Pulmonary Embolism
A Practical Guide for the Busy Clinician

Pablo Demelo-Rodriguez, MD, PhD[a,b,c], Francisco Galeano-Valle, MD[a,b,c], Andrea Salzano, MD[d], Eweline Biskup, MD[e,f], Olga Vriz, MD, PhD[g], Antonio Cittadini, MD[h], Lorenzo Falsetti, MD, PhD[i], Brigida Ranieri, PhD[d], Valentina Russo, MD[j], Anna Agnese Stanziola, MD, PhD[k,l], Eduardo Bossone, MD, PhD, FCCP, FESC, FACC[m], Alberto M. Marra, MD, PhD[h,n,*]

KEYWORDS

• Echocardiography • Biomarkers • Chronic thromboembolic pulmonary hypertension
• Deep venous thrombosis • Pulmonary embolism • Thrombolysis • Venous thromboembolism

KEY POINTS

- Acute pulmonary embolism (PE) is the third most common acute cardiovascular condition, and its prevalence tends to grow over time.
- Echocardiography is the most available, bedside, low-cost, diagnostic procedure for patients with PE.
- D-dimer has a very high negative predictive value, and if normal levels of D-dimer are detected, the diagnosis of PE is very unlikely.
- In case of persisting dyspnea during follow-up of a patient with PE, a transthoracic echocardiography should be performed in order to assess the risk of pulmonary hypertension.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

[a] Venous Thromboembolism Unit, Internal Medicine, Hospital General Universitario Gregorio Marañón, Calle doctor Esquerdo, 46, Madrid 28007, Spain; [b] Sanitary Research Institute Gregorio Marañón, Calle doctor Esquerdo, 46, Madrid 28007, Spain; [c] Universidad Complutense de Madrid, School of Medicine, Spain; [d] IRCCS SDN, Diagnostic and Nuclear Research Institute, Via Gianturco 131, Naples 80137, Italy; [e] Department of Basic Medical College, Shanghai University of Medicine and Health Sciences, Shanghai 201315, China; [f] Division of Internal Medicine, University Hospital of Basel, University of Basel, Basel, Switzerland; [g] Heart Centre Department, King Faisal Specialist Hospital & Research Center, Riyadh, Kingdom of Saudi Arabia; [h] Department of Translational Medical Sciences, "Federico II" School of Medicine, "Federico II" University of Naples, Via Pansini 5, Naples 80131, Italy; [i] Internal and Subintensive Medicine Department, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Ancona, Italy; [j] Department of Advanced Biomedical Sciences, Federico II University of Naples, Via Pansini 5, Naples I-80138, Italy; [k] Section of Respiratory Diseases, Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy; [l] Centre for Rare Respiratory Diseases, Monaldi Hospital, Via Leonardo Bianchi, Naples 80131, Italy; [m] Division of Cardiology, Cardarelli Hospital, Via A. Cardarelli, 9, Naples 80131, Italy; [n] Centre for Pulmonary Hypertension, Thoraxklinik at Heidelberg University Hospital
* Corresponding author. Department of Translational Medical Sciences, "Federico II" School of Medicine, "Federico II" University of Naples, Via Pansini 5, Naples 80131, Italy.
E-mail address: alberto_marra@hotmail.it
Twitter: @alberto_marra (A.M.M.)

Heart Failure Clin 16 (2020) 317–330
https://doi.org/10.1016/j.hfc.2020.03.004

heartfailure.theclinics.com

INTRODUCTION

Pulmonary embolism (PE), along with deep vein thrombosis (DVT), is the clinical manifestation of venous thromboembolism (VTE).[1] Acute PE is the third most common acute cardiovascular condition,[2] and its prevalence tends to grow over time.[3] PE is particularly prevalent in elderly patients,[4] leading to an estimated annual cost of 8.5 billion euros in the European Union.[5] Acute PE is burdened by remarkable mortality, up to 34% in severely ill patients presenting with hemodynamic instability.[6] However, when correctly diagnosed and promptly treated, acute PE is associated with a mortality close to 7% of patients.[7] On the other hand, the development of new imaging and biochemical tools has led to an increase in overdiagnosis of PE, which is likely to generate significant costs for health care systems.[8] Given this magnitude, special attention should be paid to ensuring that an accurate diagnosis is made within a reasonable time. Last but not least, PE might develop into chronic thromboembolic pulmonary hypertension (CTEPH), which is also burdened by remarkable morbidity and mortality.[9] Taken all together, optimal background knowledge of PE diagnosis and management and its complications should belong to all physicians, in particular, those daily dealing with acutely ill patients.

Throughout this review, 5 burning questions are addressed concerning those issues that might dramatically impact the management of PE patients, respectively:

1. Cardiac ultrasound and PE
2. Biomarkers in PE: is there something beyond D-dimer?
3. Risk stratification (RS) strategies in PE
4. Thrombolysis: to be or not to be?
5. CTEPH screening after an acute PE

CARDIAC ULTRASOUND AND PULMONARY EMBOLISM

Echocardiography is the most available, bedside, low-cost diagnostic procedure for patients with PE. Acute PE is responsible for the increase in right ventricle (RV) pressure/volume and eventually RV dysfunction. The RV is a complex structure whose evaluation poses a diagnostic challenge. For all of these reasons, there is not a single strong parameter that can be considered diagnostic itself, but there is a cluster of parameters that can lead to the suspicion of PE. The negative predictive value of echocardiography for the diagnosis of acute PE is 40% to 50%, and a negative result cannot exclude it. Transthoracic echocardiography (TTE) can visualize intracardiac thrombi (right atrium/RV) that occur in about 5% of patients and very seldom in the pulmonary arteries (**Fig. 1**). Transesophageal echocardiography (TEE) can detect thrombus in the central pulmonary artery (main, right, and left artery) but with a sensitivity of 30% in unselected populations.[10]

The most useful parameters for the diagnosis of PE are reported in **Table 1**. RV enlargement is used for the disease stratification but is present only in 25% of cases.[11] Besides, RV dilation can be also found in patients with significant left ventricular dysfunction or valvular disease. RV overload can help in the differential diagnosis between PE and RV hypokinesia/akinesia, such as in RV infarction.

A relatively new 2-dimensional RV speckle-tracking echocardiography has been clearly involved in patients with PE related to the increased afterload of the RV. According to recent studies, there is a good relationship between RV global longitudinal strain (GLS) with outcomes and response to therapy in pulmonary hypertension (PH).[12] However, there is no agreement among different investigators in the relationship between RV strain and in-hospital and long-term mortality.[13,14] The persistence of RV free-wall GLS impairment after PE correlates with worse prognosis.[15]

As general consent, because of the limited specificity of the TTE, invasiveness of TEE, and low sensitivity for both procedures, echocardiography is not considered a routine methodology to rule out PE.[16] Although echocardiography is nondiagnostic for PE, it can still provide important

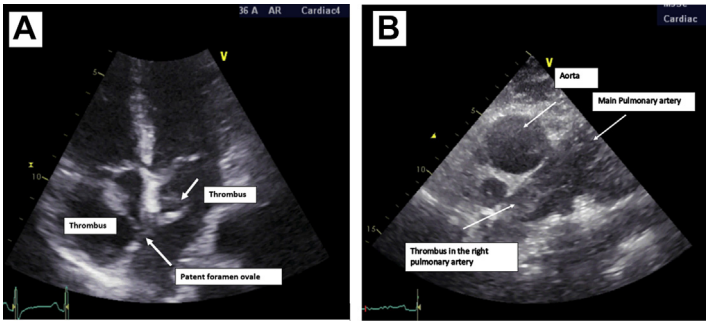

Fig. 1. TTE (*A*) and TEE (*B*) show a large horseshoe-shaped clot in the right ventricle and right atrium straddling the patent foramen ovale and arriving up to the left atrium and left ventricle.

Table 1
Echocardiographic parameters for the diagnosis of pulmonary embolism

Window	Parameters
Long axis	Dilated RV
4-Chamber view	Basal diameter RV/left ventricle >1 RV basal diameter >41 mm RV middiameter >35 mm McConnell sign: akinesia of the mid free wall but normal motion at the apex (present in 10%–20% of the patients)
Parasternal short axis	Flattened interventricular septum (D-shape)
Subcostal	Dilated inferior vena cava (>21 mm) and noncollapsible during inspiration
Short axis	60/60 sign: acceleration time on pulsed wave in right ventricle outflow tract <60 ms and mid systolic notch Mild to moderate increase in pulmonary systolic pressure at the tricuspid valve (>30 and <60 mm Hg)
4-Chamber view	Reduced tricuspid annular systolic excursion by M-mode <16 mm
4-Chamber view	Decreased S′ velocity (<9.5 cm/s)
4-Chamber view	RV thrombus

information by helping to exclude other causes of severe heart dysfunction (acute left ventricular dysfunction, tamponade, acute valvular disease, and aortic dissection) and/or right-to-left shunt through a patent foramen ovale and the presence of thrombi, which are both related to increased mortality in patients with PE[17] (**Figs. 2–5**).

BIOMARKERS IN PULMONARY EMBOLISM: IS THERE SOMETHING BEYOND D-DIMER?

Biomarkers in the Right Context

Clinical symptoms and signs of PE are not specific; therefore, an unmet need of clinicians in the clinical practice is to have useful tools helping in performing fast and accurate diagnosis of PE. Following the definition of the *Biomarkers and Surrogate End Point Working Group*, a biomarker can be defined as "*a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention*."[18] In addition, 3 criteria have been recently defined to consider a biomarker useful in the clinical context: (i) the biomarker has to be an accurate, repeated measurement, possible to measure with a reasonable cost and in short time; (ii) the biomarker must provide information not already available from a careful clinical assessment; and (iii) the biomarker should support the clinician in decision making.[19,20] Accordingly, biomarkers can derive from blood, urine, genetics, imaging, and biopsies. For the aim of this review, the authors focus only on circulating biomarkers. Furthermore, based on available evidence, the authors have divided into 2 categories the usefulness of clinical biomarkers in PE: (i) diagnosis; and (ii) RS.

Diagnosis of Pulmonary Embolism

D-dimer

D-dimer is a fibrin degradation product, resulted from the degradation of blood clot by plasmin (the main fibrinolysis enzyme).[21] Specifically, D-dimer is made of 2 D-fragments of the fibrin joined by a cross-link. D-dimer levels are usually not detectable in human blood plasma, and the presence of D-dimer indicates the activation of coagulation process. However, because the coagulation process can be activated by several different processes (eg, inflammation, cancer, pregnancy), D-dimer has a very low specificity. Furthermore, D-dimer levels increase with age; therefore, age-adjusted cutoff levels have been suggested.

To date, it is not arguable that D-dimer is the most important biomarker in PE. In particular, D-dimer has a very high negative predictive value, and if normal levels of D-dimer are detected, the diagnosis of PE is very unlikely. For this reason, in patients with low or intermediate clinical probability of PE (based on the combination of symptoms and clinical findings through prediction scores such as Geneve score and Wells score[22]), guidelines recommend to assess D-dimer levels[1]; if D-dimer is negative, this biomarker is enough to rule out the presence of PE. On the other hand, in the presence of a high level of D-dimer, it is necessary to perform a computed tomographic (CT) pulmonary angiogram. Using this strategy, it has been demonstrated that about

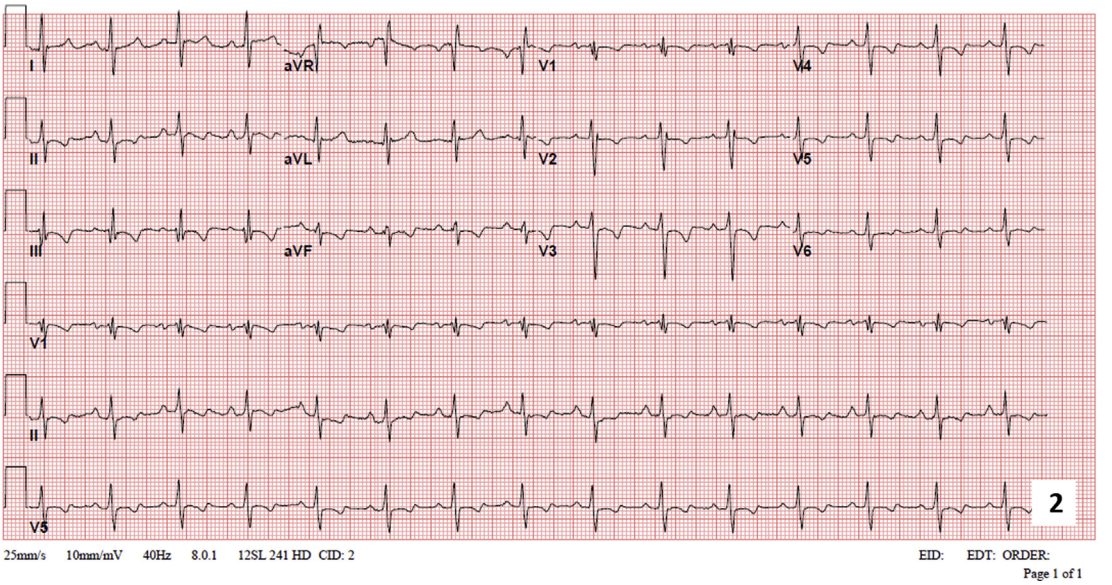

Fig. 2. A 20-year-old male patient diagnosed with intermediate-high risk, massive PE, and the presence of a mass in the RV. Upon arrival at the emergency department, the electrocardiogram showed SR. S1Q3T3 pattern of acute cor pulmonale (McGinn-White sign). Large S wave in lead I, a Q wave in lead III, and an inverted T wave in lead III together indicate acute right heart strain.

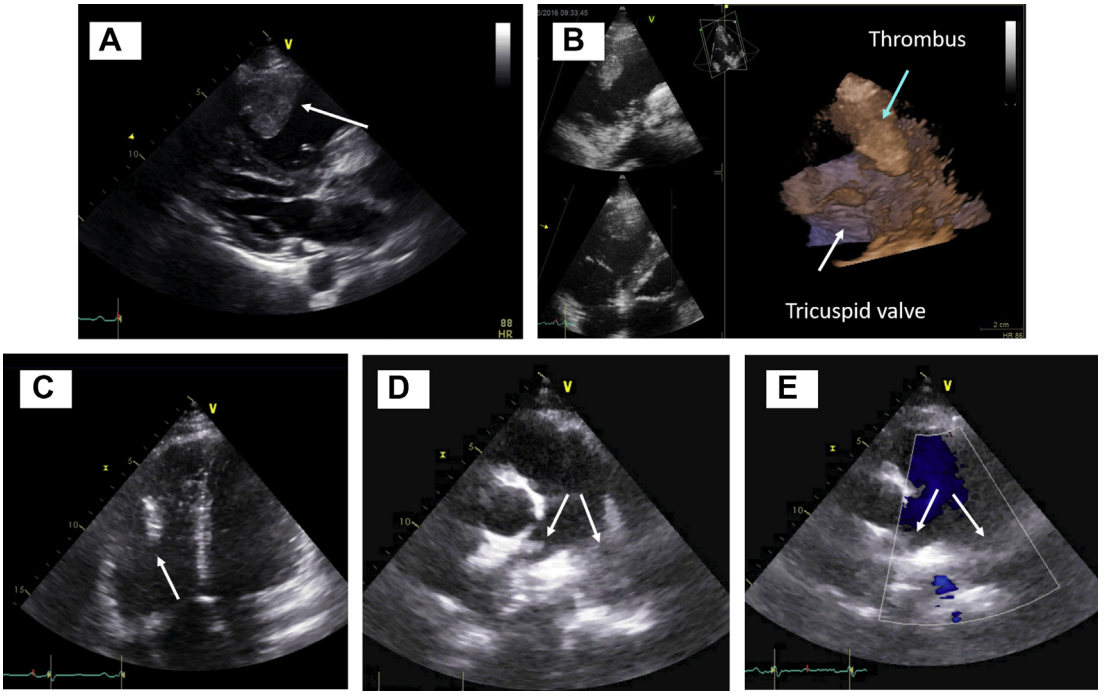

Fig. 3. Cardiac ultrasound of a 20-year-old male patient diagnosed with intermediate-high risk, massive PE, and the presence of a mass in the RV. (*A*) The RV was enlarged, and a big thrombus was seen proximal to the apex (*arrows*). (*B*) Three-dimensional echocardiogram of the RV and thrombus. (*C*) Four-chamber view showing RV enlargement with thrombus (*arrows*). (*D*) Completely obstructed right and left pulmonary artery (*arrows*). (*E*) No systolic flow in the pulmonary branches (*arrows*).

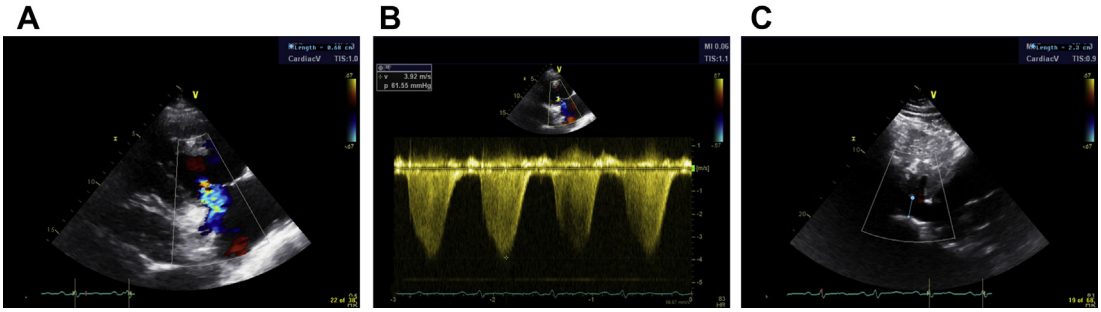

Fig. 4. Cardiac ultrasound of a 20-year-old male patient diagnosed with intermediate-high-risk PE. (*A*) Tricuspid regurgitation (TR) from the long axis for the RV. (*B*) Doppler of the TR with intense signal and triangular shape. (*C*) Dilated inferior vena cava 23 mm, noncollapsible.

30% of patients with a suspected PE in the emergency department can be safely ruled out after a negative D-dimer. D-dimer performances, however, are strongly dependent on the adopted assay. Notably, because D-dimer levels increase with age, its specificity in PE diagnosis decreases.[23] For this reason, it has been suggested to use age-adjusted cutoff levels, instead of the cutoff of 500 mg/L,[24,25] with an increase of about 25% of the number of patients ruled out without further tests.[26]

Emerging biomarkers

i. Micro-RNA (miRNA): miRNAs are circulating, noncoding RNA with a regulatory role in several processes, such as differentiation and apoptosis.[27] Because of its stability, recent research has focused on miRNAs as a novel noninvasive diagnostic biomarker of various diseases, including PE.[28,29] Recently, 2 metaanalyses have evaluated all available literature, showing that miRNAs may be considered a novel diagnostic biomarker for VTE, identifying miR-134 as the most extensive and reliable, with an average sensitivity of 0.82 and an average specificity of 0.83, with an area under the curve of 0.89.

ii. Pentraxin-3: recently, a small study involving 157 PE patients showed that pentraxin-3, an acute-phase reaction protein in inflammation derived from the pentraxin protein family (such as C-reactive protein[30]), relates to the Wells score, with higher levels in patients with high to moderate risk. Furthermore, it is associated with prognosis in PE.

iii. Lipidomic: clinical lipidomic studies lipid profiles, pathways, and networks by characterizing and quantifying the complete spectrum of lipidomes in blood samples of patients.[31] Recently, it has been demonstrated that lipidomic profiles of patients with acute lung diseases are different from healthy subjects; besides, disease-specific portions of lipidomics among patients with PE have been demonstrated, in particular when compared with patients with other pulmonary diseases (eg, acute exacerbation of obstructive pulmonary disease or severe acute pneumonia).[31] Further studies are needed to evaluate the use of this novel strategy in the clinical context.

Risk Stratification of Pulmonary Embolism

Once PE has been diagnosed, RS is due to allocate each patient to the appropriate treatment.[1]

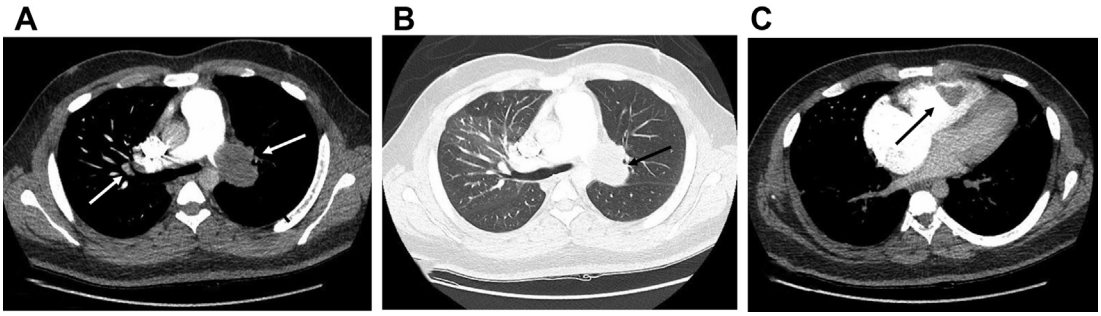

Fig. 5. CT scan of pulmonary arteries of a 20-year-old male patient diagnosed with intermediate-high risk PE shows massive bilateral PE with PH and RV strain. (*A*) Mediastinal window. (*B*) Pulmonary window (*arrows* indicate pulmonary artery thrombus). (*C*) Right ventricular thrombus (*arrow*).

Initial RS is based on symptoms and signs of hemodynamic instability, which requires an immediate emergency diagnostic and therapeutic strategy; on the other hand, patients with a situation of hemodynamic stability require further risk assessment, based on clinical, imaging, and circulating biomarkers (mostly related to RV function and myocardial injury), and presence of comorbidities. Among circulating biomarkers, 3 groups of biomarkers can be considered: (i) biomarkers of myocardial injury; (ii) biomarkers of right ventricular dysfunction; and (iii) other biomarkers.

Myocardial injury

Troponins Elevated troponins (defined as a detected value above the normal limits of the assay used) can be found in between 30% and 60% of the patients with a diagnosis of PE. An elevation in troponin levels is associated with an increased risk of mortality, identifying patients with high risk of short-term death and adverse outcome.[32] As for D-dimer as well as for troponins, the use of age-adjusted cutoff has been suggested.[33]

Based on this evidence, together with the simplified Pulmonary Embolism Severity Index (sPESI),[34] European Society of Cardiology (ESC) guidelines recommend assessing troponins levels in hemodynamically stable patients with PE, to distinguish between intermediate- to high-risk (if troponins positive) and intermediate- to low-risk (if troponins negative) patients, with a possible rescue reperfusion treatment in the first group if necessary.[1]

In regard to cutoffs, the lower detection limits for myocardial ischemia reported by the manufacturer should be adopted for troponins in the setting of PE.[35]

Myoglobin It has been demonstrated that sex-specific myoglobin levels are elevated in serum on admission in patients with PE, predicting in-hospital mortality.[36] However, its use in clinical practice is not routinely recommended.

Heart-type fatty acid-binding protein It has been demonstrated that heart-type fatty acid-binding protein (H-FABP), an early marker of myocardial injury, is associated with poor short-term outcome and mortality in patients with PE.[37–39] In some small pilot studies, H-FABP levels showed superiority to troponins, natriuretic peptides, and myoglobin in prediction of short-term outcomes.[40,41]

Right ventricular dysfunction

B-type natriuretic peptides B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are released as a response to myocardial stretch, reflecting the severity of ventricular dysfunction. Notably, in PE, it has been demonstrated that levels of natriuretic peptides are related closer to right ventricular dysfunction than to left dysfunction.[42] High concentrations of BNP or NT-proBNP distinguish between PE patients at higher risk of complicated in-hospital course and death and those with a better prognosis.[43]

With regard to the cutoffs, it has been suggested that a BNP level of less than 50 pg/mL for triage assay was able to predict positive outcome in PE patients (lower than those used in congestive heart failure),[44] whereas for NT-proBNP, a cutoff between 500 and 600 pg/mL has been suggested.[45,46]

Other biomarkers

i. Lactate: as result of an imbalance among tissue oxygen demand and supply, elevated levels of lactate (>2 mmol/L) have been associated with poor outcome in PE patients.[47,48]
ii. Renal function: a decreased renal function estimated with glomerular filtration rate, and increased levels of creatinine are related to poor short-term outcomes as well as other biomarkers of acute kidney damage (ie, cystatin C and neutrophil gelatinase–associated lipocalin).[49,50]
iii. Hyponatremia: It has been shown that the presence of hyponatremia is associated with poor outcome in patients with acute PE.[51,52]
iv. Copeptin and adrenomedullin (ADM): Midregional proadrenomedullin (MR-pro-ADM) and copeptin, vasopressin-related biomarkers of which levels increase with stress, hypotension, and low CO, have been reported to be associated with poor outcome in PE.[53] In particular, copeptin and MR-pro-ADM were independent predictors of PE-related mortality, but they were not independent predictors of PE-related complications. In a post hoc analysis of a cohort of about 800 patients, when copeptin was used on top of the ESC RS algorithm in intermediate- to high-risk patients, copeptin was able to improve RS of PE patients.[54]

In summary, despite a large number of biomarkers that have been investigated in PE, to date, only a few of them can be considered useful in the clinical setting and able to modify the decision process in medical practice. It is not arguable that D-dimer represents the gold-standard circulating biomarker in the diagnostic process of PE, with its ability in the rule out patients with low-intermediate clinical probability of PE, or when PE is unlikely. On the other hand, troponins and

brain natriuretic peptides have shown their usefulness in the RS of PE, with a pivotal role in the decision process of the treatment strategy of the patient; indeed, because of their high negative predictive value for adverse outcomes, low cardiac troponins and natriuretic peptides discriminate low-risk patients.[55]

To date, PE represents a typical condition in which a multimarker strategy, with the combination of clinical, imaging, and circulating biomarkers, appears to be the best strategy, as it has been demonstrated in several other clinical settings.[56]

RISK STRATIFICATION STRATEGIES IN PULMONARY EMBOLISM

RS of the severity and mortality owing to PE is a crucial part of everyday clinical engagement of hospitalists.[57,58] Therapeutic approaches are not unambiguous, so mastering an accurate and rapid assessment patients' PE-specific risk factors and immediate implementation of therapy are of uttermost importance in order to reduce related morbidity and lethality.[59,60]

PE mortality risks have conventionally been divided into high, intermediate (high/low), and low level. Evaluating patient's hemodynamic state (shock, severe hypotension, and similar) and right ventricular dysfunction/damage (RVD), which allow discriminating between high and not high risk, is rather unequivocal. Assessment of moderate-risk acute PE subtypes, however, are challenging and involve a variety of supporting diagnostic steps in a differentiated algorithm, which can and should be individually tailored to a given clinical situation and patient's (especially comorbidity) profile. In most cases, PE is a consequence of DVT; therefore, patients should be considered holistically.[61] Because of the acuteness and seriousness of PE, clinicians widely reach out to objective predictive scales, such as Wells, Geneva, or YEARS score.[26,62,63] However, these are to be viewed as solely supportive tools, because they do not reflect the complexity of the cases.

Further measures toward RS partially overlap with diagnostics and can be divided into laboratory testing, imaging, and clinical characteristics of the patient.[64] These 3 pillars reflect the 3 main causalities for early mortality: extent of the pulmonary circulation, associated RVD, and comorbidities.[65]

As discussed in the previous section, most valuable laboratory tests for RS include general (eg, lactate), RVD (eg, BNP), and cardiac (myocardial damage) biomarkers. Despite the fact that mostly the latter are included in the current PE risk classification, the remaining ones are of value for a comprehensive decision on further action and provide a base for recoalescence monitoring.

Although CT of the pulmonary arteries is the gold-standard diagnostic procedure, it also provides information for RS, for example, right ventricular load, (non)-movable RV clots. Similar and additional parameters can be collected via further, but inferior appliances, such as lower limb ultrasound (sensitivity 90%, specificity 95%, false positives in incomplete vein compression), ventilation and perfusion scintigraphy (insensitivity consecutively to ventilation disorders), CT angiography (positive predictive value for high and intermediate PE risk: 92%–96%; for low: 58%; negative predictive value for low and intermediate PE risk: 96% and 89%; for high: 60%), magnetic resonance angiography, echocardiography, depending on their availability and clinical condition of the patient.[66–68] Novel technologies, such as "dual-energy" imaging, "high-pitch" techniques, or monoenergetic reconstruction, are beneficial in order to further improve image quality and diagnostics.[69]

Patient-specific factors go beyond clinical symptoms and often coincide with comorbidities, especially prothrombolitic, CTEPH, hormonal (including antihormonal therapy in cancer survivors), cardiorhythmic and oncologic conditions, as well as postsurgical cases.[70,71] Pregnant patients require special consideration and approach.[72] Thus, a careful anamnesis is imperative and just as important as above-mentioned methods.

The current ESC algorithm[1] sets up 4 risk groups of PE patients: high, intermediate high, intermediate low, and low risk. This distinction can be made with 4 main diagnostic tools: hemodynamic instability combined with RV dysfunction is always to be considered high risk, independently of the PESI score or cardiac markers (troponin). If the patient is stable, there is no RV dysfunction, and the PESI score is not higher than 2, there is no obligation of measuring the troponins, and the patient is to be categorized as low risk. In the case of a PESI score III to IV, the patient is at intermediate risk. If there is an RV dysfunction or an elevated troponin level accompanying the PESI score of III to IV, intermediate-high risk is present. In case of one or both being negative, an intermediate-low risk is present. Thus, combined risk markers are the sPESI, evidence of RV dysfunction, and evidence of myocardial ischemia. If the latter two are positive, these are patients with intermediate-high risk. These patients are potential candidates for thrombolysis, either systemically or with interventional procedures (**Fig. 6**).

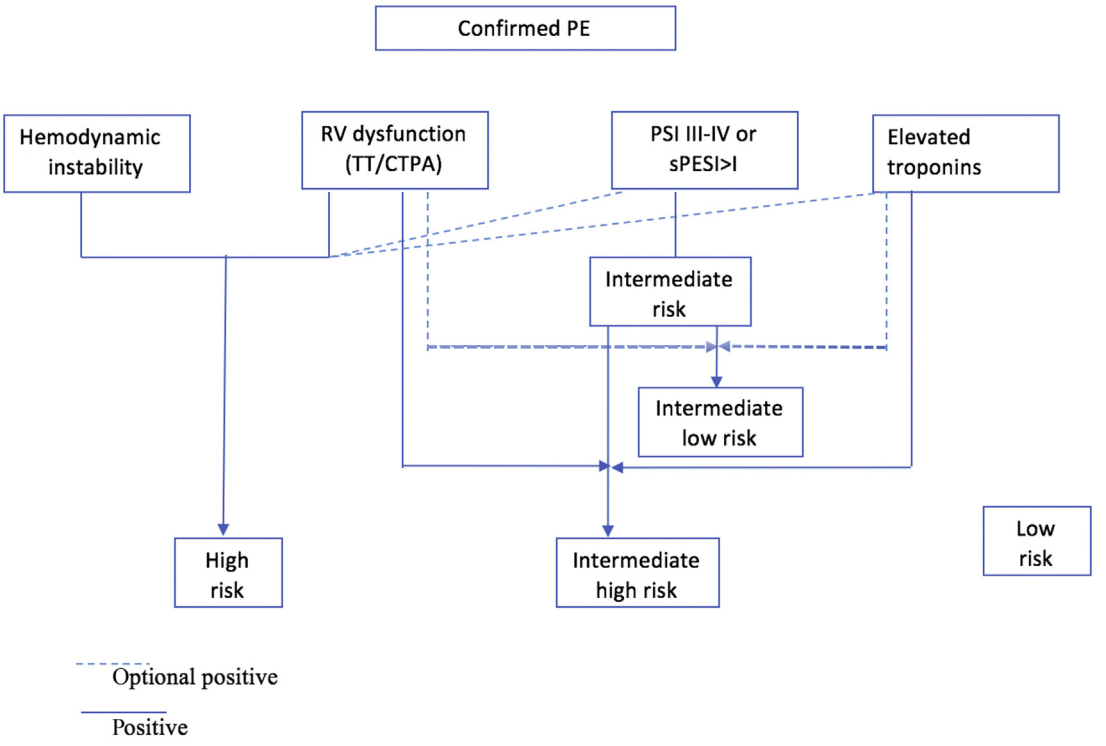

Fig. 6. RS algorithm of the severity and mortality owing to PE. TT, transthoracic echocardiography.

So far, depending on signs of RV dysfunction and/or myocardial damage, patients were differentiated as per "intermediate" and "low" mortality risk. For the first time in the new guidelines, the heterogeneous group of normotensive patients with "intermediate" risk is further stratified.

THROMBOLYSIS: TO PULMONARY EMBOLISM OR NOT TO PULMONARY EMBOLISM?

Thrombolysis in Pulmonary Embolism

The standard treatment for most patients with PE in the acute phase is anticoagulation with low-molecular-weight heparin (LMWH), unfractionated heparin (UFH), direct-acting oral anticoagulants (specifically, rivaroxaban and apixaban), or fondaparinux. Use of UFH is nowadays largely restricted to patients with hemodynamic instability or patients at high risk of hemodynamic decompensation in whom primary reperfusion treatment will be necessary.[1,73]

Pharmacologic thrombolysis (fibrinolysis)

Several studies have shown that fibrinolysis favors early lysis of the thrombus, with a reduction in pulmonary arterial pressure and an improvement in RVD faster than heparin in patients with acute PE.[74–76] In patients with high-risk PE (those who associate hemodynamic instability), fibrinolysis appears to be associated with a reduction in mortality or recurrence of PE.[77] The recently published ESC guidelines for the diagnosis and management of acute PE have deeply defined hemodynamic instability in these patients, and it includes the following: (1) cardiac arrest; (2) obstructive shock (with systolic blood pressure <90 mm Hg or vasopressors requirement to achieve blood pressure ≥90 mm Hg and end-organ hypoperfusion); or (3) persistent hypotension (defined as systolic blood pressure <90 mm Hg or a drop of ≥40 mm Hg lasting longer than 15 minutes and not caused by arrhythmia, hypovolemia, or sepsis).[1] However, only a randomized clinical trial has been published to date that demonstrates the benefit of fibrinolysis in terms of survival in patients with high-risk PE; in that study, only 8 patients were randomized, and the trial was stopped because the 4 patients who received streptokinase survived and the 4 who received heparin died.[78] Therefore, currently, all PE treatment guidelines agree that fibrinolysis is the initial treatment of choice in patients with PE and hemodynamic instability.[1,78,79] Fibrinolytics with indication in PE are streptokinase, urokinase, and recombinant tissue plasminogen activator (eg, alteplase). Contraindications for fibrinolysis are listed in **Box 1**.

Box 1
Absolute and relative contraindications for fibrinolysis

Absolute contraindications

- Hemorrhagic stroke or stroke of unknown origin (at any time)
- Ischemic stroke in the previous 6 months
- Lesions or neoplasms of the central nervous system
- Surgery/major trauma/head trauma in the previous 3 weeks
- Gastrointestinal bleeding in the last month
- Hemorrhagic diathesis

Relative contraindications

- Transient ischemic accident in the previous 6 months
- Oral anticoagulation
- Pregnancy or 1 week after delivery
- Noncompressible puncture site
- Traumatic resuscitation
- Refractory arterial hypertension (systolic blood pressure >180 mm Hg)
- Advanced liver disease
- Infective endocarditis
- Active peptic ulcer

In patients with intermediate-risk PE (ie, without hypotension but with data of RVD), the main evidence available is the PEITHO trial. In PEITHO, the largest trial to date involving only patients with intermediate-risk PE (n = 1006), thrombolysis halved the number of patients who developed the primary outcome (a composite of death from any cause and hemodynamic decompensation or collapse within 7 days) from 5.6% with heparin to 2.6% with tenecteplase. However, this benefit extracted a high price, a 10-fold increase in hemorrhagic stroke (0.2% with heparin vs 2.0% with tenecteplase).[80–82] Previously, a randomized study compared heparin versus alteplase in patients with similar characteristics, finding that fibrinolysis reduced the incidence of treatment progression (catecholamines, rescue fibrinolysis, and similar), but without affecting mortality.[83] Interestingly, long-term follow-up (median 37.8 months) of patients included in the PEITHO trial (709 of 1006 initially randomized patients) showed that there was no reduction in mortalities, no reduction in persistent dyspnea or functional limitation, and no reduction in CTEPH among those patients who received thrombolysis.[82,84]

Therefore, current guidelines coincide in not advising onset fibrinolysis in patients with intermediate-risk PE.[1,78,79] However, "rescue" thrombolysis would be indicated in these patients if they developed instability or data of poor clinical evolution in the first hours despite anticoagulant treatment.[1,78]

Interventional thrombolysis

The goal of interventional thrombolysis is to remove the thrombus from the main pulmonary arteries and thus facilitate RV recovery and improve symptoms and survival. In patients with high-risk PE and contraindication for fibrinolysis (see **Table 1**) or in whom fibrinolysis has not been effective, surgical embolectomy is recommended in centers where such technique is available.[1,78] In selected patients, a perioperative mortality of 6% or less has been described, with an increase in the World Health Organization functional class and quality of life.[85–87]

As an alternative to surgery, percutaneous catheter-directed thrombolysis can be considered in centers with experience and available resources. Percutaneous thrombolysis can be performed mechanically (without drug administration) in patients at high risk of bleeding. Percutaneous thrombolysis can also be performed with administration of local fibrinolysis (catheter-directed fibrinolysis) in selected cases, primarily in patients with moderate-low risk of bleeding with contraindication for systemic fibrinolysis or those in which systemic fibrinolysis has proven ineffective. There are no clinical trials that have compared catheter-directed fibrinolysis with systemic fibrinolysis.[1] The acute-phase therapeutic strategies for patients with PE are summarized in **Table 2**.

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION SCREENING AFTER AN ACUTE PULMONARY EMBOLISM

As mentioned before, CTEPH is a fearsome chronic complication of acute PE whose hallmark is a persistent increase in pulmonary pressures that is closely linked to right heart failure and death.[9] The steric encumbrance caused by the presence of organized thromboembolic material may lead to an initial hemodynamic overload of those segments of the pulmonary circulation initially not affected by thromboembolic disease, which likely results in a chronic vascular remodeling.[88] CTEPH is a rare complication of acute PE, considering the data of a recently published systematic review reporting a pooled incidence of CTEPH after acute PE of

Table 2
Acute-phase therapeutic strategies for patients with pulmonary embolism

PE Type	Destination	Treatment
I. High-risk PE (cardiac arrest, obstructive shock, persistent hypotension)	Admission in intensive care unit	• Hemodynamic and respiratory support • Early fibrinolysis (streptokinase, urokinase, rTPA) • UFH (at least 24–48 h) • Once stabilized, continue treatment as in III
II. Intermediate-high risk PE (RV dysfunction by imaging AND cardiac enzymes WITHOUT hemodynamic instability)	Admission in intensive care unit or intermediate care unit (if available)	• UFH preferably if there is no contraindication for eventual thrombolysis (at least 24–48 h) • Subsequently, anticoagulation (LMWH, fondaparinux, rivaroxaban, or apixaban) • Monitoring: in case of instability, consider rescue fibrinolysis
III. Intermediate-low risk PE (RV dysfunction by imaging OR cardiac enzymes WITHOUT hemodynamic instability)	Acute ward admission	• Anticoagulation (LMWH, fondaparinux, rivaroxaban, or apixaban)
IV. Low-risk PE (no RV dysfunction and hemodynamically stable)	Consider early discharge (24–48 h) or short hospital admission	• Anticoagulation (LMWH, fondaparinux, rivaroxaban, or apixaban)

Abbreviation: rtPA, recombinant tissue plasminogen activator.

3.4% (95% confidence interval 2.1%–4.4%).[89] On the other hand, 25% of CTEPH patients do not present a previous acute PE.[90] If undiagnosed and left untreated, CTEPH is associated with a 3-year mortality of 30%.[91] For this reason, an accurate and prompt screening has a not-negligible clinical relevance. Whether PE survivors should undergo a systematic screening procedure for CTEPH was matter of debate. A post hoc analysis of the PEITHO trial reported that a long-term screening after PE lead to a CTEPH diagnosis only in 10 of 709 patients, although almost one-third of PE survivors were still symptomatic after 24 months of follow-up.[84] For this reason, the recently published European guidelines suggest to perform a routine clinical evaluation after 3 to 6 months of effective anticoagulation therapy.[1] This timeframe is necessary to ensure enough time for thrombi resolution.[92] In the case of persisting dyspnea or significant functional limitation, a Doppler TTE should be performed in order to assess the risk of PH. However, sometimes the symptoms of CTEPH can be subtle and misleading. For this reason, it is quite challenging to perform a correct RS in patients who survived an acute PE. **Box 2** provides an overview of all the clinical conditions and risk factors that are associated with the development of a CTEPH after PE.

The results of cardiac ultrasounds may be integrated also with cardiopulmonary exercise test and/or with serum levels of natriuretic peptides.[1] Those patients with high probability of having PH should promptly undergo V/Q scan, and if mismatch perfusion defects are present, should be referred to a PH expert center for further diagnostic workup (Right heart catheterization (RHC)). It is crucial to establish a CTEPH diagnosis in a reasonable timeframe because different therapeutic options are available. The gold standard for CTEPH patients is pulmonary endoarterectomy (PEA), that when performed in a large-volume center, is likely to grant acceptable survival rates.[1] When PEA cannot be performed because of technical difficulties, or when CTEPH persists even after PEA, oral administration of Riociguat is indicated,[1] taking also into account its positive effects on RV size and function.[93,94] Balloon angioplasty should be considered alone or in addition to Riociguat.[1]

Box 2
Clinical conditions and risk factors associated with chronic thromboembolic pulmonary hypertension

Pulmonary embolism–related factors

Previous pulmonary embolism or deep venous thrombosis

Evidence of large thrombi in main pulmonary artery

Echocardiographic signs

Early signs of RV dysfunction

Ventricle-arterial shunts

Hematological conditions and/or disorders

Non-O blood group

Splenectomy

Thrombophilic disorders (antiphospholipid syndrome, high coagulation factor VIII levels)

Infections

Infected endovenous (EV) lines or pacemakers

Chronic osteomyelitis

Comorbidities

Thyroid replacement therapy

Cancers and myeloproliferative disorders

Inflammatory bowel disease

SUMMARY

Acute PE is the third most common acute cardiovascular condition, and its prevalence increases over time. With regards to diagnosis, D-dimer has a very high negative predictive value, and if normal levels of D-dimer are detected, the diagnosis of PE is very unlikely. The final diagnosis should be confirmed by CT scan. However, echocardiography is the most available, bedside, low-cost, diagnostic procedure for patients with PE. RS is of utmost importance and is mainly based on hemodynamic status of the patient. Thus, patients with PE and hemodynamic stability require further risk assessment, based on clinical symptoms, imaging, and circulating biomarkers (mainly NT-proBNP and troponin). Finally, in the case of persisting dyspnea during follow-up of a patient with PE, a TTE should be performed in order to assess the risk of PH.

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. Konstatinides SV, Meyer G, Becattini C, et al. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2019;41(4):543–603.
2. Raskob GE, Angchaisuksiri P, Blanco AN, et al. ISTH Steering Committee for World Thrombosis Day. Thrombosis: a major contributor to global disease burden. Arterioscler Thromb Vasc Biol 2014;34: 2363–71.
3. Keller K, Hobohm L, Ebner M, et al. Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany. Eur Heart J 2020;41(4):522–9.
4. Wendelboe AM, Raskob GE. Global burden of thrombosis: epidemiologic aspects. Circ Res 2016; 118:1340–7.
5. Barco S, Woersching AL, Spyropoulos AC, et al. European Union-28: an annualised cost-of-illness model for venous thromboembolism. Thromb Haemost 2016;115:800–8.
6. Cohen AT, Agnelli G, Anderson FA, et al. VTE Impact Assessment Group in Europe (VITAE). Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. Thromb Haemost 2007;98:756–64.
7. Bělohlávek J, Dytrych V, Linhart A. Pulmonary embolism, part I: epidemiology, risk factors and risk stratification, pathophysiology, clinical presentation, diagnosis and nonthrombotic pulmonary embolism. Exp Clin Cardiol 2013;18:129–38.
8. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. Arch Intern Med 2011; 171:831–7.
9. Kim NH, Delcroix M, Jais X, et al. Chronic thromboembolic pulmonary hypertension. Eur Respir J 2019; 53 [pii:1801915].
10. Cohen R, Loarte P, Navarro V, et al. Echocardiographic findings in pulmonary embolism: an important guide for the management of the patient. World Journal of Cardiovascular Diseases 2012;2: 161–4. https://doi.org/10.4236/wjcd.2012.23027.
11. Kurnicka K, Lichodziejewska B, Goliszek S, et al. Echocardiographic pattern of acute pulmonary embolism: analysis of 511 consecutive patients. J Am Soc Echocardiogr 2016;29:907–13.
12. Haeck ML, Scherptong RW, Marsan NA, et al. Prognostic value of right ventricular longitudinal peak systolic strain in patients with pulmonary hypertension. Circ Cardiovasc Imaging 2012;5:628–36.
13. Khemasuwan D, Yingchoncharoen T, Tunsupon P, et al. Right ventricular echocardiographic parameters are associated with mortality after acute pulmonary embolism. J Am Soc Echocardiogr 2015;28: 355–62.

14. Platz E, Hassanein AH, Shah A, et al. Regional right ventricular strain pattern in patients with acute pulmonary embolism. Echocardiography 2012;29:464–70.
15. Vitarelli A, Barillà F, Capotosto L, et al. Right ventricular function in acute pulmonary embolism: a combined assessment by three-dimensional and speckle-tracking echocardiography. J Am Soc Echocardiogr 2014;27:329–38.
16. Leibowitz D. Role of echocardiography in the diagnosis and treatment of acute pulmonary thromboembolism. J Am Soc Echocardiogr 2001;14:921–6.
17. Konstantinides S, Geibel A, Kasper W, et al. Patent foramen ovale is an important predictor of adverse outcome in patients with major pulmonary embolism. Circulation 1998;97:1946–51.
18. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 2001;69:89–95.
19. Morrow DA, de Lemos JA. Benchmarks for the assessment of novel cardiovascular biomarkers. Circulation 2007;115:949–52.
20. Salzano A, Marra AM, D'Assante R. Biomarkers and imaging: complementary or subtractive? Heart Fail Clin 2019;15:321–31.
21. Linkins LA, Takach Lapner S. Review of D-dimer testing: good, bad, and ugly. Int J Lab Hematol 2017;39(Suppl 1):98–103.
22. Wells PS, Anderson DR, Rodger M, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. Ann Intern Med 2001;135:98–107.
23. Righini M, Goehring C, Bounameaux H, et al. Effects of age on the performance of common diagnostic tests for pulmonary embolism. Am J Med 2000;109:357–61.
24. Righini M, Van Es J, Den Exter PL, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. JAMA 2014;311:1117–24.
25. Woller SC, Stevens SM, Adams DM, et al. Assessment of the safety and efficiency of using an age-adjusted D-dimer threshold to exclude suspected pulmonary embolism. Chest 2014;146:1444–51.
26. van der Hulle T, Cheung WY, Kooij S, et al. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. Lancet 2017;390:289–97.
27. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 2004;116:281–97.
28. Deng HY, Li G, Luo J, et al. MicroRNAs are novel non-invasive diagnostic biomarkers for pulmonary embolism: a meta-analysis. J Thorac Dis 2016;8:3580–7.
29. Xiang Q, Zhang HX, Wang Z, et al. The predictive value of circulating microRNAs for venous thromboembolism diagnosis: a systematic review and diagnostic meta-analysis. Thromb Res 2019;181:127–34.
30. Mantovani A, Garlanda C, Doni A, et al. Pentraxins in innate immunity: from C-reactive protein to the long pentraxin PTX3. J Clin Immunol 2008;28:1–13.
31. Gao D, Zhang L, Song D, et al. Values of integration between lipidomics and clinical phenomes in patients with acute lung infection, pulmonary embolism, or acute exacerbation of chronic pulmonary diseases: a preliminary study. J Transl Med 2019;17:162.
32. Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. Circulation 2007;116:427–33.
33. Kaeberich A, Seeber V, Jiménez D, et al. Age-adjusted high-sensitivity troponin T cut-off value for risk stratification of pulmonary embolism. Eur Respir J 2015;45:1323–31.
34. 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.
35. Kucher N, Goldhaber SZ. Cardiac biomarkers for risk stratification of patients with acute pulmonary embolism. Circulation 2003;108:2191–4.
36. Pruszczyk P, Bochowicz A, Kostrubiec M, et al. Myoglobin stratifies short-term risk in acute major pulmonary embolism. Clin Chim Acta 2003;338(1–2):53–6.
37. Dellas C, Lobo JL, Rivas A, et al. Risk stratification of acute pulmonary embolism based on clinical parameters, H-FABP and multidetector CT. Int J Cardiol 2018;265:223–8.
38. Bajaj A, Rathor P, Sehgal V, et al. Risk stratification in acute pulmonary embolism with heart-type fatty acid-binding protein: a meta-analysis. J Crit Care 2015;30:1151.e1-7.
39. Dellas C, Puls M, Lankeit M, et al. Elevated heart-type fatty acid-binding protein levels on admission predict an adverse outcome in normotensive patients with acute pulmonary embolism. J Am Coll Cardiol 2010;55:2150–7.
40. Kaczyñska A, Pelsers MM, Bochowicz A, et al. Plasma heart-type fatty acid binding protein is superior to troponin and myoglobin for rapid risk stratification in acute pulmonary embolism. Clin Chim Acta 2006;371(1–2):117–23.
41. Bajaj A, Rathor P, Sehgal V, et al. Prognostic value of biomarkers in acute non-massive pulmonary embolism: a systematic review and meta-analysis. Lung 2015;193:639–51.

42. Pasha SM, Klok FA, van der Bijl N, et al. NT-pro-BNP levels in patients with acute pulmonary embolism are correlated to right but not left ventricular volume and function. Thromb Haemost 2012;108:367–72.
43. Klok FA, Mos IC, Huisman MV. Brain-type natriuretic peptide levels in the prediction of adverse outcome in patients with pulmonary embolism: a systematic review and meta-analysis. Am J Respir Crit Care Med 2008;178:425–30.
44. Jovanovic L, Subota V, Stavric M, et al. Biomarkers for the prediction of early pulmonary embolism related mortality in spontaneous and provoked thrombotic disease. Clin Chim Acta 2019;492: 78–83.
45. Agterof MJ, Schutgens RE, Snijder RJ, et al. Out of hospital treatment of acute pulmonary embolism in patients with a low NT-proBNP level. J Thromb Haemost 2010;8:1235–41.
46. Lankeit M, Jiménez D, Kostrubiec M, et al. Validation of N-terminal pro-brain natriuretic peptide cut-off values for risk stratification of pulmonary embolism. Eur Respir J 2014;43:1669–77.
47. Vanni S, Viviani G, Baioni M, et al. Prognostic value of plasma lactate levels among patients with acute pulmonary embolism: the thrombo-embolism lactate outcome study. Ann Emerg Med 2013;61: 330–8.
48. Vanni S, Nazerian P, Bova C, et al. Comparison of clinical scores for identification of patients with pulmonary embolism at intermediate-high risk of adverse clinical outcome: the prognostic role of plasma lactate. Intern Emerg Med 2017;12:657–65.
49. Kostrubiec M, Pływaczewska M, Jiménez D, et al. The prognostic value of renal function in acute pulmonary embolism–a multi-centre cohort study. Thromb Haemost 2019;119:140–8.
50. Kostrubiec M, Łabyk 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.
51. Zhou XY, Chen HL, Ni SS. Hyponatremia and short-term prognosis of patients with acute pulmonary embolism: a meta-analysis. Int J Cardiol 2017;227: 251–6.
52. Scherz N1, Labarère J, Méan M, et al. Prognostic importance of hyponatremia in patients with acute pulmonary embolism. Am J Respir Crit Care Med 2010;182:1178–83.
53. Vuilleumier N, Simona A, Méan M, et al. Comparison of cardiac and non-cardiac biomarkers for risk stratification in elderly patients with non-massive pulmonary embolism. PLoS One 2016;11:e0155973.
54. Hellenkamp K, Pruszczyk P, Jiménez D, et al. Prognostic impact of copeptin in pulmonary embolism: a multicentre validation study. Eur Respir J 2018;51 [pii:1702037].
55. Pradhan NM, Mullin C, Poor HD. Biomarkers and right ventricular dysfunction. Crit Care Clin 2020; 36:141–53.
56. Salzano A, Israr MZ, Yazaki Y, et al. Combined use of trimethylamine N-oxide with BNP for risk stratification in heart failure with preserved ejection fraction: findings from the DIAMONDHFpEF study. Eur J Prev Cardiol 2019. https://doi.org/10.4236/wjcd.2012.23027. 2047487319870355.
57. Butler SP, Quinn RJ. The clinical course of pulmonary embolism. N Engl J Med 1992;327:957–8.
58. Goldhaber SZ, Elliott CG. Acute pulmonary embolism: part II: risk stratification, treatment, and prevention. Circulation 2003;108:2834–8.
59. Becattini C, Agnelli G. Acute pulmonary embolism: risk stratification in the emergency department. Intern Emerg Med 2007;2:119–29.
60. 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.
61. Di Nisio M, van Es N, Büller HR. Deep vein thrombosis and pulmonary embolism. Lancet 2016;388: 3060–73.
62. Penaloza A, Verschuren F, Meyer G. Comparison of the unstructured clinician gestalt, the wells score, and the revised Geneva score to estimate pretest probability for suspected pulmonary embolism. Ann Emerg Med 2013;62:117–24.e2.
63. Hendriksen JM, Geersing GJ, Lucassen WA, et al. Diagnostic prediction models for suspected pulmonary embolism: systematic review and independent external validation in primary care. BMJ 2015;351: h4438.
64. Giannitsis E, Katus HA. Risk stratification in pulmonary embolism based on biomarkers and echocardiography. Circulation 2005;112:1520–1.
65. Fesmire FM, Brown MD, Espinosa JA, et al. Critical issues in the evaluation and management of adult patients presenting to the emergency department with suspected pulmonary embolism. Ann Emerg Med 2011;57:628–52.e75.
66. Oudkerk M, van Beek EJ, Wielopolski P, et al. Comparison of contrast-enhanced magnetic resonance angiography and conventional pulmonary angiography for the diagnosis of pulmonary embolism: a prospective study. Lancet 2002;359: 1643–7.
67. Wittram C, Maher MM, Yoo AJ, et al. CT angiography of pulmonary embolism: diagnostic criteria and causes of misdiagnosis. Radiographics 2004;24: 1219–38.
68. Stein PD, Woodard PK, Weg JG, et al. Diagnostic pathways in acute pulmonary embolism: recommendations of the PIOPED II investigators. Am J Med 2006;119:1048–55.

69. Moore AJE, Wachsmann J, Chamarthy MR, et al. Imaging of acute pulmonary embolism: an update. Cardiovasc Diagn Ther 2018;8:225–43.
70. Sørensen HT, Mellemkjaer L, Steffensen FH, et al. The risk of a diagnosis of cancer after primary deep venous thrombosis or pulmonary embolism. N Engl J Med 1998;338:1169–73.
71. Rali PM, Criner GJ. Submassive pulmonary embolism. Am J Respir Crit Care Med 2018;198:588–98.
72. van der Pol LM, Tromeur C, Bistervels IM, et al. Pregnancy-adapted YEARS algorithm for diagnosis of suspected pulmonary embolism. N Engl J Med 2019;380:1139–49.
73. Peñaloza-Martínez E, Demelo-Rodríguez P, Proietti M, et al. Update on extended treatment for venous thromboembolism. Ann Med 2018;50:666–74.
74. Miller GA, Sutton GC, Kerr IH, et al. Comparison of streptokinase and heparin in treatment of isolated acute massive pulmonary embolism. Br Med J 1971;2:681–4.
75. Goldhaber SZ, Haire WD, Feldstein ML, et al. Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. Lancet 1993;341:507–11.
76. Becattini C, Agnelli G, Salvi A, et al. Bolus tenecteplase for right ventricle dysfunction in hemodynamically stable patients with pulmonary embolism. Thromb Res 2010;125:e82–6.
77. Wan S, Quinlan DJ, Agnelli G, et al. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. Circulation 2004;110:744–9.
78. Konstantinides SV, Barco S, Lankeit M, et al. Management of pulmonary embolism: an update. J Am Coll Cardiol 2016;67:976–90.
79. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016;149:315–52.
80. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 2014;370:1402–11.
81. Eberle H, Lyn R, Knight T, et al. Clinical update on thrombolytic use in pulmonary embolism: a focus on intermediate-risk patients. Am J Health Syst Pharm 2018;75:1275–85.
82. Goldhaber SZ. PEITHO long-term outcomes study: data disrupt dogma. J Am Coll Cardiol 2017;69:1545–8.
83. Konstantinides S, Geibel A, Heusel G, et al. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med 2002;347:1143–50.
84. Konstantinides SV, Vicaut E, Danays T, et al. Impact of thrombolytic therapy on the long-term outcome of intermediate-risk pulmonary embolism. J Am Coll Cardiol 2017;69:1536–44.
85. Takahashi H, Okada K, Matsumori M, et al. Aggressive surgical treatment of acute pulmonary embolism with circulatory collapse. Ann Thorac Surg 2012;94:785–91.
86. Leacche M, Unic D, Goldhaber SZ, et al. Modern surgical treatment of massive pulmonary embolism: results in 47 consecutive patients after rapid diagnosis and aggressive surgical approach. J Thorac Cardiovasc Surg 2005;129:1018–23.
87. Aymard T, Kadner A, Widmer A, et al. Massive pulmonary embolism: surgical embolectomy versus thrombolytic therapy–should surgical indications be revisited? Eur J Cardiothorac Surg 2013;43:90–4.
88. Dorfmüller P, Günther S, Ghigna MR, et al. Microvascular disease in chronic thromboembolic pulmonary hypertension: a role for pulmonary veins and systemic vasculature. Eur Respir J 2014;44:1275–88.
89. Simonneau G, Torbicki A, Dorfmüller P, et al. The pathophysiology of chronic thromboembolic pulmonary hypertension. Eur Respir Rev 2017;26 [pii: 160112].
90. Pepke-Zaba J, Delcroix M, Lang I, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation 2011;124:1973–81.
91. Delcroix M, Lang I, Pepke-Zaba J, et al. Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. Circulation 2016;133:859–71.
92. Wartski M, Collignon MA. Incomplete recovery of lung perfusion after 3 months in patients with acute pulmonary embolism treated with antithrombotic agents. THESEE Study Group. Tinzaparin ou heparin standard: evaluation dans l'Embolie Pulmonaire Study. J Nucl Med 2000;41:1043–8.
93. Marra AM, Egenlauf B, Ehlken N, et al. Change of right heart size and function by long-term therapy with riociguat in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. Int J Cardiol 2015;195:19–26.
94. Marra AM, Halank M, Benjamin N, et al. Right ventricular size and function under riociguat in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension (the RIVER study). Respir Res 2018;19(1):258.