



Universiteit
Leiden
The Netherlands

Risk stratification of acute pulmonary embolism

Roy, P.M.; Sanchez, O.; Huisman, M.; Jimenez, D.

Citation

Roy, P. M., Sanchez, O., Huisman, M., & Jimenez, D. (2024). Risk stratification of acute pulmonary embolism. *La Presse Médicale*, 53(3). doi:10.1016/j.lpm.2024.104243

Version: Publisher's Version

License: [Licensed under Article 25fa Copyright Act/Law \(Amendment Taverne\)](#)

Downloaded from: <https://hdl.handle.net/1887/4283251>

Note: To cite this publication please use the final published version (if applicable).



Available online at
ScienceDirect
 www.sciencedirect.com

Elsevier Masson France
EM|consulte
 www.em-consulte.com



Quarterly Medical Review - Venous thromboembolic disease: a tribute to Professor Guy Meyer

Risk stratification of acute pulmonary embolism



Pierre-Marie Roy^{1,2,3}, Olivier Sanchez^{3,4,5}, Menno Huisman⁶, David Jimenez^{7,8,9,*}

¹ CHU Angers, 4 rue Larrey, Emergency Department, Angers F-49000, France

² Univ. Angers, INSERM, CNRS, MITOVASC, Equipe CARME, SFR ICAT, Angers, France

³ F-CRIN, INNOVTE, Saint-Etienne, France

⁴ University of Paris, INSERM UMR-S 1140 Innovat Therapies in Haemostasis, Paris, France

⁵ Hôpital Européen Georges Pompidou, APHP, Pneumology Department and Intensive Care, 20-40 rue Leblanc, Paris F-75908, France

⁶ Leiden University Medical Center, Department of Medicine - Thrombosis and Hemostasis, Leiden, the Netherlands

⁷ Ramón y Cajal Hospital (IRICYS), Respiratory Department, Madrid, Spain

⁸ Universidad de Alcalá (IRICYS), Medicine Department, Madrid, Spain

⁹ CIBER de Enfermedades Respiratorias (CIBERES), Madrid, Spain

ARTICLE INFO

Article History:

Available online 5 September 2024

Keywords:

Pulmonary embolism
 Mortality
 Prognostication
 Survival

ABSTRACT

Risk stratification of patients with acute pulmonary embolism (PE) assists with the selection of appropriate initial therapy and treatment setting. Patients with acute symptomatic PE that present with arterial hypotension or shock have a high risk of death, and treatment guidelines recommend strong consideration of reperfusion in this setting. For haemodynamically stable patients with PE, the combination of a negative clinical prognostic score and the absence of computed tomography-assessed right ventricle enlargement may accurately identify those at low-risk of short-term complications after the diagnosis of PE, and such patients might benefit from an abbreviated hospital stay or outpatient therapy. Some evidence suggests that the accumulation of factors indicating worse outcomes from PE on standard anticoagulation identifies the more severe stable patients with acute PE who might benefit from intensive monitoring and recanalization procedures, particularly if haemodynamic deterioration occurs. Current risk classifications have several shortcomings that might adversely affect clinical and healthcare decisions. Ongoing initiatives aim to address many of those shortcomings, and will hopefully help optimize risk stratification algorithms and treatment strategies.

© 2024 Elsevier Masson SAS. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

1. Introduction

Once the diagnosis of acute symptomatic pulmonary embolism (PE) is objectively confirmed, accurate risk stratification is key for selecting the optimal treatment (i.e., anticoagulation, systemic thrombolysis, percutaneous interventions, surgical embolectomy) and intensity of care (i.e., outpatient, hospitalization, intermediate care unit, intensive care unit) for patients [1,2]. Risk stratification and use of a management pathway for patients with PE reduces the length of hospital stay without compromising safety [3]. In a randomized, controlled trial that enrolled 498 stable adults with acute PE, patients were assigned to a prognostic assessment and management pathway involving risk stratification, followed by predefined criteria for mobilization and discharge (intervention group), or usual care (control group). The median length of

hospital stay was 4 days (interquartile range [IQR], 3.7 to 4.2 days) in the intervention group and 6.1 days (IQR, 5.7 to 6.5 days) in the control group ($P < 0.001$). The intervention resulted in a net reduction in the mean hospitalization costs, and did not adversely affect patient outcomes [3].

In addition, risk stratification "per se" might be associated with increased short-term survival [4]. In a retrospective cohort study that included 2096 patients with acute symptomatic PE, lack of prognostic assessment was independently significantly associated with 30-day all-cause mortality (adjusted odds ratio [OR], 1.7; 95 % confidence interval [CI], 1.1 to 2.6; $P = 0.01$).

2. Current risk stratification schemas

Several international scientific societies have proposed risk classification schemas for patients with acute symptomatic PE (Table 1). Of them, the European Society of Cardiology (ESC) schema is the most widely used [1].

* Corresponding author.

E-mail address: djimenez.hrc@gmail.com (D. Jimenez).

Table 1
Recommendations from major international medical societies for risk stratification of acute pulmonary embolism.

Society	Recommendations
ACCP [2]	<i>Low-risk PE</i> : negative PESI or sPESI. Absence of RV dysfunction or increased cardiac biomarker levels. <i>Deteriorating PE (but still without hypotension)</i> : progressive increase in heart rate, a decrease in SBP (which remains >90 mmHg), an increase in jugular venous pressure, worsening gas exchange, signs of shock (eg, cold sweaty skin, reduced urine output, confusion), progressive RV dysfunction on echocardiography, or an increase in cardiac biomarkers. <i>PE with hypotension</i> : SBP <90 mmHg.
AHA [5]	<i>Low-risk PE</i> : Stable patients who do not meet criteria for submassive PE. <i>Submassive PE</i> : RV strain without hypotension. <i>Massive PE</i> : hypotension, defined as a SBP <90 mm Hg or a decrease in SBP ≥40 mmHg from baseline, or need for vasopressor support.
ASH [6]	<i>Low risk PE</i> : negative PESI or sPESI. <i>Submassive PE</i> : echocardiography and/or biomarkers compatible with RV dysfunction but without hemodynamic compromise. <i>Massive PE</i> : Haemodynamic compromise (defined as a SBP <90 mmHg or a decrease in systolic blood pressure ≥40 mmHg from baseline).
ESC/ERS [1]	<i>Low-risk PE</i> : stable patients with a negative clinical rule (i.e., PESI, sPESI or Hestia) and absence of RV dysfunction on TTE or CT angiogram. If assessed, absence of increased cardiac biomarker levels. <i>Intermediate-low-risk PE</i> : stable patients who do not meet criteria for low- or intermediate-high risk PE. <i>Intermediate-high risk PE</i> : stable patients with a positive clinical rule who display evidence of both RV dysfunction (on echocardiography or CT angiogram) and elevated cardiac biomarker levels in the circulation (particularly a positive cardiac troponin test). <i>High-risk PE</i> : haemodynamic instability defined as one of the following clinical presentations: cardiac arrest, obstructive shock (SBP <90 mmHg or vasopressors required to achieve a SBP >90 mmHg despite an adequate filling status, in combination with end-organ hypoperfusion), or persistent hypotension (SBP <90 mmHg or a SBP drop >40 mmHg for >15 min, not caused by new-onset arrhythmia, hypovolaemia, or sepsis).

Abbreviations: ACCP, American College of Chest Physicians; PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index; sPESI, simplified Pulmonary Embolism Severity Index; RV, right ventricle; SBP, systolic blood pressure; AHA, American Heart Association; ASH, American Society of Hematology; ESC, European Society of Cardiology; ERS, European Respiratory Society; TTE, transthoracic echocardiography; CT, computed tomography.

2.1. Identification of high-risk PE

The first critical step is identification of haemodynamically unstable patients (i.e., *high-risk* PE) with acute PE. Haemodynamic instability is defined as one of the following clinical presentations: cardiac arrest, obstructive shock (systolic blood pressure [SBP] <90 mmHg or vasopressors required to achieve a SBP >90 mmHg despite an adequate filling status, in combination with end-organ hypoperfusion), or persistent hypotension (SBP <90 mmHg or a SBP drop >40 mmHg for >15 min, not caused by new-onset arrhythmia, hypovolaemia, or sepsis). The treatment of choice for high-risk patients with acute PE is reperfusion (systemic fibrinolysis, catheter-directed therapies, or surgical embolectomy) added to parenteral anticoagulation [1,2,5,6].

In the remaining group of patients with PE who present without haemodynamic instability, further risk stratification aims at differentiating patients with a favorable prognosis (*low-risk* PE) for consideration of outpatient treatment, from those deemed as having a high risk for PE-related adverse clinical events (*intermediate-high risk* PE) for close observation and consideration of escalation of therapy.

2.2. Identification of low-risk PE

According to recent guidelines, low-risk PE patients are identified by the combination of a negative clinical prognostic score and the absence of right ventricle (RV) enlargement/dysfunction (by computed tomography [CT] pulmonary angiogram or transthoracic echocardiography) [1]. Among clinical prognostic scores, some have a high sensitivity and are intended to identify low-risk patients (e.g., Pulmonary Embolism Severity Index [PESI], simplified PESI [sPESI] or Hestia criteria) (Table 2) [7–9]; while others have a higher specificity and may assist with classification of patients into intermediate-high risk categories (Table 3) [10–13].

The international HOME-PE study randomized 1970 normotensive patients with acute PE to a triaging strategy for home therapy based on the Hestia criteria vs. a strategy based on the sPESI [14]. The primary outcome was composed of recurrent venous thromboembolic disease (VTE), major bleeding, or all-cause mortality within 30 days after randomization. In the per-protocol population, the primary outcome occurred in 3.82% in the Hestia arm and 3.57% in the sPESI arm (P = 0.004 for non-inferiority). In the intention-to-treat population, 38.4 % of the Hestia patients were treated at home vs. 36.6 % of the sPESI patients (P = 0.41 for superiority), with a 30-day composite outcome rate of 1.3 % and 1.1 %, respectively. There were no recurrent or fatal PEs in either group of the trial.

Recently, investigators used a cohort of haemodynamically stable patients from the Registro Informatizado de la Enfermedad TromboEmbólica (RIETE) registry to compare the false-negative rate for 30-day all-cause and PE-related mortality of four strategies: the

Table 2
Scores for identification of low-risk patients with acute PE.

A) Simplified Pulmonary Embolism Severity Index	
Variable	Points
Age >80 years	1
History of cancer	1
History of chronic cardiopulmonary disease	1
Pulse ≥110 beats/min	1
Systolic blood pressure <100 mm Hg	1
Arterial oxyhemoglobin saturation (SaO ₂) <90 %	1
B) Hestia criteria	
Variable	
Hemodynamically unstable?*	
Thrombolysis or embolectomy necessary?	
Active bleeding or high risk of bleeding?†	
Oxygen supply to maintain oxygen saturation > 90 % > 24 h?	
Pulmonary embolism diagnosed during anticoagulant treatment?	
Intravenous pain medication > 24 h?	
Medical or social reason for treatment in the hospital > 24 h?	
Creatinine clearance of less than 30 mL/min?‡	
Severe liver impairment?§	
Pregnant?	
Documented history of heparin-induced thrombocytopenia?	

A/ A total point score for a given patient is obtained by summing the points. The score corresponds with the following risk classes: 0, low risk; ≥ 1, high risk.

B/ If one of the questions is answered with YES, the patient cannot be treated at home.

* Include the following criteria, but scoring is left to the discretion of the investigator: systolic blood pressure < 100 mmHg with heart rate > 100 beats per minute; condition requiring admission to an intensive care unit.

† Gastrointestinal bleeding in the preceding 14 days, recent stroke (less than 4 weeks ago), recent operation (less than 2 weeks ago), bleeding disorder or thrombocytopenia (platelet count < 75 × 10⁹/L), uncontrolled hypertension (systolic blood pressure > 180 mm Hg or diastolic blood pressure > 110 mm Hg).

‡ Calculated creatinine clearance according to the Cockcroft-Gault formula.

§ Left to the discretion of the physician.

Table 3
Scores for identification of intermediate-high risk patients with acute PE.

A) 2019 ESC model	
Combination of a positive clinical rule plus right ventricle dysfunction plus elevated troponin.	
B) PEITHO-3 model	
Combination of right ventricle dysfunction plus elevated troponin plus one of the following: Systolic blood pressure ≤110 mmHg Oxygen saturation <90 % on room air History of chronic heart failure	
C) Bova score	
Predictor variable	Points
Systolic blood pressure 90–100 mm Hg	2
Cardiac troponin elevation	2
Right ventricular dysfunction (echocardiogram or computed tomography)	2
D) Modified FAST score	
Predictor variable	Points
Positive cardiac troponin I	1.5
Syncope	1.5
Heart rate ≥100 beats per minute	2

A/ Abbreviations: PESI, Pulmonary Embolism Severity Index; C/ Points are assigned for the presence of each variable. The sum of the variable points produces the total point score (Bova risk score; range, 0–7). Bova risk staging increased with point totals: stage I (0–2 points), stage II (3–4 points), or stage III (> 4 points); D/ Points are assigned for the presence of each variable. The sum of the variable points produces the total point score (FAST risk score; range, 0–5). Patients are low-risk if the sum of the points is <3, and intermediate-high risk if the sum of the points is ≥3.

sPESI; a modified (i.e., heart rate cutoff of 100 beats/min) sPESI; and a combination of the original and the modified sPESI with CT-assessed RV/left ventricle (LV) ratio [15]. Among patients identified as low-risk, the 30-day mortality rate was lowest with the combination of a modified sPESI and CT-assessed RV/LV ratio and highest with the sPESI (0.4 % versus 1.0 %; *P* = 0.03). The 30-day PE-related mortality rates for patients designated as low-risk by the sPESI, the modified sPESI, and the combination of the original and modified sPESI with CT-assessed RV/LV ratio were 0.7 %, 0.4 %, 0.7 %, and 0.2 %, respectively.

An individual patient data meta-analysis that included 5010 PE patients at low-risk for death based on clinical prognostic models showed that elevated troponin (OR, 2.8; 95 % CI, 1.1 to 7.3) and elevated brain natriuretic peptide (BNP) (OR, 6.7; 95 % CI, 1.3 to 34.6) were associated with short-term death [16]. However, whether the addition of a negative troponin or BNP test to the combination of a negative clinical model plus the absence of RV enlargement in the CT scan is clinically useful for identifying low-risk PE patients lacks formal proof. Therefore, clinical practice guidelines do not routinely recommend cardiac biomarker testing to classify patients with acute PE in the low-risk category [1].

In summary, clinicians might use the Hestia criteria or the sPESI (preferably, the modified version) in combination with the CT-assessed RV/LV ratio to select low-risk PE patients who might benefit from home therapy (i.e., discharge in the first 24 h after diagnosis) of their disease. This information is available for the vast majority of patients at the time of PE diagnosis (i.e., most are diagnosed with a CT scan), and studies have shown that the risk of short-term complications in those with a negative clinical rule and a normal CT-assessed RV size is very low.

2.3. Identification of intermediate-high risk PE

Haemodynamically stable patients with acute PE who have a positive Hestia rule (or a positive sPESI) and/or a CT-assessed RV/LV ratio >1 and/or an elevated troponin testing (if it was ordered) constitute a group with an *intermediate-risk* for short-term complications [17].

Within this subgroup of patients, there is great interest to identify those who are at highest risk of early adverse events, such as death, or hemodynamic collapse requiring pharmacological or mechanical circulatory support (i.e., *intermediate-high risk PE*) [1]. Historically, the guidelines have designated intermediate-high risk patients as those who have evidence of myocardial injury and also RV enlargement/dysfunction [1]. However, findings from the Pulmonary Embolism Thrombolysis Trial (PEITHO) suggested relatively low event rates among participants, all of whom met these criteria [18]. Therefore, investigators have developed models with a higher specificity, that may help identify patients with acute PE at intermediate-high risk for short-term PE-related complications [10–13].

The latest ESC guidelines suggest a combination of an sPESI of 1 or greater, myocardial injury and RV dysfunction to identify intermediate-high risk patients [1]. Using data from the PEITHO trial, investigators retrospectively developed a new set of criteria (myocardial injury, RV dysfunction and ≥1 of the following: systolic blood pressure <110 mmHg, oxygen saturation <90 % on room air, history of chronic heart failure) [10] that are being used in the ongoing PEITHO-3 trial [19]. The Bova score was also derived and has been validated for identifying patients with intermediate-high risk acute PE [11,20]. The score consists of 4 variables assessed at the time of PE diagnosis: two clinical variables (i.e., heart rate and systolic blood pressure), a laboratory biomarker (i.e., cardiac troponin), and a marker of RV dysfunction (i.e., RV size/function measured by echocardiography or CT scan). FAST (H-FABP, Syncope, Tachycardia) combines heart-type fatty acid binding protein (H-FABP) (>6 ng/mL), heart rate (>110 bpm) and syncope, and predicts 30-day complications in stable patients with acute PE [12]. A study that included 848 hemodynamically stable patients with acute symptomatic PE from the PROgnosTic valUe of Computed Tomography scan in haemodynamically stable patients with acute symptomatic PE (PROTECT) cohort compared the ability of these 4 models (ESC, PEITHO III, Bova and FAST) for predicting a 30-day complicated clinical course (defined as death from any cause, hemodynamic collapse and/or recurrent PE) [21]. The proportion of intermediate-high risk patients was 6.7 % with the ESC model, 5.2 % with the PEITHO III criteria, 4.4 % with the Bova score, and 15.7 % with the modified FAST score. Among intermediate-high risk patients, a complicated clinical course was more common with the Bova score (21.6 %) than with the ESC model (17.5 %), the PEITHO III criteria (15.9 %) or the modified FAST score (14.3 %).

Using data from 500 patients with intermediate-risk PE enrolled in the prospective, multicenter FLASH registry (FlowTrierer All-Corner Registry for Patient Safety and Hemodynamics), investigators derived a composite score that identified stable patients with a low cardiac index by invasive haemodynamics [13]. The composite PE shock (CPES) score is based on markers of RV function (i.e., moderate or severe echocardiographic RV dysfunction, elevated B-type natriuretic peptide [BNP]) and ischemia (i.e., elevated troponin), central thrombus burden (i.e., saddle PE), potential additional thrombus embolization (i.e., concomitant deep vein thrombosis [DVT]), and cardiovascular compensation (i.e., tachycardia). A recent study showed that, at a threshold of 3 points for a positive test, the CPES score classified nearly 10 % of patients with PE as positive, and the specificity and positive predictive value for a complicated course were high [22].

In summary, observational studies have suggested that the accumulation of factors indicating worse outcomes from PE on standard anticoagulation identifies the more severe intermediate-high risk patients with acute PE who might benefit from intensive monitoring and recanalization procedures if haemodynamic deterioration occurs.

3. Limitations of current strategies for pulmonary embolism prognostication

Current risk classification schemas for patients with acute symptomatic PE may have several shortcomings: i) heterogeneity of risk

classes; ii) lack of relationship between the outcomes and the therapeutic options; iii) use of a limited number of prognostic tests; and iv) similar risk thresholds for reperfusion therapies with different risk-benefit ratios.

3.1. Heterogeneity of risk classes

The existing risk stratification tools, including those by the ESC guidelines (1), show marked heterogeneity in actual risk within the strata, which are composed of patients with different short-term prognosis, and who might not benefit from uniform treatment recommendations (e.g., anticoagulation and outpatient treatment for low-risk PE; anticoagulation and monitoring for intermediate-high risk PE).

3.2. Lack of relationship between the outcomes and the therapeutic options

The outcomes assessed by prognostic tools for patients with acute PE should have a relationship to the therapeutic options. Recently, an international expert panel identified six clinical outcomes that might be employed to evaluate the safety of prognostic strategies identifying low-risk patients with PE: 1) new onset of hypoxemia requiring oxygen or ventilatory support; 2) new onset of severe hypotension; 3) new confirmed symptomatic cardiac arrhythmia requiring urgent treatment; 4) major bleeding; 5) symptomatic VTE recurrence; 6) death possibly or confirmed to be related to PE. Importantly, the optimal timing for assessing outcomes was set at 7 days after discharge (Servent M, personal communication).

3.3. Limited number of prognostic tests

Clinical practice guidelines schemas employ a limited number of prognostic tests to risk classify patients with acute symptomatic PE (mainly a highly sensitive clinical prognostic model [i.e., Hestia criteria or sPESI], cardiac troponins, and assessment of RV size/function). Given the expansion of options in anticoagulation and reperfusion therapy, these criteria may appear insufficient for providing personalized treatment recommendations.

New prognostication strategies should include variables associated with medical history and physical examination (e.g., age, comorbidities [including new-onset atrial fibrillation], concomitant medications, systolic blood pressure, heart rate), general laboratory testing (haemoglobin, leukocyte count, platelet count, creatinine), and tests that assess for the presence and the degree of hypoxemia, RV dysfunction (e.g., electrocardiogram, CT, echocardiography, BNP, N-terminal-proBNP, adrenomedullin [23]), myocardial injury (e.g., troponins, high-sensitivity troponins, heart-type fatty acid-binding protein [H-FABP]), clot burden in the proximal veins, in the right heart and in the pulmonary arteries (e.g., D-dimer, lower limb venous compression ultrasonography, echocardiography, contrast-enhance PE-protocol chest CT), organ perfusion (e.g., lactate [24], copeptin [25]), and possibly biomarkers of systemic inflammation (Table 4). The contribution of such models to PE prognostication, compared to the existing ones, will require further assessment.

3.4. Similar thresholds for different reperfusion therapies

Although the vast majority of randomized clinical trials have only evaluated the efficacy and safety of full-dose systemic thrombolysis

Table 4
Pulmonary embolism markers of severity.

Clinical variables	Heart rate [29] Blood pressure [8] Oxygen saturation [8] Respiratory rate [7] Temperature [7] Syncope [30] Diuresis [31] Consciousness [7]	These clinical variables are usually combined into clinical prognostic scores (eg, PESI, sPESI, Hestia criteria).
Comorbidities	Chronic pulmonary disease [8] Heart failure [8] Cancer [8] Atrial fibrillation [32]	Aggravating conditions and comorbidities identify patients who might not benefit from full outpatient therapy.
Inflammation	Cytokines [33] Erythrocyte sedimentation rate [33] Fibrinogen [33] Leukocyte count [34]	Information on the prognostic significance of different inflammatory biomarkers is still scarce.
Tissue hypoxia	Lactate [24] Copeptin [25]	Lactate may reflect tissue hypoperfusion also in the presence of normal blood pressure.
Acute kidney injury	Creatinine [35] Neutrophil gelatinase-associated lipocalin [35] Cystatin C [35]	Renal dysfunction is one of the generally accepted indications of an increased mortality in various cardiovascular diseases, including PE.
Right ventricular dysfunction	ECG [36] Echocardiogram [37] Computed tomography [38] BNP or NT-proBNP [39] Proadrenomedullin [23]	RV enlargement/dysfunction is associated with an elevated risk of short-term mortality in patients who appear haemodynamically stable at presentation.
Clot burden	Concomitant DVT [40] D-dimer [41] CT angiogram [42]	Although life-threatening PE has traditionally been equated with anatomically massive PE (defined as a > 50 % obstruction of the pulmonary vasculature or the occlusion of two or more lobar arteries), it seems reasonable to propose that the outcome from PE is a function of both the size of the embolus and the underlying cardiopulmonary function.
Myocardial injury	cTnl or cTnT [43] hsTnT [44] H-FABP [45]	A meta-analysis showed that elevated troponin concentrations were associated with an increased risk of mortality, both in unselected patients (OR 5.2; 95 % CI, 3.3–8.4) and in those who were haemodynamically stable at presentation (OR 5.9; 95 % CI, 2.7–13.0).

Abbreviations: PESI, Pulmonary Embolism Severity Index; sPESI, simplified Pulmonary Embolism Severity Index; PE, pulmonary embolism; ECG, electrocardiogram; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; RV, right ventricle; DVT, deep vein thrombosis; CT, computed tomography; cTnl, cardiac troponin I, cTnT, cardiac troponin T; hsTnT, high-sensitivity troponin T; H-FABP, heart-type fatty acid binding protein.

Table 5
Randomized controlled trials testing the efficacy and safety of different mode of catheter-directed thrombolysis in intermediate-risk pulmonary embolism.

Trial name	Year	Sample Size	Intervention	Control	Administered total fibrinolytic dose (mg) ²	Primary outcome	Effectiveness	Safety
ULTIMA [46]	2014	59	USAT (10 mg/15h1)	Anticoagulation monotherapy	20.8 ± 3.0	Change in 24-hour TTE-based RV/LV ratio	The mean decrease in RV/LV ratio from baseline to 24 h was 0.30 ± 0.20 (intervention) versus 0.03 ± 0.16 (control) (<i>P</i> < 0.001)	At 90 days, there was 1 death (control), no major bleeding, 4 minor bleeding episodes (3 in the intervention group and 1 in the heparin group; <i>P</i> = 0.61), and no recurrent VTE
OPTALYSE PE [47]	2018	100	USAT (4 mg/2hr1) (arm 1)	USAT (4 mg/4hr1) (arm 2) (6 mg/6hr1) (arm 3) (12 mg/6hr1) (arm 4)	4–24	Change in the 48-hour CT-based RV/LV ratio	Arm 1: 24.0 % Arm 2: 22.6 % Arm 3: 26.3 % Arm 4: 25.5 %	Major bleeding event rates: Arm 1: 0 % Arm 2: 3.7 % Arm 3: 3.6 % Arm 4: 11.1 %
SUNSET-sPE [48]	2021	82	USAT (8 mg/8h1)	cCDT (8 mg/8h1)	USAT: 19±7 cCDT: 18±7	Change in the 48-hour CT-based thrombus burden	USAT: 0.37 cCDT: 0.59	Major bleeds: Intervention 4 vs. control 0
CANARY [27]	2022	94	cCDT (12 mg/24h1)	Anticoagulation monotherapy	24	Proportion of patients with a TTE-based RV/LV ratio >0.9 at a 3-month follow-up	4.3 % in the cCDT group and 12.8 % in the anticoagulation monotherapy group	One case of nonfatal major gastrointestinal bleeding occurred in the cCDT group
HI-PEITHO (NCT04790370)	–2	406	USAT (9 mg/7h1)	Anticoagulation monotherapy	–2	Composite of PE related mortality, PE recurrence or cardiorespiratory decompensation or collapse	–2	–2
BETULA (NCT03854266)	–2	60	cCDT (4 mg/2h1)	Anticoagulation monotherapy	–2	24-hour CT-based RV/LV ratio	–2	–2
PE-TRACT (NCT05591118)	–2	500	CDT consisting of mechanical thrombectomy or cCDT	Anticoagulation monotherapy	–2	Peak oxygen consumption at a 3-month follow-up	–3	–2
PEERLESS (NCT05111613)	–2	550	mechanical thrombectomy	cCDT	–2	Composite clinical endpoint of all-cause mortality, ICH, major bleeding, clinical deterioration, ICU admission, and ICU length of stay during hospitalization	–2	–2
STORM-PE (NCT05684796)	–2	100	Mechanical aspiration	Anticoagulation monotherapy	–2	Change in the 48-hour CT-based RV/LV ratio	–2	–2
STRATIFY (NCT04088292)	–2	210	USAT (20 mg/6 h) cCDT (20 mg/6 h)	Anticoagulation monotherapy	–2	Reduction in Miller score 48 to 96 h post randomization	–2	–2

Abbreviations: USAT, ultrasound-assisted catheter-directed thrombolysis; TTE, transthoracic echocardiography; RV, right ventricle; LV, left ventricle; VTE, venous thromboembolism; CT, computed tomography; cCDT, conventional catheter-directed thrombolysis; PE, pulmonary embolism; ICH, intracranial hemorrhage; ICU, intensive care unit.

¹Thrombolytic dosage per pulmonary artery.

²Still recruiting.

for intermediate-high risk PE patients [18,26], clinical practice guidelines recommend against the use of any reperfusion treatment for these patients, even though the risk-benefit ratio might be different for each of them. Ongoing randomized trials will help agree on prognostic thresholds for specific recanalization therapies with different complication rates (Table 5). For example, $\alpha \geq 15\%$ estimated rate of PE-related serious complications shortly after PE could lead to a recommendation of systemic thrombolytic therapy, while the threshold of estimated short-term PE-related serious complication risk to provide catheter-directed therapies might be lower (e.g., short-term PE-related complication rate of $\geq 10\%$), since the percutaneous treatment might have a lower bleeding risk than systemic thrombolysis [27].

At the other end of the spectrum, researchers should agree on a given threshold (upper limit) for estimated risk of all-cause mortality rate below which it would be acceptable to recommend immediate outpatient PE therapy. (e.g., short-term all-cause mortality rate of $\leq 0.5\%$).

4. A new approach to risk stratification of pulmonary embolism

Recently, a new paradigm for severity classification of PE was proposed by a group of international experts [28]. Briefly, they aim to overcome the aforementioned shortcomings by developing a risk classification that mainly relies on the available therapeutic options (i.e., anticoagulation, systemic thrombolysis, percutaneous interventions, surgical embolectomy) and treatment settings (i.e., outpatient, hospitalization, intermediate care unit, intensive care unit). The risks and benefits of treatment options will vary based on individual estimation of patient risk. In conjunction with patient preferences, clinicians will be able to use the new risk classification to recommend the appropriate level of care and to prioritize available treatment options.

5. Conclusion

Risk stratification of patients with acute PE assists with the selection of appropriate initial therapy and treatment setting. Current classifications have several shortcomings that might adversely affect clinical and healthcare decisions. Ongoing initiatives aim to address many of those shortcomings, and will hopefully help optimize risk stratification algorithms and treatment strategies.

Declaration of competing interest

The author has not declared any interests related to this article.

References

- Konstantinides SV, Meyer G, Becattini C, et al. ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J* 2020;41:543–603.
- Stevens SM, Woller SC, Baumann Kreuziger L, et al. Executive summary: antithrombotic therapy for VTE disease: second update of the CHEST Guideline and Expert Panel Report. *Chest* 2021;160:2247–59.
- Jiménez D, Rodríguez C, León F, et al. Randomized controlled trial of a prognostic assessment and management pathway to reduce the length of hospital stay in normotensive patients with acute pulmonary embolism. *Eur Respir J* 2022;59:2100412.
- Barbero E, Bikkeli B, Chiliza D, et al. Performance of early prognostic assessment independently predicts the outcomes in patients with acute pulmonary embolism. *Thromb Haemost* 2018;118:798–800.
- Jaff MR, McMurtry S, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension. *Circulation* 2011;123:1788–830.
- Ortel TL, Neumann I, Ageno W, et al. American society of hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv* 2020;4:4693–738.
- Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. *Am J Respir Crit Care Med* 2005;172:1041–6.
- Jiménez D, Moores L, Gómez V, et al. Simplification of the pulmonary embolism severity index for prognosis in patients with acute symptomatic pulmonary embolism. *Arch Intern Med* 2010;170:1383–9.
- Zondag W, Mos IC, Creemers-Schild D, et al. Hestia Study Investigators. Outpatient treatment in patients with acute pulmonary embolism: the Hestia study. *J Thromb Haemost* 2011;9:1500–7.
- Barco S, Vicaut E, Klok FA, et al. PEITHO Investigators. Improved identification of thrombolysis candidates among intermediate-risk pulmonary embolism patients: implications for future trials. *Eur Respir J* 2018;51:1701775.
- Bova C, Sanchez O, Prandoni P, et al. Identification of intermediate-risk patients with acute symptomatic pulmonary embolism: analysis of individual participants' data from six studies. *Eur Respir J* 2014;44:694–703.
- Dellas C, Tschepe M, Seeber V, et al. A novel H-FABP assay and a fast prognostic score for risk assessment of normotensive pulmonary embolism. *Thromb Haemost* 2014;111:996–1003.
- Bangalore S, Horowitz JM, Dean B, et al. Prevalence and predictors of cardiogenic shock in intermediate-risk pulmonary embolism. *JACC Cardiovasc Interv* 2023;16:958–72.
- Roy PM, Penalzoa A, Hugli O, et al. Triaging acute pulmonary embolism for home treatment by Hestia or simplified PESI criteria: the HOME-PE randomized trial. *Eur Heart J* 2021;42:3146–57.
- Jimenez D, Bikkeli B, Rodriguez C, et al. Identification of low-risk patients with acute symptomatic pulmonary embolism. *Arch Bronconeumol* 2023;59:575–80.
- Becattini C, Maraziti G, Vinson DR, et al. Right ventricle assessment in patients with pulmonary embolism at low-risk for death based on clinical models: an individual patient data meta-analysis. *Eur Heart J* 2021;42:3190–9.
- Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism: the task force for the diagnosis and management of acute pulmonary embolism of the European society of cardiology (ESC) endorsed by the European respiratory society (ERS). *Eur Heart J* 2014;35:3033–73.
- Meyer G, Vicaut E, Danays T, et al. PEITHO investigators. fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med* 2014;370:1402–11.
- Sanchez O, Charles-Nelson A, Ageno W, et al. PEITHO-3 Investigators. Reduced-dose intravenous thrombolysis for acute intermediate high-risk pulmonary embolism: rationale and design of the PEITHO-3 trial. *Thromb Haemost* 2022;122:857–66.
- Bova C, Vigna E, Gentile M, Pignatario FS. Comparison of two scores in predicting pulmonary embolism-related adverse events in intermediate-high-risk patients: a systematic review and meta-analysis. *Intern Emerg Med* 2022;17:1543–6.
- Mirambeaux R, Rodriguez C, Muriel A, et al. Comparison of various prognostic scores for identification of patients with intermediate-high risk pulmonary embolism. *Thromb Res* 2023;223:61–8.
- Najarro M, Briceño W, Rodriguez C, et al. Shock score for prediction of clinical outcomes among stable patients with acute symptomatic pulmonary embolism. *Thromb Res* 2023;233:18–24.
- Pedowska-Włoszek J, Kostrubiec M, Kurnicka K, et al. Midregional proadrenomedullin (MR-proADM) in the risk stratification of patients with acute pulmonary embolism. *Thromb Res* 2013;132:506–10.
- Vanni S, Jimenez D, Nazerian P, et al. Short-term clinical outcome of normotensive patients with acute PE and high plasma lactate. *Thorax* 2015;70:333–8.
- Hellkamp K, Schwung J, Rossmann H, et al. Risk stratification of normotensive pulmonary embolism: prognostic impact of copeptin. *Eur Respir J* 2015;46:1701–10.
- Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. *JAMA* 2014;311:2414–21.
- Sadeghipour P, Jenab Y, Moosavi J, et al. Catheter-directed thrombolysis versus Anticoagulation in patients with Acute intermediate-high Risk pulmonary embolism: the CANARY trial. *JAMA Cardiol* 2022;7:1189–97.
- Jiménez D, Tapson V, Yusen RD, et al. Revised paradigm for acute pulmonary embolism prognosis and treatment. *Am J Respir Crit Care Med* 2023;208:524–7.
- Jaureguizar A, Jiménez D, Bikkeli B, et al. Heart rate and mortality in patients with acute symptomatic pulmonary embolism. *Chest* 2022;161:524–34.
- Barco S, Ende-Verhaar YM, Becattini C, et al. Differential impact of syncope on the prognosis of patients with acute pulmonary embolism: a systematic review and meta-analysis. *Eur Heart J* 2018;39:4186–95.
- Harjola VP, Mebazaa A, Celutkienė J, et al. Contemporary management of acute right ventricular failure: a statement from the heart failure association and the working group on pulmonary circulation and right ventricular function of the European society of cardiology. *Eur J Heart Fail* 2016;18:226–41.
- Bikkeli B, Jimenez D, Del Toro J, et al. Association between preexisting versus newly identified atrial fibrillation and outcomes of patients with acute pulmonary embolism. *J Am Heart Assoc* 2021;10:e021467.
- Galeano-Valle F, Ordieres-Ortega L, Oblitas CM, et al. Inflammatory biomarkers in the short-term prognosis of venous thromboembolism: a narrative review. *Int J Mol Sci* 2021;22:2627.
- Siddiqui F, García-Ortega A, Kantarcioglu B, et al. Cellular indices and outcome in patients with acute venous thromboembolism. *Clin Appl Thromb Hemost* 2022;28:1076029622113346.
- Kostrubiec M, Labyk A, Pedowska-Włoszek J, et al. Neutrophil gelatinase-associated lipocalin, cystatin C and eGFR indicate acute kidney injury and predict prognosis of patients with acute pulmonary embolism. *Heart* 2012;98:1221–8.
- Qaddoura A, Digby GC, Kabali C, Kukla P, Zhan ZQ, Baranchuk AM. The value of electrocardiography in prognosticating clinical deterioration and mortality in acute pulmonary embolism: a systematic review and meta-analysis. *Clin Cardiol* 2017;40:814–24.

- [37] Sanchez O, Trinquart L, Colombet I, et al. Prognostic value of right ventricular dysfunction in patients with hemodynamically stable pulmonary embolism: a systematic review. *Eur Heart J* 2008;29:1569–77.
- [38] Trujillo-Santos J, den Exter PL, Gomez V, et al. Computed tomography-assessed right ventricular dysfunction and risk stratification of patients with acute non-massive pulmonary embolism: systematic review and meta-analysis. *J Thromb Haemost* 2013;11:1823–32.
- [39] Pieralli F, Olivotto I, Vanni S, et al. Usefulness of bedside testing for brain natriuretic peptide to identify right ventricular dysfunction and outcome in normotensive patients with acute pulmonary embolism. *Am J Cardiol* 2006;97:1386–90.
- [40] Jimenez D, Aujesky D, Diaz G, et al. Prognostic significance of deep vein thrombosis in patients presenting with acute symptomatic pulmonary embolism. *Am J Respir Crit Care Med* 2010;181:983–91.
- [41] Lobo JL, Zorrilla V, Aizpuru F, et al. RIETE Investigators. D-dimer levels and 15-day outcome in acute pulmonary embolism. Findings from the RIETE Registry. *J Thromb Haemost* 2009;7:1795–801.
- [42] Furlan A, Aghayev A, Chang CC, et al. Short-term mortality in acute pulmonary embolism: clot burden and signs of right heart dysfunction at CT pulmonary angiography. *Radiology* 2012;265:283–93.
- [43] Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. *Circulation* 2007;116:427–33.
- [44] Lankeit M, Jiménez D, Kostrubiec M, et al. Predictive value of the high-sensitivity troponin T assay and the simplified Pulmonary Embolism Severity Index in hemodynamically stable patients with acute pulmonary embolism: a prospective validation study. *Circulation* 2011;124:2716–24.
- [45] Bajaj A, Rathor P, Sehgal V, Shetty A, Kabak B, Hosur S. Risk stratification in acute pulmonary embolism with heart-type fatty acid-binding protein: a meta-analysis. *J Crit Care* 2015;30:1151 e1–7.
- [46] Kucher N, Boekstegers P, Müller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. *Circulation* 2014;129:479–86.
- [47] Tapson VF, Sterling K, Jones N, et al. A randomized trial of the optimum duration of acoustic pulse thrombolysis procedure in acute intermediate-risk pulmonary embolism: the OPTALYSE PE trial. *JACC Cardiovasc Interv* 2018;11:1401–10.
- [48] Avgerinos ED, Jaber W, Lacomis J, et al. Randomized trial comparing standard versus ultrasound-assisted thrombolysis for submassive pulmonary embolism: the SUNSET sPE Trial. *JACC Cardiovasc Interv* 2021;14:1364–73.