% of patients, most commonly related to access-site thrombosis of the common femoral vein. When the filter is placed in the superior vena cava, the most serious risk is pericardial tamponade (128). The incidence of late complication is higher and consists on recurrent DVT (20%) and post-thrombotic syndrome (40%), IVC penetration, IVC migration (129).

Filters can be distinguished into two categories:

- **Permanent filters** have a reduced risk of recurrent PE (on the contrary the risk of recurrent DVT) and no overall effect on survival.
- **Non-permanent filters**: they are classified as temporary or retrievable devices. Temporary filters are intended to be removed within a few days, whereas retrievable filters may remain in place for a longer period. In both cases, removal is recommended as soon as anticoagulant

therapy can be safely initiated or resumed. When left in situ for prolonged periods, these devices are associated with complications such as filter migration, tilting or deformation, penetration of the caval wall, fracture of the filter, embolisation of fragments, and thrombosis of the device (130).

Thrombolytic treatment

The thrombolytic therapy is administered in patients with a massive PE while it is controversial the use in submassive PE patients.

The effectiveness of thrombolytic therapy is closely related to how early treatment is initiated: benefits are mainly limited to the first days after the acute event. Although some benefit may still be observed up to 14 days after symptom onset, the greatest efficacy is achieved when treatment is started **within the first 48 hours** (131). Compared with anticoagulant therapy alone, thrombolysis offers more rapid reversal of haemodynamic impairment through improvement of RV dysfunction, along with lower rates of death and recurrent PE. Thrombolytic therapy is able to dissolve a large part of the thrombotic obstruction and may also prevent the persistent release of serotonin and other neurohumoral mediators involved in the development of pulmonary hypertension. In addition, it contributes to thrombus lysis in the pelvic and deep veins of the lower limbs (132).

The administration of fibrinolytic therapy is generally combined with heparin anticoagulation. Fibrinolytic agents act by promoting fibrin degradation through the conversion of plasminogen into plasmin. Plasmin, a serine protease, cleaves fibrin at multiple sites, leading to the formation of fibrin degradation products, including D-dimer fragments. The only fibrinolytic drug currently approved in Europe for this indication is recombinant tissue plasminogen activator (rtPA), with alteplase being the most widely used agent, although tenecteplase may also be employed. Alteplase is usually administered according to an accelerated regimen at a dose of 100 mg (or 0.6 mg/kg) by continuous peripheral intravenous infusion over 2 hours. A favourable clinical response is observed in more than 90% of patients within the first 36 hours (132).

Controindications to thrombolysis

Contraindications to thrombolytic treatment can be sorted into two categories:

- Absolute contraindications: previous intracranial haemorrhage; known structural

intracranial cerebrovascular disease; known malignant intracranial neoplasm; ischemic stroke within 3 months; suspected aortic dissection; active bleeding or bleeding diathesis; recent surgery encroaching on the spinal canal or brain; recent significant closed-head or facial trauma with radiographic evidence of bony fractures or brain injury;

- Relative contraindications: age >75 years; current use of anticoagulation; pregnancy; non-compressive vascular punctures; traumatic or prolonged cardiopulmonary resuscitation (>10 minutes); recent internal bleeding (within 2-4 weeks); history of chronic, severe and poorly controlled hypertension; severe uncontrolled hypertension blood pressure (systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg); dementia; remote ischemic stroke (>3 months); major surgery within 3 weeks.

Surgical embolectomy

The surgical approach is indicated to those patients who belong to C3-E categories, accordingly to the 2026 AHA/ACC/ACCP/ACEP/CHEST/SCAI/SHM/SIR/SVM/SVN Guideline categories, (high-risk PE or intermediate-high-risk PE, following previous classifications) who cannot receive thrombolysis, or it has failed.

Rapid transfer to the operating room is essential. Once the patient reaches surgery, anaesthesia is induced and a median sternotomy is performed, followed by the establishment of normothermic cardiopulmonary bypass. This approach allows direct removal of thrombotic material from both pulmonary arteries down to the segmental branches through bilateral pulmonary artery incisions. The procedure may also be carried out under normothermic conditions without aortic cross-clamping, cardioplegic arrest, or fibrillatory arrest. The use of extracorporeal circulation guarantees adequate systemic perfusion and oxygenation throughout the intervention (8).

Recovery of RV function is generally slower after surgical treatment, compared with thrombolytic therapy and may require prolonged postoperative cardiopulmonary bypass support. Nevertheless, echocardiographic FU has demonstrated significant improvement in RV function following the procedure (133).

When pulmonary embolectomy is performed with appropriate timing, before the onset of haemodynamic collapse, perioperative mortality rates can be ≤6%. Previous thrombolytic therapy has been associated with an increased risk of bleeding during surgery; however, prior thrombolysis is not considered a contraindication to surgical embolectomy (134).

Patients presenting with an episode of acute PE superimposed on a history of chronic dyspnoea and pulmonary hypertension are likely to have CTEPH. Approximately 2–4% of patients with acute PE may eventually develop this condition. In such cases, pulmonary endarterectomy should be considered, as it can significantly reduce pulmonary hypertension and, in some patients, even provide definitive resolution. Pulmonary endarterectomy is a complex surgical procedure requiring median sternotomy, cardiopulmonary bypass, deep hypothermia, and periods of circulatory arrest under hypothermic conditions. The reported mortality rate is around 5%. One of the main limitations of this treatment is the need to transfer patients to highly specialised expert centres.

Percutaneous catheter-directed treatment

Percutaneous treatment is generally reserved for patients with absolute contraindications to thrombolytic therapy when emergency surgical thrombectomy is either unavailable or contraindicated. The patients most likely to benefit from a percutaneous approach are those presenting with massive or submassive PE.

This technique enables the removal of partially or completely obstructive thrombi from the main pulmonary arteries. Thrombus extraction can lead to improvement in both symptoms and survival. Several percutaneous strategies are available, often combining catheter-directed clot fragmentation with local thrombolytic therapy. These approaches include:

- Thrombus fragmentation with **pigtail or balloon catheter**;
- **Rheolytic thrombectomy** with hydrodynamic catheter devices;
- **Suction thrombectomy** with aspiration catheters;
- **Rotational thrombectomy**.

All of them allow a rapidly reduction of pulmonary artery pressure and consequent RV strain and pulmonary vascular resistance (PVR), an increasing systemic perfusion and facilitate RV recovery (135).

One of the most severe, although uncommon, complications is **cardiac tamponade;** secondary to pulmonary haemorrhage or perforation of the right atrium or right ventricle. In addition, perforation or dissection of a major branch of the pulmonary artery may result in acute pulmonary haemorrhage

or even death. The risk of vascular perforation appears to increase when the treated vessels have a diameter smaller than 6 mm (136).

Therapeutic strategy

In summary, the AHA/ACC recommends a category-specific, escalating therapeutic approach for acute PE, with anticoagulation as the foundation across all categories and advanced therapies reserved for Categories D–E (45).

The table below provides a concise overview of the different therapeutic strategies recommended for each clinical class.

Category	Setting	Anticoagulation	Advanced Therapies	Key Evidence	References
A (Asymptomatic)	ED discharge / outpatient	DOACs preferred	Not indicated	—	(45)
B (Low risk)	Early discharge / outpatient	DOACs or LMWH → DOAC	Not indicated	—	(45)
C1 (Elevated risk, no RV dysfunction/biomarkers)	Hospitalization	Anticoagulation + monitoring	Not routinely indicated	—	(45)
C2–C3 (Elevated risk + RV dysfunction/biomarkers)	Hospitalization	Anticoagulation; rescue thrombolysis if deterioration	CDL/MT not routinely indicated; rescue reperfusion if decompensation	PEITHO, PEERLESS	(45)
D1–D2 (Pre-cardiopulmonary failure)	ICU / intermediate care	Parenteral anticoagulation	CDL, MT, surgical embolectomy, or systemic thrombolysis can be considered	PEITHO, PEERLESS, surgical series	(45)
D3 (Respiratory compromise)	ICU / intermediate care	Parenteral anticoagulation	Supportive care; advanced therapies as indicated	—	(45)
E1 (Persistent hypotension)	ICU	Parenteral anticoagulation (UFH)	Systemic thrombolysis, CDL, MT, or surgical embolectomy are reasonable	Meta-analyses, surgical series	(45)
E2 (Refractory shock/arrest)	ICU	Anticoagulation on ECMO	VA-ECMO ± adjunctive reperfusion	Observational registries	(45,137)

Table 6: Summary table of therapeutic strategies by category.

Invasive haemodynamic assessment

The importance of invasive haemodynamic assessment in the acute phase

In acute PE, right heart catheterization (RHC) is not routinely indicated for initial haemodynamic assessment; rather, it is primarily used in the context of catheter-based interventions (CDL, mechanical thrombectomy) or when invasive haemodynamic data are needed to refine risk stratification in Categories C–D, particularly to identify normotensive shock (isolated hypoperfusion without hypotension) (45,138).

The 2026 AHA/ACC guideline emphasizes haemodynamic assessment as a key component of risk stratification for Categories C1 through D, but the initial assessment relies primarily on noninvasive parameters (e.g., MAP, echocardiography, CT-derived RV/LV ratio, and biomarkers) (45). Invasive haemodynamic assessment via RHC becomes relevant in specific scenarios:

- **During catheter-based interventions**: RHC is performed at the time of catheter-directed thrombolysis (CDL) or mechanical thrombectomy, providing real-time measurement of mean pulmonary artery pressure (mPAP), cardiac index (CI), and pulmonary artery pulsatility index (PAPi). The *FLASH registry* demonstrated that 34% of intermediate-risk PE patients undergoing thrombectomy had isolated hypoperfusion (reduced CI without hypotension), and approximately one-third achieved normalization of CI post-thrombectomy (45,138). In the Lauder et al. prospective study, RHC was performed before thrombectomy, immediately after, and at 3 months. The proportion of patients with a TAPSE/sPAP ratio <0.31 mm/mmHg (indicating RV-PA uncoupling) decreased from 28% at baseline to 0% at discharge and at 3 months, confirming sustained haemodynamic recovery (139).
- **Identifying normotensive shock** (Category D2): Invasive haemodynamics can unmask patients with a normal blood pressure but reduced cardiac index and end-organ hypoperfusion; a group at high risk for deterioration. Markers of end-organ malperfusion (elevated lactate, AKI, reduced CI) were associated with higher in-hospital mortality than hypotension alone in the *SHOCK trial* (45).

This finding fundamentally changed risk stratification: blood pressure alone is insufficient to identify all haemodynamically compromised patients. RHC provides the definitive measurement of CI that cannot be reliably obtained noninvasively in many acute PE patients.

A recent study of 70 PE patients who underwent simultaneous echocardiography and pulmonary artery catheterization found that the noninvasive TAPSE/PASP ratio (cutoff 0.34 mm/mmHg) was a strong predictor of reduced CI, with an AUC of 0.97, sensitivity 97.3%, and specificity 90.9%

(140). This suggests that echocardiographic RV-PA coupling assessment may serve as a noninvasive surrogate for invasive CI measurement, though validation in larger cohorts is needed.

The following figure from the FLASH registry illustrates the sustained improvement in RV function at 30 days, stratified by the presence or absence of normotensive shock at baseline:

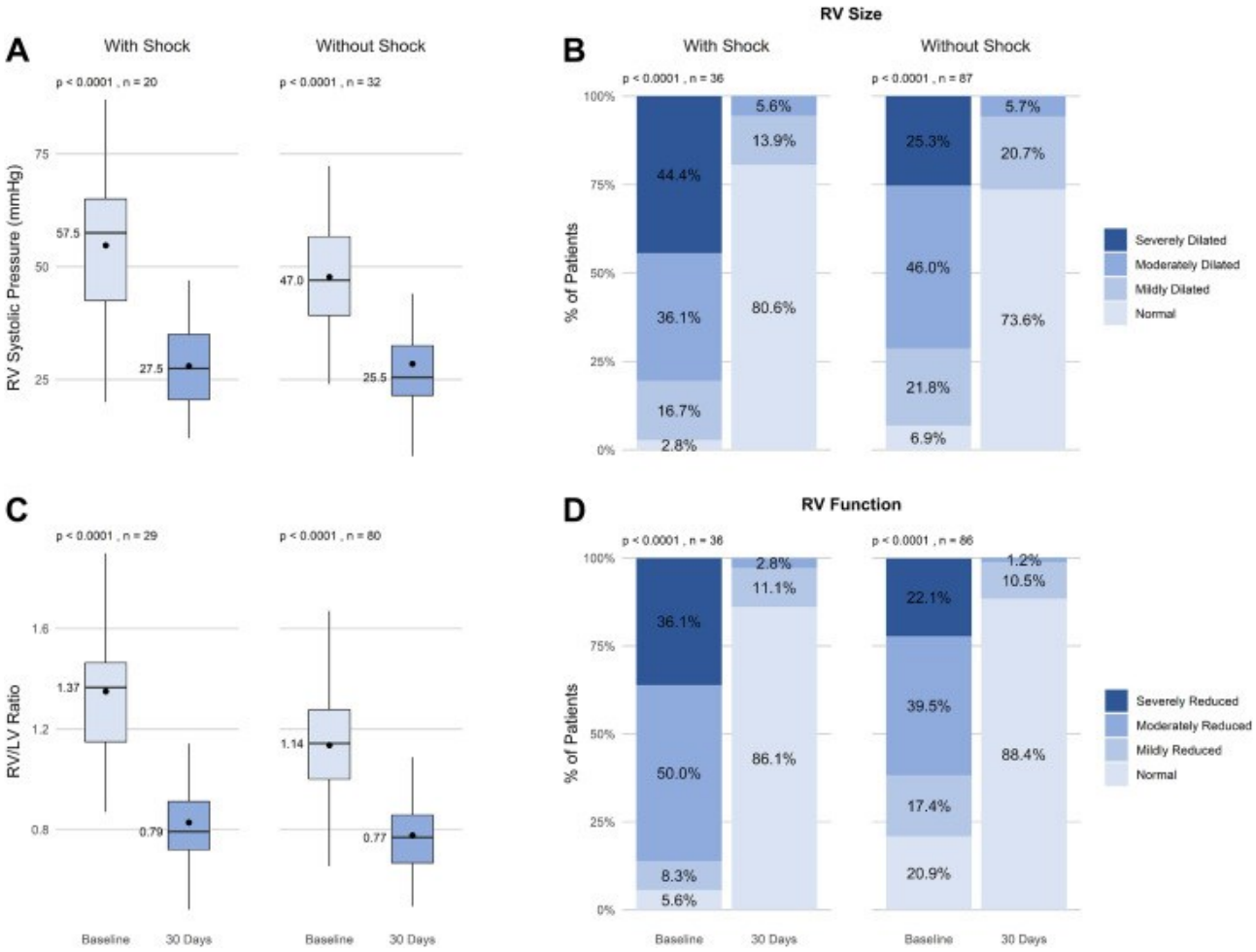

Figure 12: Improvement in RV Function at 30-Day Visit (138)

Limitations of RHC in Acute PE

RHC is not without risk in the acute PE setting. Catheter passage through the right heart in the presence of thrombus-in-transit carries a theoretical risk of embolization. Additionally, the procedure requires time and expertise that may not be available in all settings. The 2019 AHA scientific statement noted that the decision to use active thrombus removal is driven primarily by PE severity and secondarily by patient-specific risk factors, with haemodynamic data serving to refine, not replace, clinical judgment (141).

The importance of invasive haemodynamic assessment in the post acute phase

The AHA/ACC recommends that haemodynamic assessment in the post-acute phase of PE (≥3 months) is essential for detecting chronic thromboembolic pulmonary disease (CTEPD) and CTEPH, which complicate approximately 2.3%–4% of acute PEs and are frequently underdiagnosed due to symptom overlap with deconditioning, anemia, heart failure, and obstructive sleep apnea (45).

A dedicated visit at approximately 3 months after acute PE is recommended to evaluate for ongoing symptoms, discuss anticoagulation duration, and assess the need for further testing. Between one-third and one-half of patients who have had a symptomatic PE will report dyspnea or limitations to physical activity for months to years, with the prevalence of shortness of breath being higher after PE associated with RV dysfunction. A study of follow-up protocols at 2–4 months after PE with RV dysfunction revealed limited activity due to fatigue or shortness of breath in half of patients; among those, 77% had an abnormal perfusion scan or echocardiogram, while in the remaining 23%, other etiologies were identified (45).

While the AHA/ACC guideline emphasizes noninvasive screening first, RHC remains the gold standard for confirming CTEPH and is the final step in the diagnostic algorithm. CTEPH is defined by the presence of chronic thromboembolic material obstructing the pulmonary arteries in the setting of confirmed precapillary PH: mPAP >20 mmHg, PVR >3 Wood units, and PAOP <15 mmHg; after at least 3 months of therapeutic anticoagulation (142,143). RHC is ideally coupled with selective digital subtraction pulmonary angiography (DS-PA), which provides combined haemodynamic and radiographic disease assessment and is critical for determining surgical operability (142).

Figure 13, below, illustrates characteristic pulmonary angiographic findings in CTEPH, including pouch defects, web defects, and the value of biplane imaging.

It is strongly recommended that RHC with DS-PA be performed at a CTEPH center with relevant procedural and interpretive expertise to obtain optimal data and avoid repetition of invasive testing (142).

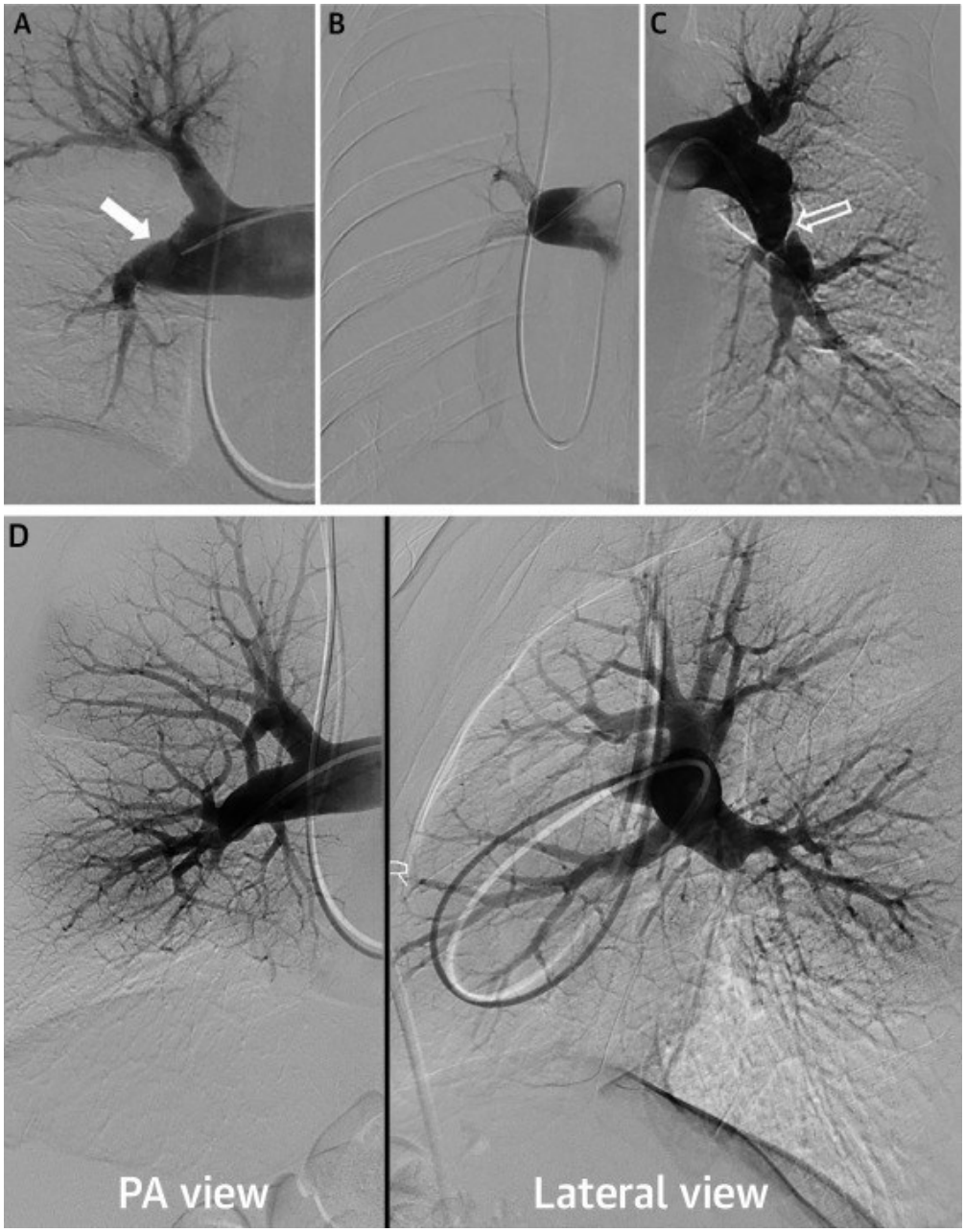

FIgure 13: Pulmonary Angiographic Findings in CTEPH (144).

The SEARCH algorithm

Morris et al. proposed the **SEARCH** algorithm: a stepwise diagnostic protocol validated in a prospective study of 150 consecutive post-PE patients; that places RHC as the final confirmatory step (145,146):

1. **S**ymptom screening (≥3–6 months post-PE)
2. **E**xercise testing (noninvasive CPET to identify elevated dead space ratios, decreased stroke volume augmentation)
3. **A**rterial perfusion (V/Q scanning for mismatched perfusion defects)
4. **R**esting echocardiography (evidence of PH)
5. **C**onfirmatory chest imaging (CT pulmonary angiography for chronic thromboembolic findings)
6. **Haemodynamic**s measured by right heart catheterization

In the prospective validation study, 12% of patients were diagnosed with chronic thromboembolism phenotypes. Critically, CTEPH was found in only 2.1%, while chronic thromboembolism with exercise-induced PH occurred in 3.5%, and chronic thromboembolism with ventilatory inefficiency but without PH in 6.3% (146). This highlights that the majority of chronic thromboembolism is not associated with resting PH and would be missed without exercise haemodynamic assessment.

Exercise RHC

When resting haemodynamics are normal but clinical suspicion remains high, exercise RHC can disclose exercise-induced defects. The ESC/ERS defines exercise PH as an mPAP/CO slope >3 mmHg/L/min with normal PAWP and elevated PVR during exercise (147). This is particularly relevant for patients with CTEPD without resting PH, who may have only modest levels of PH at rest but demonstrate increasing dead space ventilation or pulmonary pressures during activity (142,148).

A recent narrative review confirmed that exercise RHC remains the gold standard for confirming exercise-induced PH in CTEPD, though due to its invasive nature and limited availability, noninvasive tests (CPET, exercise stress echocardiography) are preferred for first-line screening, with exercise RHC reserved for selected cases with inconclusive findings or complex physiology (148).

The following figure illustrates the diagnostic work-up of CTEPH, showing how RHC serves as the confirmatory step after noninvasive screening:

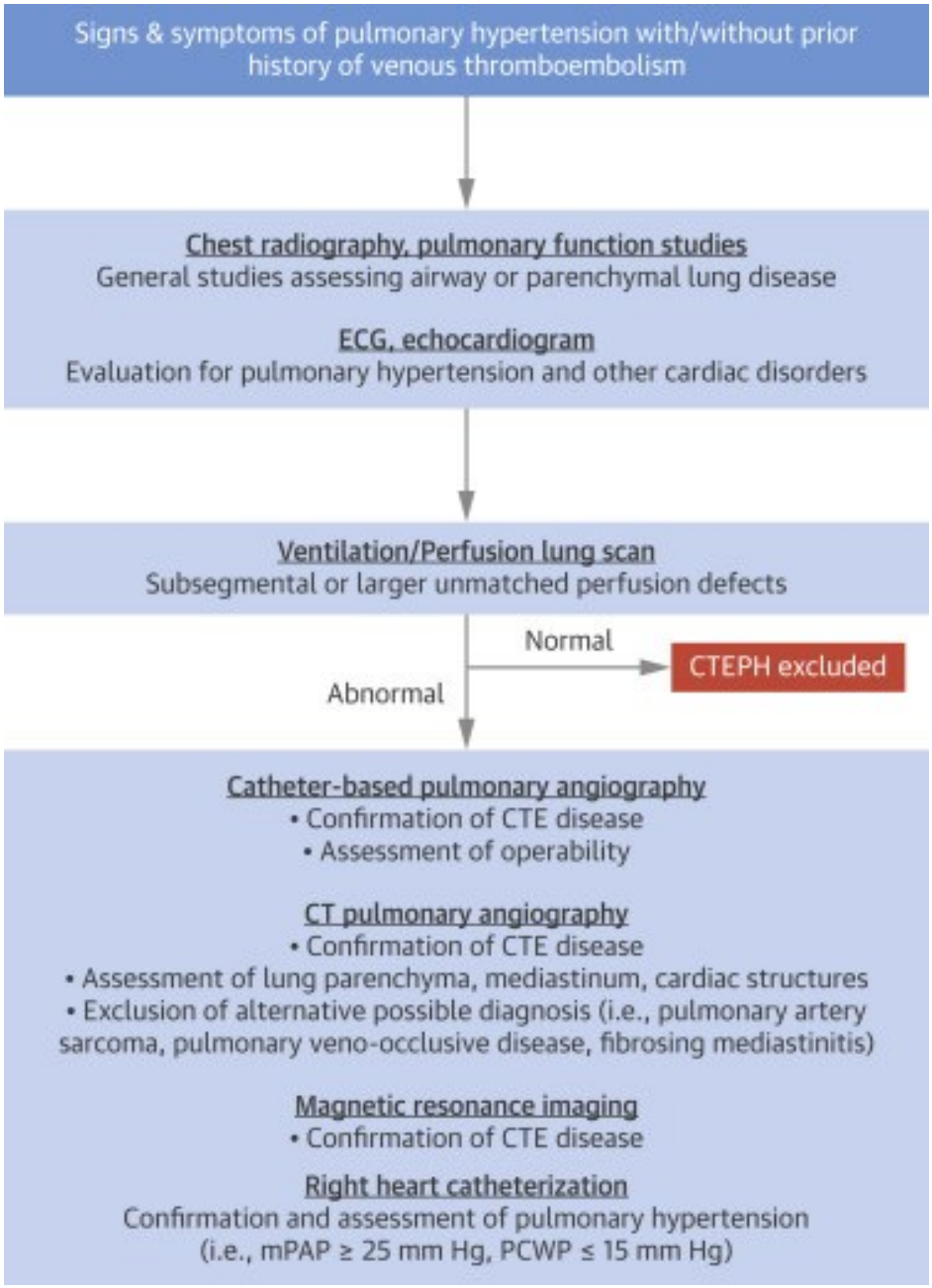

Figure 14: Diagnostic Work-Up of CTEPH (149).

Research purpose

The long-term prognostic role of invasive haemodynamic assessment after acute PE has not been fully established. The present study was designed to investigate the potential value of right heart catheterization performed after hospital discharge in patients who survived an intermediate-high risk acute PE. To address this objective, consecutive patients admitted to the Intensive Care Unit of the Cardiology Department of Modena University Hospital were prospectively enrolled and underwent a comprehensive haemodynamic evaluation after stabilization of the acute event. Clinical, echocardiographic, and invasive haemodynamic data were collected and subsequently analyzed in relation to long-term follow-up outcomes.

The main end-point of the present study was to assess the impact of various invasive haemodynamic parameters, measured by right heart catheterization, on the incidence of all-cause mortality, in a long-term follow-up.

Study protocol

Our study enrolled a cohort of consecutive patients with a confirmed diagnosis of PE, associated with elevated troponin levels and right ventricular dilatation, admitted to the intensive care unit of the Cardiology Department at the Modena University Hospital.

The study included all patients who survived the acute phase of the disease; therefore, patients who died during hospital admission were excluded. All surviving patients underwent haemodynamic classification by means of RHC performed at hospital discharge.

The aim of the study was to assess whether this haemodynamic classification could have prognostic significance, specifically with regard to long-term mortality. Accordingly, all patients admitted between 01/01/2015 and 31/12/2025, corresponding to a 10-year period, were enrolled. The last FU was completed on 31/05/2026. The total duration of FU was variable, ranging from 5 to 125 months. The long-term endpoint was exclusively all-cause mortality.

Patient population

Our study enrolled all patients aged over 18 years with a confirmed diagnosis of acute PE, whose first symptoms had occurred no more than 15 days prior to hospital admission. All patients who survived the acute phase underwent RHC immediately before hospital discharge (9 ± 3 days after admission). All patients received treatment with heparin or DOACs, according to the protocol in use at the time of hospitalization. In addition, all patients were invited to undergo repeat RHC after six months of FU.

Invasive haemodynamics using right heart catheterization

Catheterization was performed in the cath lab using a 7F balloon-tipped (Swan-Ganz catheter), triple lumen thermodilution catheters (Edwards Life Sciences, Irvine, CA, USA). All measurements were performed with patients at rest in the supine position, while breathing room air. The pressures were all averaged in three consecutive heart beats at end-expiration. Variables collected included: mean right atrial pressure (mRAP), systolic, diastolic and mean pulmonary artery pressure (mPAP), pulmonary capillary wedge pressure (PCWP), heart rate, mixed venous oxygen saturation (pulmonary artery) (SvO2), and cardiac output (CO) by thermodilution technique. The transpulmonary gradient was calculated by subtracting the mPAP from PCWP. PVR was calculated by dividing the transpulmonary gradient by CO (in Wood Unit). CO was indexed by body surface area and expressed as cardiac index (CI).

Statistical analysis

Continuous variables were evaluated using Student's *t*-test to compare mean values. Nominal or dichotomous variables were summarized as percentages or proportions and compared using the χ^2 test. Long-term mortality rates were analyzed using two-sided χ^2 tests for proportions. Kaplan–Meier survival curves were compared using the log-rank test. For patients who were still alive at the time of the most recent FU, the date of last contact was considered the censoring date. The significant determinants of events were assessed using Cox proportional hazard model. Clinical, demographic and haemodynamic variables were analyzed in an univariable and multivariable model. All variables were introduced in the model in a conditional forward stepwise method.

Statistical significance was set a priori at an $\alpha = 0.05$ and 95% confidence intervals (CI) were determined for the hazard ratios (HR).

Results

Over a period of approximately **10 years**, **156 patients** were enrolled in our study.

The demographic characteristics, clinical data, and medical history of the enrolled patients are summarized in Table 7.

Baseline charachteristics of 156 enrolled patients with acute PE who underwent RHC	
Demographic data	
Age, years	72 ± 15
Male gender	45.5% (n=71)
Weight, kg	81 ± 17
Clinical data	
Systolic pressure, mmHg	125 ± 17
HR, bpm	93 ± 18
Respiratory rate, bpm	22 ± 6
O_2 treatment	73.7% (n=125)
Medical history and concomitant diseases	
Chronic pulmonary diseases	10.2% (n=16)
Chronic heart failure	11.5% (n=18)
Previous VTE	12.8% (n=20)
Active cancer	20.5% (n=32)
Surgery or trauma	9.6% (n=15)
Immobilization	19.2% (n=30)
Medical treatment	
Heparin	100% (n=156)
DOACs	95.5% (n=149)
Coumadin	4.5% (n=7)
Patients discontinuing anticoagulation	
After 3 months	6.5% (n=10)
After 6 months	11.5% (n=18)
Patients on anticoagulation therapy for ≥ 6 months or indefinitely	
	82.0% (n=128)

Table 7. HR: heart rate; VTE: venous thromboembolism; DOACs: direct oral anti coagulants

Long term follow-up

After a median FU of 65 months (interquartile range: 9–121 months), 39 out of 156 patients (25%) died.

The comparison between surviving and deceased patients is illustrated in Table 8.

Comparison between patients who died and patients who survived an acute PE event during long-term FU. Analysis of demographic, clinical, and haemodynamic factors obtained by RHC.			
Parameter	***Deceased patients*** *(n=39)*	***Surviving patients*** *(n=117)*	***p***
ANAGRAPHIC			
Age, years	72 ± 16	71 ± 14	0.8
Male gender	46.1% (18/39)	45.2% (53/117)	0.5
Weight, kg	83.18	79.16	0.6
ECOCARDIOGRAPHIC			
Right ventricular end diastolic diameter > 30mm	25.6% (10/39)	19.6% (23/117)	0.01
Right to left ventricular end diastolic diameter > 0.9	30.7% (12/39)	17.1% (21/117)	0.001
Hypokinesia of right ventricle's free wall	12.8% (5/39)	11.1% (13/117)	0.4
Tricuspid anular plain systolic excursion reduced (< 20mm)	23 ± 5	24 ± 4	0.5
Systolic pulmonary artery pressure, mmHg	31.12	30.11	0.6
HAEMODYNAMIC - RHC RELATED			
HR, bpm	98.20	78.16	0.01
mRAP, mmHg	14 ± 3	5 ± 2	0.001
mPAP, mmHg	22 ± 4	20 ± 5	0.7
Pulmonary pulse pressure, mmHg	22 ± 5	21 ± 4	0.8

PCWP, mmHg	8 ± 3	8 ± 4	0.9
mRAP/PCWP	1.7 ± 0.3	0.6 ± 0.2	0.001
SvO_2, %	63 ± 3	72 ± 4	0.01
CI, L/min/m^2	1.8 ± 0.4	2.5 ± 0.6	0.001
SV, ml	38 ± 12	66 ± 15	0.001
PVR, wood unit	1.8 ± 0.4	2.4 ± 0.4	0.3
PVC, mL/mmHg	1.68 ± 0.28	3.14 ± 0.55	0.001
PAPi	1.57 ± 0.6	4.20 ± 1.0	0.0001
RVSWI, g·m/m^2/beat	3.5 ± 1.2	13.5 ± 2.2	0.0001
Patients with right ventricular dysfunction (RVD)	64.1% (25/39)	20.5% (24/117)	0.0001

Table 8. mRAP: mean right atrial pressure; mPAP: mean pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; SvO_2: venous oxygen saturation; CI: cardiac index; SV: stroke volume; PVR: pulmonary vascular resistance; PVC: pulmonary vascular compliance; PAPi: pulmonary artery pulsatility index; RVSWI: right ventricular stroke work index; RVD: defined by mRAP ≥ 8 mmHg, PCWP < 15 mmHg, and CI < 2.5 L/min/m².

The results of the univariable and multivariable Cox regression analyses are presented in Table 9.

Uni-and-multivariables Cox regression analyses, to identify determinance of all cause mortality in our patients with PE.						
Parameter	**UNIVARIABLE**			**MULTIVARIABLE**		
	HR	95% C.I.	p	HR	95% C.I.	p
ANAGRAPHIC						
Age, years	1.024	0.986 – 1.019	0.1	1.000	0.976 – 1.035	0.15
Male gender	0.588	0.304 – 1.124	0.1	0.601	0.294 – 1.235	0.26
Weight, kg	1.019	0.905 – 1.327	0.45	1.012	0.984 – 1.042	0.35
ECOCARDIOGRAPHIC						
RV EDD > 30	1.031	1.005 – 1.057	0.02	1.006	0.896 – 1.116	0.65
R/L V EDD > 0.9	1.079	1.058 – 1.101	0.001	1.025	0.988 – 1.062	0.1

Hypokinesia of RV's free wall	1.015	0.896 – 1.134	0.38	1.014	0.890 – 1.132	0.4
TAPSE	1.023	0.988 – 1.020	0.15	1.020	0.985 – 1.015	0.2
sPAP	1.025	0.987 – 1.021	0.15	1.018	0.980 – 1.016	0.25
HAEMODYNAMIC - RHC RELATED						
HR, bpm	1.025	1.012 – 1.028	0.01	1.010	0.997 – 1.013	0.4
mRAP, mmHg	1.078	1.034 – 1.116	0.001	1.100	0.982 – 1.044	0.3
mPAP, mmHg	1.010	0.988 – 1.132	0.6	1.008	0.986 – 1.130	0.6
PCWP, mmHg	1.001	0.996 – 1.119	0.9	1.001	0.989 – 1.226	0.85
SvO_2, %	1.015 *	1.004 – 1.022	0.03	1.005	0.899 – 1.027	0.8
CI, L/min/m^2	1.640 *	1.027 – 1.098	0.001	1.12	0.920 – 1.330	0.1
PVR, wood unit	1.013 *	0.998 – 1.028	0.4	1.009	0.991 – 1.035	0.6
PVC, mL/mmHg	1.094 *	1.056 – 1.169	0.001	1.027	0.999 – 1.055	0.1
PAPi	1.125 *	1.095 – 1.155	0.0001	1.055	1.160 – 1.172	0.01
RVSWI, g·m/m^2/beat	1.205 *	1.168 – 1.242	0.0001	1.215	1.165 – 1.250	0.001
Patients with RVD	3.126	2.584 – 3.668	0.0001	4.234	2.864 – 5.604	0.0001

Table 9. RV EDD: right ventricular end diastolic diameter; R/L EDD: right to left-ventricular end diastolic diameter; TAPSE: tricuspid anular plain systolic excursion; SPAP: systolic pulmonary artery pressure.
** The hazard ratio was inverted to facilitate interpretation.*

Univariable Cox regression analysis identified several echocardiographic and haemodynamic parameters as significant predictors of all-cause mortality. However, in the multivariable model, only RVD, PAPi, and RVSWI remained independently associated with mortality, with RVD emerging as the strongest predictor.

The prognostic impact of RVD in patients with PE is graphically illustrated in Figure 15 below.

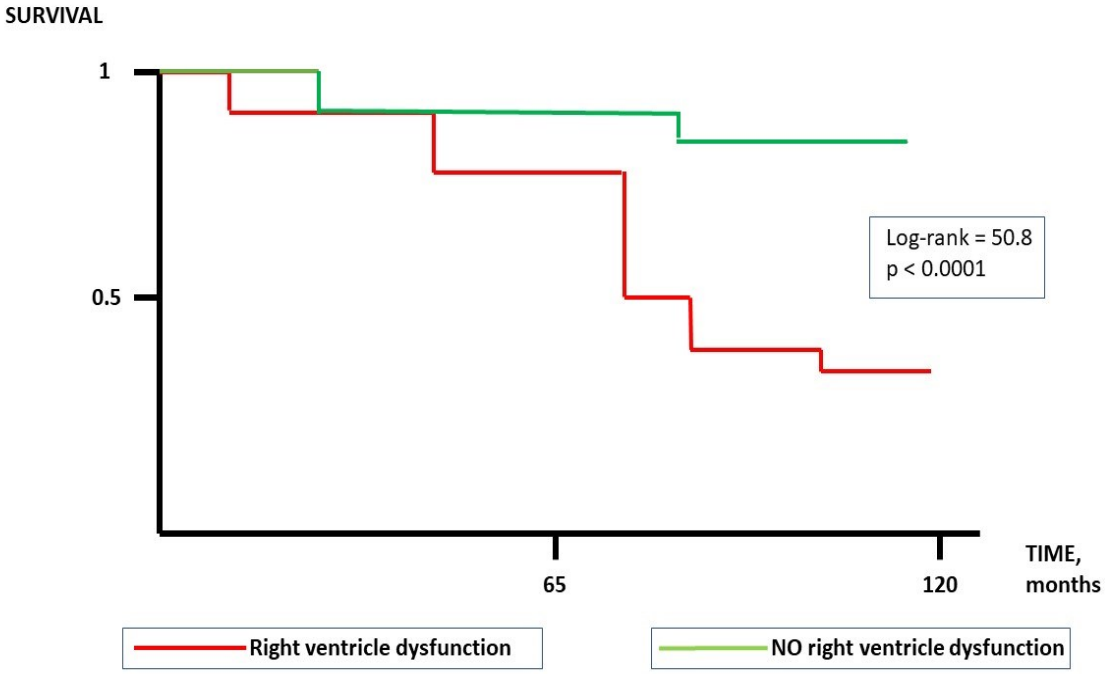

Figure 15: prognostic impact of RVD in patients with PE.

Right heart catheterization at 6-months follow-up

All patients who underwent catheterization at hospital discharge were invited to undergo a follow-up invasive examination 6 months later.

RVD was present in 49 patients at discharge. Considering the second catheterization data: 28 out of 49 patients (57.1%) showed resolution of RVD, reflecting recovery of right ventricular systolic function and haemodynamic performance; 21 patients (42.9%) remained in a condition of RVD; moreover, 20 patients (47.1%) who did not have it, developed the same condition after 6 months of follow-up.

Thus, two groups were formed: the first group, defined as the "right ventricular dysfunction group", consisting of 41 patients, of whom 21 had the condition already present at discharge and 20 developed it during follow-up; the remaining population includes patients who either never had RVD or initially had it but subsequently resolved it over time.

RVD was significantly more prevalent among patients who died than among survivors, being present in 35 of 39 deceased patients (89.7%) compared with 10 of 117 survivors (8.7%) ($p<0.0001$).

These findings suggest a strong association between the presence of RVD and mortality, after an episode of acute PE.

Table 10, below, shows the importance of RVD as the foundamental parameter to predict overall mortality.

Cox multivariable regression analyses to test the prognostic value of the "persistent RVD"			
BASELINE MODEL → Model $\chi^2 = 30.8$			
Parameter	HR	95% C.I.	p
RVD (at the time of the first catheterization)	4.234	2.864 – 5.064	0.0001
PAPi	1.055	1.100 – 1.172	0.04
RVSWI	1.215	1.165 – 1.250	0.01
BASELINE MODEL + "Persistent RVD" → Model $\chi^2 = 63.4$ (p = 0.0001 vs baseline)			
Persistent RVD	8.56	5.660 – 11.460	<0.0001
RVD (at the time of the first catheterization)	1.035	0.886 – 1.184	0.8
PAPi	1.009	0.993 – 1.038	0.9
RVSWI	1.024	0.975 – 1.073	0.3

Table 10: The addition of "persistent RVD" significantly improved model fit, outperforming baseline RVD and other haemodynamic variables in predicting mortality.

In the baseline model, RVD at the first catheterization, PAPi, and RVSWI were independently associated with mortality. The addition of persistent RVD significantly improved the model fit (χ^2 increased from 30.8 to 63.4, $p = 0.0001$), demonstrating substantial incremental prognostic value. After inclusion of **persistent RVD**, this variable emerged as the **strongest independent predictor of mortality** (HR 8.56, 95% CI 5.66–11.46, $p < 0.0001$), whereas the prognostic significance of baseline RVD, PAPi, and RVSWI was no longer retained, suggesting that persistent RVD captures most of the prognostic information conveyed by the initial haemodynamic and right ventricular functional assessment.

Figure 16 graphically illustrates these findings.

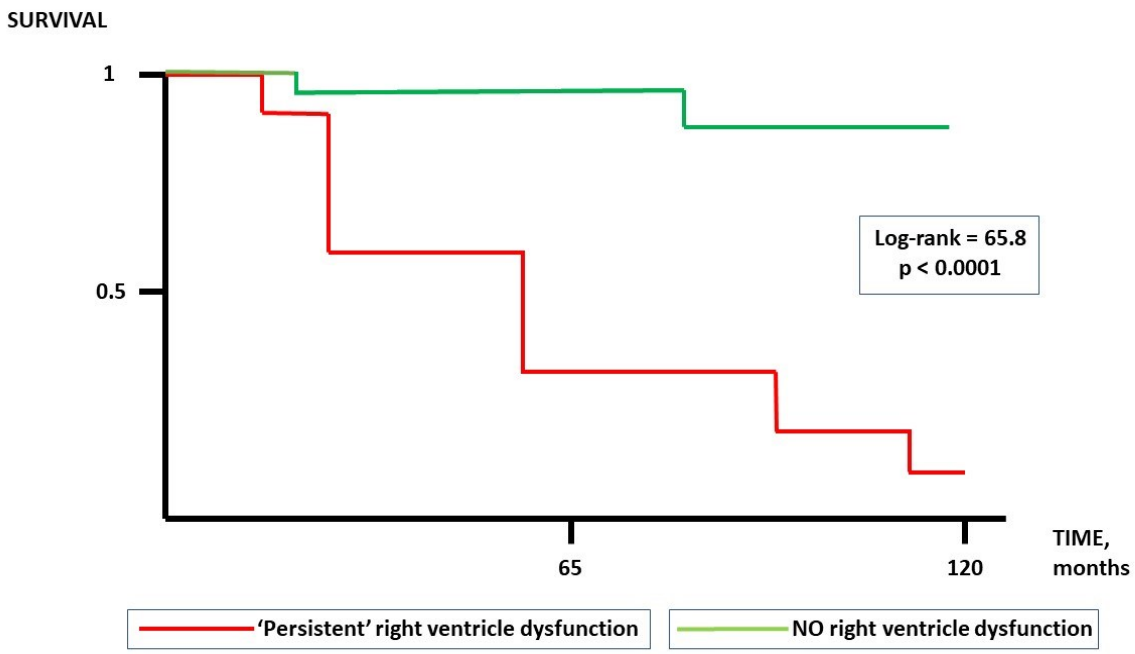

Figure 16: Kaplan–Meier survival curves showing significantly reduced survival in patients with persistent RVD compared with those without RVD (log-rank = 65.8, p < 0.0001).

Discussion

Pulmonary embolism represents **the most severe clinical manifestation of venous thromboembolism** (8). Together with myocardial infarction and stroke, it is among the leading causes of cardiovascular mortality. PE is a complex condition characterized by substantial morbidity and mortality and is frequently associated with significant comorbidities, among which CTEPH represents one of the most serious long-term complications (40).

Accurate prognostic assessment of PE remains challenging. The most widely validated prognostic tool is the Pulmonary Embolism Severity Index (PESI), which is based on patients' clinical characteristics and is currently recommended for predicting short-term outcomes according to international guidelines. However, several studies have suggested that the PESI score may also provide reliable estimates of medium- and long-term prognosis, including 6-month and 1-year mortality rates in patients with PE (150).

The ICOPER and IPER registries evaluated clinical parameters, including the PESI score, and their association with short-term (3-month) and intermediate-term (12-month) mortality in patients with

PE (94,95). However, the clinical variables, included in the PESI score, cannot fully capture the complexity of the disease or the pathophysiological changes affecting the right ventricle.

Right ventricular function can be assessed non-invasively through echocardiography and computed tomographic angiography; as well as invasively by means of right heart catheterization.

The present study enrolled 156 consecutive patients with intermediate-high risk acute PE who underwent RHC before hospital discharge and, when feasible, at 6-month follow-up. Over a median FU of 65 months, 39 patients (25%) died, and invasive haemodynamic evidence of RVD (defined by mRAP $\geq$ 8 mmHg, PCWP < 15 mmHg, and CI < 2.5 L/min/m²) emerged as the strongest independent predictor of all-cause mortality (HR 3.126; 95% CI 2.584–3.668; $p < 0.0001$). These findings extend and complement a growing body of evidence on the prognostic significance of RV assessment after acute PE, while introducing several novel elements that merit comparison with prior work.

The demographic profile of our cohort (mean age 72 ± 15 years, 45.5% male, 20.5% active cancer, 12.8% prior VTE) is broadly comparable to that of other prospective studies in intermediate-risk PE.

Kokalj et al. enrolled 615 patients with low- and intermediate-risk PE (mean age 64 ± 18 years, 46% male) and followed them for a median of 1,068 days, reporting a 14.3% all-cause mortality rate (151). The older age and higher comorbidity burden in our cohort, likely account for the higher observed mortality (25% at a median of 65 months). **Grifoni et al.** studied 209 patients with acute PE (mean age 68 years) and focused on recurrent VTE rather than all-cause mortality, reporting a cumulative recurrence rate approaching 40% at 4 years in patients with persistent echocardiographic RVD at discharge (152). **Terluk et al.** evaluated 233 PE patients (follow-up 3.0 ± 2.1 years) and found that 61 (26.2%) died, a mortality rate remarkably similar to ours, although their cohort was not restricted to intermediate-high risk patients (153). The large Swedish registry study by **Tavoly et al.** (49,596 cancer-free PE patients) reported a one-year mortality of 7.5% and demonstrated that excess mortality persisted beyond 3 years (aHR 1.54; 95% CI 1.46–1.63), with heart failure (aHR 1.97) and liver disease (aHR 2.17) as the strongest predictors (154). Our longer median follow-up of 65 months and the inclusion of patients with active cancer (20.5%) may explain the higher cumulative mortality observed in our cohort.

Right ventricular dysfunction: invasive versus non-invasive assessment

A central distinguishing feature of the present study is the use of **invasive haemodynamic criteria to define RVD**, in contrast to the echocardiographic or CT-based definitions employed by most prior investigations. Our invasive definition of RVD yielded a comparable hazard ratio (3.126), suggesting that the prognostic signal is robust regardless of the assessment modality, but the invasive approach offers the additional advantage of simultaneously quantifying parameters such as PAPi, RVSWI, PVC, and SvO_2, which are not obtainable by echocardiography alone.

Kokalj et al. found that among echocardiographic parameters, only tricuspid regurgitation systolic velocity independently predicted long-term mortality (HR 1.73 per 1 m/s increase; p = 0.037), while other markers of RV dysfunction (RV dilation, TAPSE) did not retain significance in multivariable analysis (151). Similarly, in our study, echocardiographic parameters such as TAPSE and systolic pulmonary artery pressure did not differ significantly between deceased and surviving patients (p = 0.5 and p = 0.6, respectively), whereas invasive haemodynamic markers, particularly mRAP (14 ± 3 vs. 5 ± 2 mmHg, p = 0.001), CI (1.8 ± 0.4 vs. 2.5 ± 0.6 L/min/m², p = 0.001), and SvO_2 (63 ± 3% vs. 72 ± 4%, p = 0.01), showed highly significant differences. This discrepancy underscores a potential limitation of echocardiographic assessment and supports the added value of invasive haemodynamic profiling.

Terluk et al. demonstrated that a composite of three echocardiographic markers (RVPLAX > 37 mm, RA area > 20 cm², TR velocity > 2.9 m/s) yielded a ~17-fold increased mortality risk when all three were present (HR 16.9; 95% CI 6.1–47.2), suggesting that combining multiple echocardiographic parameters may partially compensate for the limitations of individual measurements (153). However, even this composite approach does not capture the haemodynamic granularity provided by RHC.

Novel haemodynamic parameters: PAPi, RVSWI, and pulmonary vascular compliance

The present study is, to our knowledge, the first to demonstrate the long-term prognostic value of PAPi (HR 1.125; 95% CI 1.095–1.155; p < 0.0001) and RVSWI (HR 1.025; 95% CI 1.168–1.242; p < 0.0001) measured invasively in the post-acute PE setting.

PAPi has been extensively studied in advanced heart failure and cardiogenic shock, where it reflects the interplay between RV contractility and afterload, but its application to PE prognosis has been limited (155). **Moady et al.** recently evaluated echocardiography-derived PAPi in 177 patients with acute PE and found that lower PAPi was associated with increased 30-day mortality ($p < 0.05$) and higher rates of RV failure ($p < 0.001$), and was superior to TAPSE in predicting both outcomes (156). Our findings extend these observations to the long-term setting and confirm the prognostic superiority of PAPi over conventional echocardiographic markers, now validated with invasive measurements and over a substantially longer FU period.

The observation that pulmonary vascular compliance (PVC) was markedly reduced in deceased patients (1.68 ± 0.28 vs. 3.14 ± 0.55 mL/mmHg, $p = 0.001$) while pulmonary vascular resistance (PVR) did not differ between groups (1.8 ± 0.4 vs. 2.4 ± 0.4 Wood units, $p = 0.3$) is consistent with the concept that **compliance is a more sensitive marker of pulmonary vascular disease than resistance. Maron et al.** highlighted that pulmonary arterial compliance has stronger associations with RVD and heart failure prognosis than PVR, and that compliance falls precipitously with even mild increases in PVR (157). Our data support the notion that PVC may detect subclinical pulmonary vascular impairment that PVR fails to capture, and suggest that compliance should be incorporated into the haemodynamic assessment of post-PE patients.

Haemodynamic profile comparison with acute PE registries

The haemodynamic values observed in our deceased patient group (mRAP 14 ± 3 mmHg, CI 1.8 ± 0.4 L/min/m², SvO_2 63 ± 3%) are strikingly similar to those reported in the FLASH registry for intermediate-risk PE patients with normotensive cardiogenic shock undergoing mechanical thrombectomy (mRAP 11.9 ± 6.24 mmHg, CI 1.81 ± 0.30 L/min/m², SvO_2 52.9% ± 10.1%) (138). This comparison is particularly noteworthy because the FLASH data were obtained during the acute phase, whereas our measurements were performed at hospital discharge (9 ± 3 days after admission). The persistence of a haemodynamic profile resembling acute normotensive shock at the time of discharge identifies a subgroup of patients whose RV has failed to recover adequately and who carry a markedly elevated long-term mortality risk.

Serial haemodynamic assessment and dynamic RVD

The 6-month repeat RHC protocol revealed important dynamic changes in RV function: 57.1% of patients with RVD at discharge showed resolution, while 47.1% of patients without initial RVD developed it during follow-up. This bidirectional evolution of RV function has not been well characterized in prior studies using invasive assessment. The FOCUS study (1,017 patients) reported a 2-year cumulative CTEPH incidence of 2.3% and post-PE impairment (PPEI) in 16% of patients, with PPEI strongly predicting subsequent CTEPH diagnosis (HR 393; 95% CI 73–2,119) (158). While the FOCUS study relied on clinical, functional, and imaging criteria rather than invasive haemodynamics, the high rate of new-onset RVD at 6 months in our cohort (20 patients) raises the possibility that a subset of these patients may represent early chronic thromboembolic pulmonary disease, a hypothesis that warrants further investigation.

A systematic review and meta-analysis by **Wang et al.** (2023), including 33 studies and 3,920 patients, reported that the pooled prevalence of long-term RVD after acute PE was 34% at 3 months, 26% at 6 months, and 34% at 1 year (159).

Sista et al. (2017) reported a pooled prevalence of persistent RVD of 18.1% across 26 studies with a median follow-up of 18 months (160).

In the PEITHO-2 study, **Mavromanoli et al.** (2023) found that while the majority of intermediate-risk PE patients showed RV recovery within 6 days of early anticoagulation switch, almost one in four continued to have evidence of RVD at 6 months (161).

These data are consistent with the present study's observation that 42.9% of patients with RVD at discharge (21/49) remained in a state of RVD at 6 months, while 20 additional patients (who did not have RVD at discharge) developed it during follow-up. This dynamic pattern — with both persistence and new-onset RVD — underscores the **importance of serial haemodynamic assessment and supports the study's protocol of repeat RHC at 6 months.**

Right Ventricular Dysfunction: The Central Prognostic Determinant

The present study demonstrates that **invasively defined right ventricular dysfunction (RVD) is the strongest independent predictor of long-term all-cause mortality** after intermediate-high risk acute PE.

In the multivariable Cox regression analysis (Table 9), RVD at discharge carried a hazard ratio of 4.234 (95% CI 2.864–5.604, $p < 0.0001$), and this effect was dramatically amplified when persistent RVD, confirmed by repeat RHC at 6 month, was incorporated into the model (Table 10): persistent RVD emerged as the single most powerful predictor of death, with an HR of 8.56 (95% CI 5.660–11.460, $p < 0.0001$), rendering all other haemodynamic variables (baseline RVD, PAPi, RVSWI) non-significant.

The Kaplan–Meier analysis (Figure 16) confirmed a dramatic survival separation between patients with and without persistent RVD (log-rank = 65.8, $p < 0.0001$). Notably, RVD was present in 35 of 39 deceased patients (89.7%) compared with only 10 of 117 survivors (8.7%, $p < 0.0001$), underscoring the near-universal association between persistent haemodynamic impairment and death in this population.

These findings are consistent with, but substantially extend, the existing literature. The largest meta-analytic evidence comes from Prosperi-Porta et al. (2022), who pooled 55 studies encompassing 17,090 haemodynamically stable PE patients and found that echocardiographic RVD was associated with all-cause mortality (OR 2.00; 95% CI 1.66–2.40) and PE-related mortality (OR 4.01; 95% CI 2.79–5.78) (162). Among intermediate-risk patients specifically, RVD conferred an even higher odds of PE-related death (OR 6.16; 95% CI 1.33–28.4) (162). The 2026 AHA/ACC PE guidelines cite an individual patient data meta-analysis of 5,010 patients demonstrating that RVD was associated with short-term death (OR 4.81; 95% CI 1.98–11.68) and PE-related death (OR 22.9; 95% CI 2.89–181) (45).

However, these studies assessed RVD using echocardiographic or CT-based surrogates and focused predominantly on short-term outcomes (30-day or in-hospital mortality). The present study is unique in demonstrating that invasively defined RVD (using the composite haemodynamic criteria of mRAP ≥ 8 mmHg, PCWP < 15 mmHg, and CI < 2.5 L/min/m²) carries even greater prognostic weight over a median follow-up of 65 months, with hazard ratios substantially exceeding those reported in echocardiography-based studies.

Superiority of Invasive Over Non-Invasive Assessment

A critical finding of the present study is that while echocardiographic parameters such as RV EDD > 30 mm ($p = 0.01$) and RV/LV ratio > 0.9 ($p = 0.001$) were significantly associated with mortality

in univariable analysis (Table 8), **none retained independent significance in the multivariable model** (Table 9): RV EDD > 30 mm (HR 1.006, p = 0.65), RV/LV ratio > 0.9 (HR 1.025, p = 0.1), TAPSE (HR 1.020, p = 0.2), and sPAP (HR 1.018, p = 0.25) all lost significance when invasive haemodynamic parameters were included.

This finding is consistent with the observation by Kokalj et al. that **most echocardiographic RVD parameters failed to independently predict long-term mortality** (151)**.** In contrast, the invasive haemodynamic parameters, particularly PAPi (multivariable HR 1.055, p = 0.01) and RVSWI (multivariable HR 1.215, p = 0.001), retained independent significance; and the composite invasive RVD definition was by far the strongest predictor (HR 4.234, p < 0.0001).

This suggests that RHC provides prognostic information that cannot be fully captured by non-invasive imaging, likely because it directly measures the haemodynamic consequences of RV failure (elevated filling pressures, reduced cardiac output) rather than relying on morphological surrogates.

Moady et al. (2025) demonstrated that echocardiography-derived PAPi was associated with 30-day mortality and RV failure in 177 acute PE patients and was superior to TAPSE in predicting both outcomes (156).

Sławek-Szmyt et al. (2022) showed that invasive PAPi with a cut-off of 3.9 predicted RV failure-related mortality in inoperable CTEPH (log-rank p < 0.0001), with the low-PAPi group having significantly higher mRAP (14.9 vs. 7.8 mmHg, p = 0.0001) (163).

The present study extends these findings to the long-term PE setting, demonstrating that invasive PAPi (1.57 ± 0.6 in deceased vs. 4.20 ± 1.0 in survivors, p < 0.0001) and RVSWI (3.5 ± 1.2 vs. 13.5 ± 2.2, p < 0.0001) are powerful discriminators of long-term mortality; though both are ultimately subsumed by the persistent RVD variable in the final model (Table 10).

Strengths

The present study has several notable strengths.

First, it is one of the few prospective studies to employ comprehensive invasive haemodynamic assessment in the post-acute PE setting, providing direct measurements of parameters (PAPi, RVSWI, PVC, mRAP/PCWP ratio) that are not obtainable by non-invasive methods.

Second, the 10-year enrollment period and median follow-up of 65 months represent the longest reported follow-up for this type of haemodynamic evaluation, allowing assessment of truly long-term prognostic significance.

Third, the serial RHC protocol at discharge and 6 months provides unique insight into the dynamic evolution of RV function, capturing both recovery and deterioration trajectories.

Fourth, the use of a composite invasive definition of RVD (mRAP $\geq$ 8 mmHg, PCWP < 15 mmHg, CI < 2.5 L/min/m^2) integrates multiple haemodynamic dimensions into a single clinically actionable classification.

Fifth, the prospective, consecutive enrollment design minimizes selection bias within the single-center framework.

Limitations

Several limitations should be acknowledged.

First, this is a single-center study with a relatively modest sample size (n = 156), which limits the generalizability of the findings and the statistical power for subgroup analyses. By comparison, Kokalj et al. enrolled 615 patients, Terluk et al. 233 patients, and registry-based studies such as Tavoly et al. and Mandigers et al. included tens of thousands of patients (151,153,154,164).

Second, the invasive nature of RHC inherently limits its applicability as a routine risk stratification tool; echocardiographic assessment, while less precise, is more widely available and carries lower procedural risk.

Third, the study endpoint was exclusively all-cause mortality, and cause-specific mortality (PE-related vs. non-PE-related) was not adjudicated, which limits the ability to determine whether the observed deaths were directly attributable to persistent RVD or to competing causes, particularly given the high prevalence of active cancer (20.5%) and advanced age (72 ± 15 years) in the cohort.

Fourth, the 6-month repeat RHC was offered to all patients but was not mandatory, and the proportion of patients who declined or were unable to undergo the second catheterization is not specified, introducing potential attrition bias.

Fifth, the study did not incorporate advanced imaging modalities such as cardiac MRI, which could have provided complementary information on RV volumes, fibrosis, and myocardial strain.

Finally, the absence of a formal comparison with established risk stratification scores (PESI, sPESI) or biomarker-based algorithms limits the ability to determine the incremental prognostic value of invasive haemodynamic assessment over currently recommended non-invasive approaches.

Summary

In conclusion, the present study provides the strongest evidence to date that **persistent RVD, defined by invasive haemodynamic criteria and confirmed by serial RHC, is the single most powerful predictor of long-term all-cause mortality after intermediate-high risk acute PE**. The magnitude of the prognostic effect (HR 8.56) far exceeds that reported in any prior echocardiography-based study, and the addition of persistent RVD to the prognostic model rendered all other haemodynamic variables non-significant (Table 10, model χ^2 increased from 30.8 to 63.4, $p = 0.0001$). These findings support the concept that invasive haemodynamic assessment at discharge and at 6 months provides uniquely valuable prognostic information that cannot be replicated by non-invasive imaging alone, and that persistent RVD should be considered a key target for risk stratification and potentially for therapeutic intervention in PE survivors.

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