Chapter 6
Risk Stratification and Prognosis: Identifying Patients Who May Benefit from Advanced Therapies

Abstract A subset of initially normotensive patients with pulmonary embolism (PE) may clinically deteriorate and develop systemic arterial hypotension, cardiogenic shock, and sudden death, despite prompt therapeutic-level anticoagulation. Elevated cardiac biomarkers and right ventricular (RV) enlargement on imaging studies identify such vulnerable PE patients who may benefit from more advanced therapies. Clinical examination, electrocardiography, cardiac biomarker determination, chest computed tomogram (CT), and echocardiography are key instruments in the detection of RV dysfunction and risk stratification of patients with acute PE.

Keywords Cardiac biomarkers • Pulmonary embolism • Right ventricular dysfunction • Risk stratification

Self-Assessment Questions

1. All of the following predict increased risk of adverse outcomes in the setting of acute PE except?

   (a) A PE Severity Index (PESI) score of 55
   (b) Cardiac troponin elevation
   (c) Chest CT-measured RV diameter-to-LV diameter ratio greater than 0.9
   (d) RV dilation and hypokinesis detected by transthoracic echocardiography

2. Which of the following clinical parameters in the PESI is associated with the greatest incremental increase in risk?

   (a) Cancer
   (b) Systolic blood pressure <100 mmHg
   (c) Oxygen saturation <90 %
   (d) Abnormal mental status

3. Based on the 2014 European Society of Cardiology (ESC) Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism, for which of the following patients would advanced therapy in addition to immediate anticoagulation be considered?

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(a) A 23-year-old woman with acute PE, normal blood pressure and heart rate, hypoxemia with an oxygen saturation of 88 % on room air, normal cardiac troponin level, and chest CT-measured RV diameter-to-LV diameter ratio of 0.8.
(b) A 74-year-old man with acute PE, atrial fibrillation with a heart rate of 136 beats per minute, hypotension with a blood pressure of 82/58 mmHg, hypoxemia with an oxygen saturation of 84 % on room air, increased cardiac troponin, and a chest CT-measured RV diameter-to-LV diameter ratio of 1.2.
(c) A 66-year-old woman with acute PE, normal blood pressure, heart rate of 111 beats per minute, hypoxemia with an oxygen saturation of 89 % on room air, normal cardiac troponin level, and a transthoracic echocardiogram showing RV dilation and hypokinesis.
(d) A 70-year-old woman with acute PE, normal blood pressure, heart rate of 106 beats per minute, hypoxemia with an oxygen saturation of 87 % on room air, abnormal cardiac troponin level, and a transthoracic echocardiogram showing normal RV size and function.

Clinical Vignette

A 63-year-old man with hypertension, diabetes mellitus, and a recent rheumatoid arthritis exacerbation associated with relative immobility presented to the Emergency Department with sudden onset pleuritic pain, dyspnea at rest, and palpitations. Two days prior, he noted right lower extremity edema and pain upon ambulation which he attributed to rheumatoid arthritis. Upon physical examination, he was noted to have a heart rate of 112 beats per minute, blood pressure of 102/72 mmHg, respiratory rate of 24 breaths per minute, and room air oxygen saturation of 88 %. He has moderate pitting edema up to his right knee associated with erythema and tenderness to palpation along the calf. His electrocardiogram was remarkable for sinus tachycardia to 114 beats per minute. Given that a diagnosis of PE was "likely" (based on a Wells score of 9 points), he underwent a contrast-enhanced chest CT which demonstrated large bilateral PE (Fig. 6.1). The chest CT also documented RV enlargement as defined by an RV diameter-to-LV diameter ratio of 1.0 (Fig. 6.2). His initial laboratory evaluation was remarkable for a cardiac troponin of 0.4 ng/mL (normal range <0.01 ng/mL). Because of the elevated cardiac troponin, a bedside transthoracic echocardiogram was performed and demonstrated severe RV dilation and moderate pulmonary hypertension (Figs. 6.3 and 6.4).

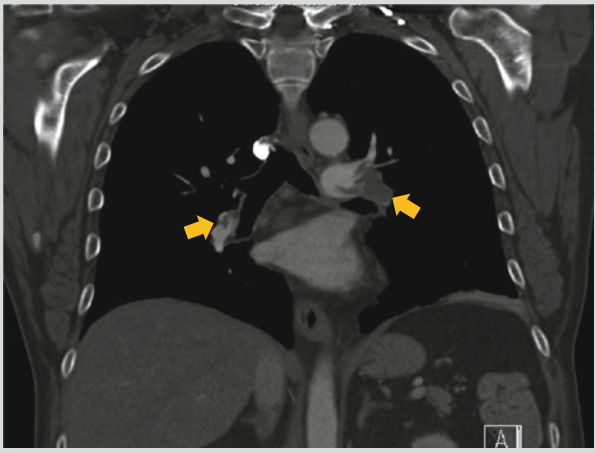

Fig. 6.1 Contrast-enhanced chest computed tomogram (CT) demonstrating large bilateral pulmonary embolism (PE) (*arrows*) in a 63-year-old man with recent rheumatoid arthritis exacerbation associated with relative immobility and sudden onset pleuritic pain and dyspnea

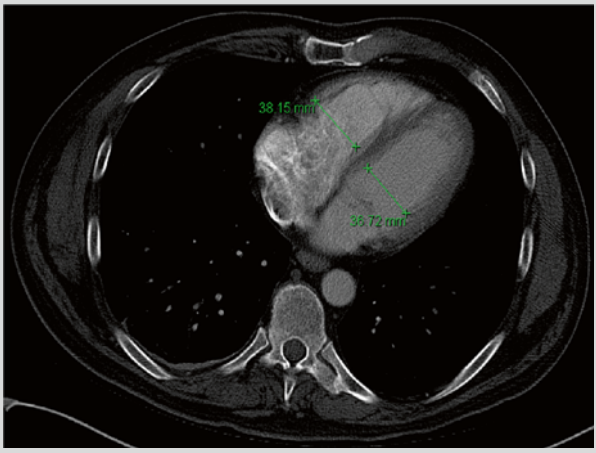

Fig. 6.2 Contrast-enhanced chest computed tomogram (CT) demonstrating right ventricular (RV) enlargement as defined by an increased RV diameter-to-left ventricular (LV) diameter ratio (3.82 cm/3.67 cm = 1.0; normal ≤ 0.9) in a 63-year-old man with acute pulmonary embolism (PE)

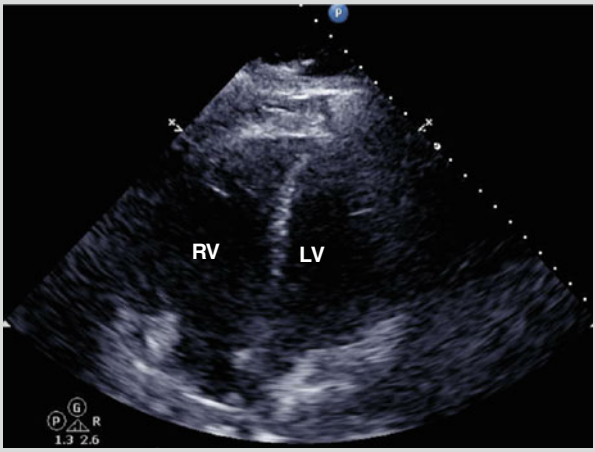

Fig. 6.3 Transthoracic echocardiogram, apical four-chamber view, demonstrating severe right ventricular (*RV*) dilatation relative to the left ventricle (*LV*) in a 63-year-old man with acute pulmonary embolism (PE)

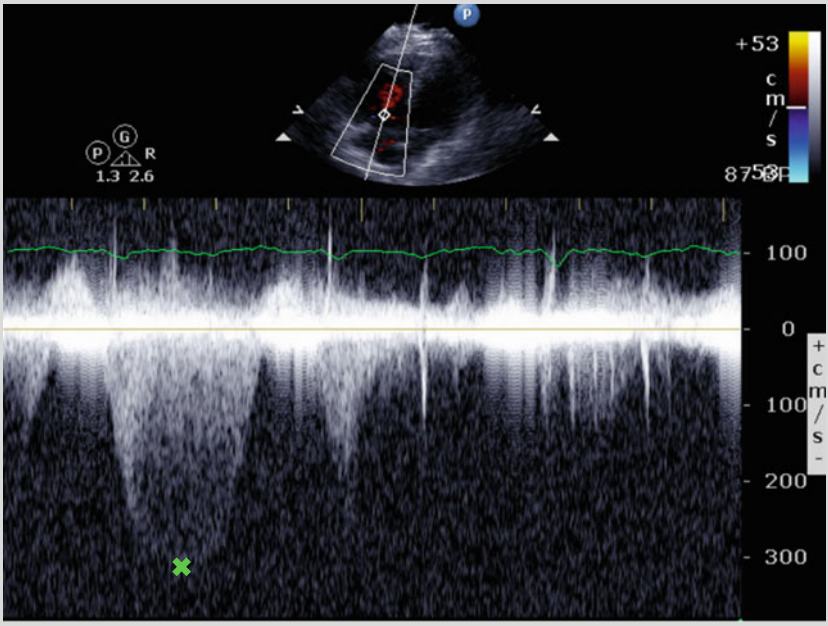

Fig. 6.4 Transthoracic echocardiogram, apical four-chamber view, demonstrating moderate pulmonary hypertension as defined by a peak tricuspid regurgitant jet velocity (*X*) of 300 cm/s in a 63-year-old man with acute pulmonary embolism (PE). Using the modified Bernoulli equation (4× [peak tricuspid regurgitant jet velocity]^2 + the estimate of right atrial pressure), the estimated pulmonary artery systolic pressure was 51 mmHg

Acute PE presents as a broad spectrum of clinical syndromes. Some patients complain of pleuritic pain, which usually results from small pulmonary emboli that affect nerve fibers in the periphery of the lung. In contrast, others may suffer massive PE resulting in syncope, systemic arterial hypotension, cardiogenic shock, or cardiac arrest. The majority of patients with acute PE presents with normal blood pressure. However, a subset of these initially normotensive patients may abruptly deteriorate and manifest systemic arterial hypotension, cardiogenic shock, and sudden death, despite prompt therapeutic-level anticoagulation. Accurate and rapid risk stratification to identify such vulnerable patients who may benefit from more advanced therapies has become a critical part of acute PE management. Clinical examination, electrocardiography, cardiac biomarker determination, chest CT, and echocardiography are key instruments in the detection of RV dysfunction and risk stratification of patients with acute PE.

Clinical Clues

The history and physical examination can provide important clues for risk stratification. The Pulmonary Embolism Severity Index (PESI) assigns 1 score point for the patient's age in years, 10 points for male sex, history of heart failure, and history of chronic lung disease, 20 points for a heart rate greater than or equal to 110 beats per minute, respiratory rate greater than or equal to 30 per minute, temperature less than 36 °C, and oxygen saturation less than 90 %, 30 points for history of cancer, and systolic blood pressure less than 100 mmHg, and 60 points for altered mental status (Table 6.1) [1, 2]. Patients with a score of 65 or less are classified as class I, or very low risk; 66–85 as class II, or low risk; 86–105 as class III, or intermediate risk; 106–125 as class IV, or high risk; and greater than 125 as class V, or very high risk. Class V corresponds with a class of patients at highest risk for 30-day mortality (25 %). In general, patients are not considered candidates for outpatient treatment of PE if their PESI score exceeds 85 points. A simplified PESI (sPESI) has also been evaluated and offers similar prognostic accuracy with greater ease of use [3]. The patient in the Clinical Vignette would be classified as high risk (Class IV) with a PESI point score of 113 (63 points for age + 10 points for male gender + 20 points for heart rate ≥100 beats per minute + 20 points for oxygen saturation <90 %).

Table 6.1 A generally accepted clinical decision rule for risk stratification of patients with acute pulmonary embolism (PE)

Variable	Points
Demographics	
Age, per year	Age, in years
Male sex	10
Comorbid illnesses	
History of cancer	30
History of heart failure	10
History of chronic lung disease	10
Clinical findings	
Heart rate ≥110 beats per minute	20
Systolic blood pressure <100 mmHg	30
Oxygen saturation <90 %[a]	20
Respiratory rate ≥30/min	20
Temperature <36 °C	20
Altered mental status[b]	60
Class I "very low risk" ≤65 points	
Class II "low risk" 66–85 points	
Class III "intermediate risk" 86–105 points	
Class IV "high risk" 106–125 points	
Class V "very high risk" >125 points	

[a]With and without the administration of supplemental oxygen
[b]Defined as disorientation, lethargy, stupor, or coma

Electrocardiography

The electrocardiogram is often one of the earliest indicators of RV dysfunction in the setting of acute PE [4]. In an analysis of the Management Strategies and Prognosis in Pulmonary Embolism Trial (MAPPET-1) registry, presence of any electrocardiographic abnormality (atrial arrhythmias, complete RBBB, low voltage in the limb leads, Q waves in leads III and aVF, or precordial ST segment changes) correlated with an increased risk of in-hospital mortality [5].

Cardiac Biomarkers

Elevations in cardiac biomarkers, including troponin, brain-type natriuretic peptide (BNP), and heart-type fatty acid-binding protein (H-FABP), are associated with RV dysfunction and are important tools for risk stratification [6]. RV pressure overload results in release of cardiac troponin due to RV microinfarction and secretion of BNP in response to increased RV shear stress [7]. Elevated levels of cardiac troponin and BNP are associated with increased short-term mortality and adverse outcomes in normotensive patients with acute PE [8, 9]. H-FABP, also released as a result of myocardial injury, diffuses more rapidly than troponin and is detectable earlier [10]. Patients with acute PE and normal H-FABP levels have an excellent prognosis regardless of echocardiographic findings, while those with increased levels of H-FABP have a higher rate of adverse events, even if echocardiography is normal [9]. The patient in the Clinical Vignette had an increased cardiac troponin consistent with myocardial necrosis due to RV pressure overload and increased risk of adverse clinical outcomes.

Imaging Studies

Chest Computed Tomography

Detection of RV enlargement by contrast enhanced chest CT is an especially convenient risk stratification tool because it utilizes data acquired from the initial diagnostic scan (Fig. 6.2). Based on measurements from an axial CT view, RV enlargement, defined as a ratio of RV diameter to LV diameter of greater than 0.9, has been found to be a significant independent predictor of mortality at 30 days [11–13]. A meta-analysis demonstrated that an increased RV diameter-to-LV diameter ratio correlated with at least a sevenfold increased risk of PE-related mortality [14]. RV diameter-to-LV diameter ratio serves as a surrogate for the RV volume-to-LV volume ratio. In the Clinical Vignette, the patient's RV diameter-to-LV diameter ratio of 1.0 identifies him as having increased risk of early mortality.

Echocardiography

Echocardiography is the best imaging study to detect RV dysfunction in the setting of acute PE and constitutes the core of risk stratification algorithms (Fig. 6.3). Normotensive patients with acute PE and evidence of RV dysfunction on echocardiography demonstrate an increased risk of systemic arterial hypotension, cardiogenic shock, and death, whereas those without RV dysfunction generally have a benign clinical course [15, 16]. Echocardiography should be performed in patients with acute PE and clinical evidence of RV failure, elevated cardiac biomarkers, suspected pulmonary arterial hypertension, clinical deterioration, or suspicion of other comorbid cardiac disease [17]. The addition of cardiac troponin levels to echocardiographic findings of RV dysfunction provides incremental information for risk stratification and helps to identify patients with a greater risk of PE-related death and all-cause mortality [18]. The patient in the Clinical Vignette had both evidence of RV dysfunction on transthoracic echocardiography and cardiac troponin elevation.

An Integrated Approach to Risk Stratification

Risk stratification in patients with acute DVT focuses on identifying those at increased risk for developing post-thrombotic syndrome which is characterized by chronic lower extremity pain, edema, and if advanced, venous ulceration. Patients with iliofemoral or femoral DVT have an increased risk of developing post-thrombotic syndrome and may benefit from advanced therapies such as catheter-directed fibrinolysis ("pharmacomechanical therapy") in addition to prompt anticoagulation [19]. Risk stratification for DVT dichotomizes patients into those with iliofemoral or femoral involvement and those with more distal disease (Fig. 6.5).

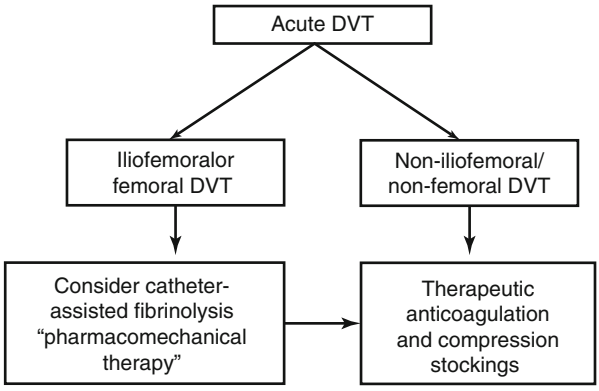

Fig. 6.5 An algorithm for risk stratification of patients with acute deep vein thrombosis (*DVT*)

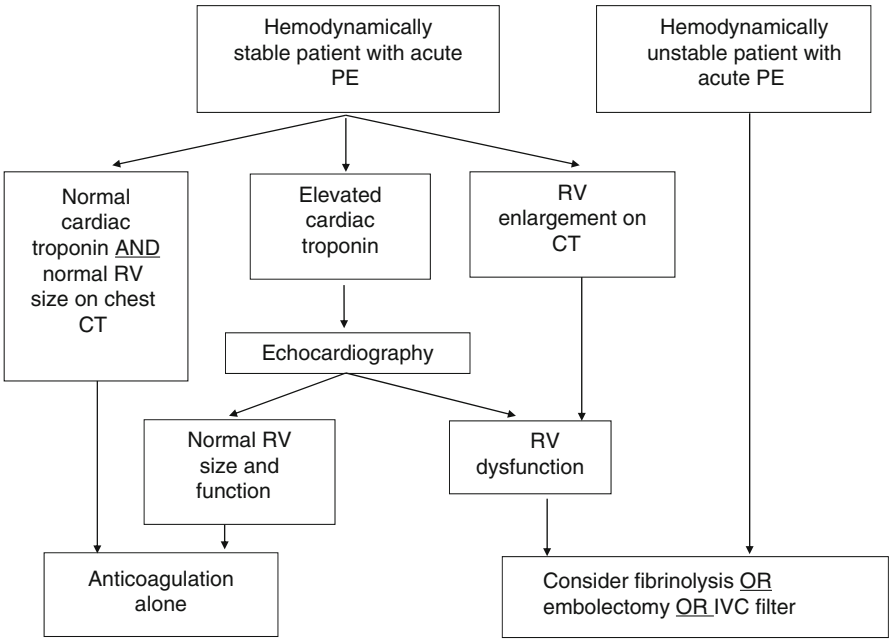

Fig. 6.6 An algorithm for risk stratification of patients with acute pulmonary embolism (*PE*). *RV* right ventricular, *CT* computed tomography, *IVC* inferior vena cava

For identification of patients with acute PE at risk for adverse outcomes, a risk stratification algorithm should integrate clinical prognostic indicators, cardiac biomarkers, and evidence of RV dysfunction as detected by either echocardiography or chest CT (Fig. 6.6) [20]. The 2014 European Society of Cardiology (ESC) Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism emphasize the importance of an integrated approach for accurate identification of PE patients who are potential candidates for advanced therapy [21]. The 2014 ESC Guidelines classify patients into four categories of risk for early mortality: low, intermediate-low, intermediate-high, and high (Table 6.2). While low risk PE patients are characterized by preserved hemodynamics, a low PESI or Simplified PESI score, and no evidence of RV dysfunction or myocardial necrosis, high risk PE patients are marked by the presence of shock or hypotension. Intermediate-low risk PE patients are characterized by preserved hemodynamics but have an increased PESI or Simplified PESI score and either signs of RV dysfunction on imaging or elevated cardiac biomarkers (or neither). Intermediate-high risk PE patients also have preserved hemodynamics and an increased PESI or Simplified PESI score but have both signs of RV dysfunction on imaging and elevated cardiac biomarkers. High risk and intermediate-high risk PE patients are recommended to be considered for advanced therapies on a case-by-case basis. According to the 2014 ESC Guidelines, the patient in the Clinical Vignette would be categorized as intermediate-high risk for adverse clinical outcomes due to PE and would be considered for advanced therapy.

Table 6.2 2014 European Society of Cardiology (ESC) guidelines risk classification for patients with acute pulmonary embolism (PE)

Early mortality risk		Shock or hypotension	PESI class III-V or sPESI >1	RV dysfunction on imaging	Myocardial necrosis
High		Yes	Not required but "Yes" if assessed	Yes	Not required but "Yes" if assessed
Intermediate	Intermediate-high	No	Yes	Yes	Yes
	Intermediate-low	No	Yes	"Yes" for either one or neither	
Low		No	No	Not required but "No" if assessed	Not required but "No" if assessed

Answer Key

1. **Correct answer**, (**a**) A PE Severity Index (PESI) score ≤65 (Class I) corresponds with a very low risk of adverse events.
2. **Correct answer**, (**d**) Abnormal mental status contributes 60 score points in the PESI. Cancer, systolic blood pressure <100 mmHg, and oxygen saturation <90 % contribute 30 points, 30 points, and 20 points, respectively.
3. **Correct answer**, (**b**) The 74-year-old man with acute PE had systemic arterial hypotension, RV dysfunction on imaging, and elevated cardiac biomarkers (increased troponin) and would be classified as high risk per the 2014 ESC Guidelines. Only intermediate-high and high risk patients are considered for advanced therapy to treat acute PE.

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