European Journal of Internal Medicine 65 (2019) 29–31

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Patients with acute pulmonary embolism at intermediate risk for death: Can we further stratify?

Cecilia Becattini*, Ludovica Anna Cimini, Maria Cristina Vedovati

Internal and Cardiovascular Medicine – Stroke Unit, University of Perugia, Perugia, Italy

International Scientific Societies (European Society of Cardiology, American Heart Association, American College of Chest Physician) recommend stratification for the risk of short-term death to drive acute clinical care in patients with acute pulmonary embolism (PE) [1–3]. However, no consensus exists on the optimal strategy for risk stratification beyond the classification in hemodynamically stable and unstable patients. The European Society of Cardiology (ESC) proposed a comprehensive strategy for risk stratification that includes both clinical and instrumental criteria [1]. Based on this strategy, patients are divided by the ESC into three categories: low (1.2%), intermediate (3.4 to 10%) or high (15 to 30%) risk for death. To qualify for the intermediate-risk group, hemodynamically stable patients should have a not-low risk for death according to PESI or simplified PESI scores [1]. This intermediate-risk group includes about 60% of patients with acute PE who can be highly heterogeneous concerning clinical features and the severity of PE [4,5]. The ESC guidelines suggest to further classify the intermediate category into intermediate-low and intermediate-high risk of death according to the presence/absence of right ventricle dysfunction assessed by echocardiography or CTPA and/or by the presence/absence of increase in troponin levels (Table 1) [1]. The aim of this stratification is the prompt identification of hemodynamically stable patients with expected short-term mortality of about 7 to 10% that could benefit from pulmonary reperfusion. In fact, according to the ESC guidelines, intermediate-high risk patients are candidates to initial monitoring and rescue reperfusion in case of clinical deterioration. An international cohort study showed that the sub-stratification of intermediate-risk patients (intermediate-high and intermediate-low) according to the ESC guidelines is probably not efficient in discriminating two categories of patients at different risk of death and requires improvement [4].

In this issue of the Journal, Beigel et al. report on a retrospective study in normotensive patients with acute PE aimed at deriving a score for patient stratification according to the risk for clinical deterioration requiring treatment upgrading [6]. The primary outcome, clinical deterioration requiring treatment upgrading, occurred in 15% of the patients. Syncope (HR 2.8 CI 1.1–7.1) and severe right ventricular dysfunction at echocardiography (HR 3.5, CI 1.4–9.3) were independent predictors of the escalation of therapy. Based on these data, the authors propose a score which combines clinical (syncope at presentation), laboratory (degree of increased troponin) and imaging (degree of right ventricle dysfunction) parameters to stratify intermediate risk patients for the risk of escalation therapy.

Several recent studies have been conducted with the aim of improving prognostic stratification in intermediate risk patients with acute PE. Some of these studies proposed the adoption of new scores and other studies proposed the implementation of existing scores (Table 1) [7–11].

The proposal by Beigel et al. is to maintain a central role for right ventricle dysfunction and troponin for risk stratification of intermediate risk patients and to add thresholds of severity to these predictors [6]. Right ventricle dysfunction at echocardiography is classified as mild, moderate and severe; right ventricle dilation at CT angiography and increased troponin are further classified by the use of severity cut-offs. The clinical plausibility for this strategy is provided by previous studies suggesting that by increasing the threshold for right ventricle dysfunction it is possible to increase its positive predictive value. Increasing values of right to left ventricle diameter ratio at CT angiography were associated with an increased risk of death (OR 1.99, 95% CI 1.38–2.86 for a cut-off of 0.9, OR 2.81, 95% CI 1.78–4.42 for cut-offs ≥ 1) in a meta-analysis of cohort studies [12]. Similarly, a linear relationship was reported for the right to left ventricle diameter ratio at echocardiography and mortality in patients with acute PE [13]. However, a standardization of cut-off levels for right ventricle dysfunction is required before applying to clinical practice. The value of syncope as a predictor of adverse outcome is debated, mainly in hemodynamically stable patients [14]. Indeed, syncope is associated with higher prevalence of hemodynamic instability (OR 3.50; 95% CI 2.67–4.58) and of echocardiographic signs of right ventricular dysfunction (OR 2.10; CI 1.60–2.77) but not consistently with adverse outcome.

An additional critical issue for risk stratification in hemodynamically stable patients is the definition of the outcome of interest. Beigel et al. identified clinical deterioration requiring escalation of therapy for their study. Although clinical deterioration may be defined according to validated criteria, the need for escalation of treatment is not a reliable

DOI of original article: https://doi.org/10.1016/j.ejim.2019.04.018
* Corresponding author.
E-mail address: Cecilia.becattini@unipg.it (C. Becattini).

https://doi.org/10.1016/j.ejim.2019.06.008
Received 8 June 2019
Available online 24 June 2019

Table 1
Risk stratification in hemodynamically stable patients with acute PE according to different scores or models [6–11].

	Model	Composition	
Validated Models	2014 ESC	RVD + increased troponin	
		RVD or increased troponin or none	
		Low risk: simplified PESI = 0 or PESI class I or II	
	Bova score	sBP 90-100 mmHg	+2
		Heart Rate ≥ 110 bpm	+1
		RVD	+2
		Increased troponin	+2
	Telos	RVD + Increased troponin + increased lactate	
		RVD + Increased troponin	
		RVD or Increased troponin or none	
	FAST	Syncope	1.5
		Heart rate ≥ 100 bpm	2
		H-FABP ≥6 ng/ml or elevated troponin	1.5
Non validated Models	2014 ESC + OXYGEN SATURATION	RVD + increased troponin + oxygen saturation < 88%	
		RVD or increased troponin + oxygen saturation < 88%	
		RVD or increased troponin	
		Low risk: simplified PESI = 0 or PESI class I or II	
	ROCky score	Positive hFABP test	+2
		Heart rate ≥ 110 bpm	+1.5
		Diabetes mellitus	+2.5
		sBP ≤ 100 mmHg	+2.5
		Low risk: simplified PESI = 0 or PESI class I or II	
	Beigel et al	Syncope	+1
		Moderate or severe RVD on echocardiography	+1
		RV/LV ratio above > 1.425 on CT tomography	+1
		Troponin in the upper tertile (> 0.7 μg/l)	+1
		Normal ECG	-1
		Low risk: simplified PESI = 0 or PESI class I or II	

RVD = Right Ventricle Dysfunction; bpm: beats per minute; hFABP: heart-type Fatty Acid Binding Peptide; PESI = Pulmonary Embolism Severity Index; sBP = systolic Blood Pressure.

outcome outside the context of blinded clinical trials. Thus, mortality is probably the outcome of choice for cohort studies assessing the course of PE. Whether mortality due to PE is an accurate outcome is debated since defining the cause of death maybe a hard task, also for expert physicians [15,16].

Moreover, the PEITHO trial showed that the incidence of major bleedings may out-weight the benefit of systemic thrombolysis in hemodynamically stable patients with PE, right ventricle dysfunction and increased troponin [19]. Thus, the optimal risk stratification strategy should result in a high positive predictive value for hard clinical outcomes to face the risk of systemic thrombolysis or interventional procedures. In this view, risk stratification strategies integrating clinical evaluation and imaging are the most promising.

In conclusion, the study by Beigel et al. shows that i) the optimal strategy for risk stratification is still undefined, mainly in intermediate risk patients with PE and that ii) we are progressively moving to personalized strategies for risk stratification integrating patients features with signs of right ventricle dysfunction. Physicians should be aware that the severity of PE is a continuum and that whatever stratification process will hardly be able to reflect such continuum (Fig. 1). Although personalized medicine is an attractive matter, it poses the issue of balancing precision with feasibility in everyday clinical practice. Further studies should be conducted to validate new stratifications tools and risk-driven management strategies. While waiting for evidence from these studies, physicians should rely on existing evidence for decision making.

Declaration of Competing Interest

Cecilia Becattini reports lecture fees and consultancies from Bayer HealthCare, Bristol Myers Squibb and Daiichi Sankyo outside the submitted manuscript.

Maria Cristina Vedovati and Ludovica Anna Cimini report no conflict of interest.

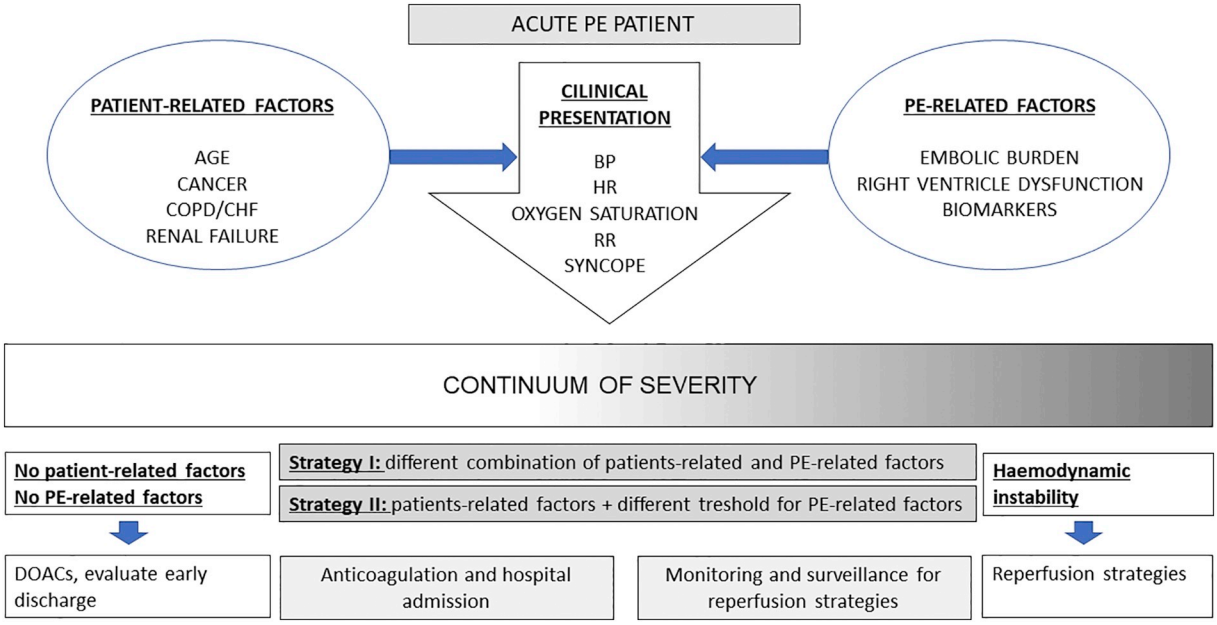

Fig. 1. Main predictors of death and potential management strategies in patients with acute PE. COPD = Chronic Obstructive Pulmonary Disease; CHF = Congestive Heart Failure. BP = Blood Pressure; HR = Heart Rate; RR = respiratory rate; DOACs = Direct Oral Anticoagulants.

Acknowledgement

No external support to declare for this manuscript.

References

[1] Konstantinides SV, Torbicki A, Agnelli G, et al. Authors/Task Force Members. 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;35:3033–69.

[2] Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation 2011;123(16):1788–830.

[3] Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest. 2016;149:315–52.

[4] Becattini C, Agnelli G, Lankeit M, et al. Acute pulmonary embolism: mortality prediction by the 2014 European Society of Cardiology risk stratification model. Eur Respir J 2016;48(3):780–6.

[5] Becattini C, Casazza F, Forgione C, et al. Acute pulmonary embolism: external validation of an integrated risk stratification model. Chest 2013;144(5):1539–45.

[6] Beigel R, Mazin I, Goitein O, et al. Intermediate-risk pulmonary embolism: aiming to improve patient stratification. Eur J Intern Med 2019 May 1. https://doi.org/10.1016/j.ejim.2019.04.018.

[7] Becattini C, Vedovati MC, Pruszczyk P, et al. Oxygen saturation or respiratory rate to improve risk stratification in hemodynamically stable patients with acute pulmonary embolism. J Thromb Haemost 2018;16(12):2397–402.

[8] Bova C, Vanni S, Prandoni P, et al. Bova Score Validation Study Investigators. A prospective validation of the Bova score in normotensive patients with acute pulmonary embolism. Thromb Res 2018;165:107–11.

[9] 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(5):996–1003.

[10] Kochmareva EA, Kokorin VA, Gordeev IG. The new bedside ROCky score to predict the complications in patients with intermediate-risk pulmonary embolism. Eur J Intern Med 2018;57:58–60.

[11] Vanni S, Jiménez D, Nazerian P, et al. Short-term clinical outcome of normotensive patients with acute PE and high plasma lactate. Thorax 2015;70(4):333–8.

[12] Becattini C, Agnelli G, Germini F, Vedovati MC. Computed tomography to assess risk of death in acute pulmonary embolism: a meta-analysis. Eur Respir J 2014;43(6):1678–90.

[13] Sanchez O, Trinquart L, Caille V, et al. Prognostic factors for pulmonary embolism: the PREP study, a prospective multicenter cohort study. Am J Respir Crit Care Med 2010;181(2):168–73.

[14] 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(47):4186–95.

[15] Girard P, Penaloza A, Parent F, et al. Reproducibility of clinical events adjudications in a trial of venous thromboembolism prevention. J Thromb Haemost 2017;15:662–9.

[16] Stuck AK, Fuhrer E, Limacher A, Méan M, Aujesky D. Adjudication-related processes are underreported and lack standardization in clinical trials of venous thromboembolism: a systematic review. J Clin Epidemiol 2014;67:278–84.

[19] Meyer G, Vicaut E, Danays T, et al. PEITHO Investigators. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 2014;370(15):1402–11.