Classification and Stratification of Pulmonary Embolisms

Cody Russell, BS[1] Suresh Keshavamurthy, MD, FACS, FRCS[2,3] Sibu Saha, MD, MBA[2,3]

[1] The American University of the Caribbean School of Medicine, Pembroke Pines, Florida
[2] Department of Surgery, University of Kentucky College of Medicine, Lexington, Kentucky
[3] Division of Cardiothoracic Surgery, Kentucky Clinic, University of Kentucky College of Medicine, Lexington, Kentucky

Address for correspondence Suresh Keshavamurthy, MD, FACS, FRCS, Division of Cardiothoracic Surgery, Kentucky Clinic, University of Kentucky College of Medicine, 740 S. Limestone, Ste.A301, Lexington, KY 40536 (e-mail: Suresh.keshavamurthy@uky.edu).

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Abstract

Pulmonary embolism remains a leading cause of cardiovascular mortality. Presentation and outcomes are variable among patients and require rapid risk stratification for assessment and prognosis, as well as selection of appropriate treatment. Over the past several decades, several different models and parameters have become available to assess risk and classify pulmonary embolism into different risk categories. Some patients may be candidates for early discharge or complete outpatient treatment, while some may require invasive diagnostics and intensive monitoring. In this review, we summarize contemporary guidelines and methods for classification and risk stratification in an effort to provide tools for physicians to use in their management of patients with acute pulmonary embolisms.

Keywords

- pulmonary embolism
- classification
- stratification
- venous thromboembolism
- computed tomography pulmonary angiography
- RV function
- prognostic scoring

Pulmonary embolism (PE) is a leading cause of morbidity and mortality.[1,2,3] Acute PEs present with variable mortality rates as low as 2% in normotensive patients without right ventricle (RV) dysfunction, and as high as 95% in patients who present with cardiac arrest.[4,5] Nearly 20 to 25% of all PE cases present with sudden death, while it is estimated 10 to 30% of patients die within 30 days.[2] Advancements in medicine over the past several decades have led to what was once viewed as an absolute death sentence, now being tackled from a more preventative public health approach. Largely thanks to computed tomography pulmonary angiography (CTPA) and advancements in laboratory techniques, venous thromboembolism (VTE) is being diagnosed more frequently and efficiently than ever before. As our population ages, obesity rates climb, and life expectancy with chronic disease increases, the index of suspicion for PE must remain prevalent. The pertinent question becomes how can we appropriately diagnose and treat patients, allocate resources, and most importantly prevent PE morbidity and mortality in patients suffering an acute PE? We aim to outline the most validated prognostic stratification tools used to classify patients based on severity and risk of mortality. Classification and stratification of PE patients are important in the assessment of prognosis and selection of treatment. It is our hope that awareness of different clinical decision rules and classification guidelines will promote the appropriate classification and identification of patients who may be at low-risk and possibly eligible for outpatient treatment, as well as those that are intermediate- or high-risk and may benefit from more aggressive treatment.

Classification Guidelines

PE severity is commonly classified by terms proposed in the most recent 2019 statements by the American Heart

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Table 1 AHA/ESC PE classification

Classification	Characteristics	Percentage of PEs	30-Day mortality rate
Massive/high-risk	- Presence of hypotension, systolic BP $<$ 90 mm Hg, or drop of $\geq$ 40 mm Hg for at least 15 minutes - Requirement of vasopressor support	5%	$\sim$ 65%
Submassive/ intermediate risk	- Presence of RV strain, dilation, or dysfunction - Intermediate to high: RV dysfunction and RV injury - Intermediate-to-low: if only one or neither	40%	5–25%
Low risk	- Do not meet criteria for submassive or intermediate risk	40–60%	$\sim$1%

Abbreviations: AHA/ESC, American Heart Association/European Society of Cardiology; BP, blood pressure; PE, pulmonary embolism; RV, right ventricular.

Source: Giri J, Sista AK, Weinberg I, et al. Interventional therapies for acute pulmonary embolism: current status and principles for the development of novel evidence: a scientific statement from the American Heart Association. Circulation 2019;140(20):e774–e801. doi:doi:10.1161/CIR.0000000000000707

Konstantinides 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): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Heart J 2019;41(4):543–603. doi:10.1093/eurheartj/ehz405

Association (AHA)[3] and the European Society of Cardiology (ESC).[6] The AHA/ESC classification guidelines are quite similar and divide PE severity into three main categories based on commonly available or easily obtainable clinical variables (see ►**Table 1**). The first category is termed massive PE/high-risk as defined by AHA/ESC, respectively.[3,6,7] Next is submassive (AHA) or intermediate risk (ESC), according to the AHA, these patients are classified by being normotensive with evidence of RV dysfunction or myocardial ischemia.[8] RV function is commonly assessed via echocardiography, while RV dilation (RV/LV ratio $>$0.9) can be diagnosed via CT or echocardiography. Myocardial ischemia is often assessed by electrocardiogram (ECG) and biomarkers such as cardiac troponin and brain natriuretic peptide (BNP). Electrocardiography may also be useful in assigning patients to the submassive group by identifying specific ECG changes (right bundle branch blocks, anteroseptal ST changes, anteroseptal T-wave inversions); however, their positive predictive value remains low.[7] ESC classification of intermediate risk patients differs slightly from the AHA by not only being broader but incorporating the use of the simplified Pulmonary Embolism Severity Index (sPESI) for short-term PE-related 30-day mortality. Patients with an sPESI more than or equal to 1 are then subdivided into intermediate subgroups, intermediate-high, and intermediate-low. The PESI and sPESI consist of objective, easily identifiable clinical parameters that can be quickly obtained immediately on patient presentation.[9] One study even reported that a decrease in PESI scores at the 48-hour interval could significantly identify an additional 8% of patients at low risk of mortality.[9] Finally, low-risk patients as defined by AHA/ESC do not meet the criteria for submassive/intermediate risk.[3,6]

Contemporary Risk Stratification

The variable presentation and mortality associated with PE require immediate risk stratification as a method to guide treatment by identification of patients most likely to experience adverse outcomes whether it is decompensation or death.[3,6,7] As mentioned previously, massive/high-risk patients are defined by the presence of hemodynamic instability, also known as severe hypotension (systolic blood pressure $\leq$ 90 mm Hg)/shock. Treatment for these patients often requires rapid anticoagulation and hemodynamic support. Assessment of hemodynamic status in PE patients is of the utmost importance in the management and evaluation of PEs due to its direct correlation with an increased risk of morbidity and mortality.[10] However, some patients classified as submassive/intermediate risk can often present as normotensive but still be at a high risk for short-term adverse PE-related events, of which a few patients might benefit from an escalation of therapy or more intensive monitoring. Recent studies have discovered that nearly 55% of normotensive patients with acute PE have asymptomatic RV dysfunction and carry an increased 30-day mortality between 3 and 10%, doubling the risk of all-cause mortality during 3 months follow-up.[10] Unfortunately, common biomarkers used such as D-dimer, cardiac troponin, or lactic acid are indirect markers of RV function and may be falsely elevated in some patients.[10] Direct identification of RV function in intermediate-risk patients, early in the hospital course, may help further risk stratification into appropriate groups, guide treatment strategies, and prevent adverse patient outcomes.

Several studies have outlined the degree of pulmonary vascular obstruction as the most important factor in determining response to an acute PE.[8,10,11,12,13] Although CTPA has become the imaging gold standard for direct diagnosis of PE, it may also be effective as a noninvasive biomarker for the risk stratification of patients diagnosed with PE. CTPA is not only widely available, is fast, non-invasive, and has an average sensitivity of 88% and specificity of 92 to 96%.[12] Research has found that in patients without existing cardiopulmonary disease, obstruction of pulmonary vascular bed more than or equal to 25 to 30% is required before a significant increase in pulmonary artery pressure develops.[8,13] Clot burden or thrombus load in the pulmonary vascular tree can be

quantified by CTPA down to the subsegmental level, while at the same time assessing RV enlargement.[10]

Classification by CTPA Findings

Massive PE patients are characteristically hemodynamically unstable; these patients are often treated off clinical suspicions and CTPA is delayed. Over recent decades, several CTPA findings have been shown to have some prognostic value in the stratification of submassive/intermediate-risk patients.

The pulmonary artery obstruction index (PAOI) can be calculated using the modified Walsh and Miller scores, or the Mastora index. More commonly, the Qanadli index is used because of its easy clinical application and additional information on thrombus load and degree of obstruction.[8,11,13,14] Measurement of the PAOI is seen as an objective and reproducible tool that can be used in interdisciplinary communication aiding in the ability to risk stratify, indicate prognosis, guide treatment, and serve as a noninvasive method of monitoring response to thrombolytics.[14] Obstruction of the pulmonary vasculature tree is a main factor in increased pulmonary vascular resistance, resulting in pulmonary hypertension and ensued RV dysfunction.[14] Prognosis correlates directly with the degree of hemodynamic compromise and presence of RV dysfunction.[12] Although data is mixed, a PAOI of more than or equal to 50% correlates well in identifying nearly 90% of patients with PE and concomitant RV dilation, which is associated with an 11.2-fold increased risk of 3-month mortality.[10,11,12,13,14]

An RV/LV ratio can objectively be measured and reproduced on CTPA aiding in risk assessment. The ability of CTPA to assess the pulmonary vasculature tree while simultaneously measuring RV and LV diameter serves as a possible more efficient and reliable method of risk stratification that could make echocardiography obsolete. One meta-analytic study found increased RV/LV ratio measured via CTPA was associated with the strongest risk of PE-related mortality at a nearly fivefold increase.[8] On axial views, an RV/LV ratio more than or equal to 0.9 to 1.5 mm has been shown to be directly correlated with RV dysfunction.[10] Another interesting CTPA finding that has been extensively studied is pulmonary artery diameter (PAD). PAD can easily be measured on CTPA, and a measurement of 29mm has long been the cutoff for diagnosing pulmonary hypertension.[15] It has also been reported that more than or equal to 29 mm correlates with RV dysfunction by echo and is associated with increased mortality in acute PE.[15] Increased PAD has also been associated with a significantly increased mortality in PE patients (odds ratio: 1.08 per 1-mm increase in PAD).[15]

Several less common often less validated CTPA measurements still deserve honorable mention and further research in their validity could be possible direction for the future. Some studies have looked at inferior vena cava contrast reflux as an indirect indication of elevated RV and RA pressure, associated with a decreased 30-day survival.[15] Another controversial method is dilation of the superior vena cava or azygous vein due to increased RV and RA pressure.[10] Interest in CTPA findings and their possibility to aid in rapid risk stratification is only continuing to grow. Larger cohort studies and clinical trials are needed to define those most associated with adverse outcomes in the setting of acute PE.

Prognostic Scoring Methods

The AHA and ESC have been consistent in their support of furthering risk stratification of hemodynamically stable PE patients to assist in therapeutic decisions.[3,6] However, individual markers of RV dysfunction (Echo, CTPA, cardiac troponin, BNP) continue to have insufficient positive predictive values for PE-specific complications.[16] In 2014, the American College of Chest Physicians (CHEST) developed a prognostic model for intermediate-risk PE patients that was based on clinical presentation, assessment of RV function, and myocardial injury.[16] The combination of one domain that quantifies RV dysfunction, one that captures myocardial injury, and two independent domains that evaluates hemodynamic status (heart rate and systolic blood pressure), has proven useful in the prediction of a sevenfold increase in PE-related mortality.[16] The Bova risk score accurately stratifies normotensive patients with acute PE into stages of increasing risk of PE-related complications that occur within 30 days of PE diagnosis.[17,18] Prognostic scoring methods are gaining traction, some like the eStiMaTe score integrate sPESI as ways to predict prognosis and treat PE patients.[19] Further study and implementation are needed to affirm best method.

Low-Risk Patients

Current guidelines suggest outpatient treatment for PE should only be considered in low-risk patients, evident via lab and imaging conformation. The Hestia rule is defined by medical and social criteria of risk markers for adverse used to assess the possibility of outpatient treatment.[20,21] Several studies have found that the Hestia rule is able to appropriately triage patients for home treatment.[20,21,22] The difference between Hestia and the current ESC guidelines is that Hestia takes into consideration the treating physician's opinion of the patient.[22] One study reported that treating appropriately selected patients with PE by Hestia criteria does not increase early mortality, recurrent VTE, or bleeding risk.[21] Further study and trials with low-risk patients are needed to confirm the ability to identify patients that could undergo outpatient or early discharge treatment.

Conclusion

PE is an important cause of morbidity and mortality, and ongoing studies, technology advancements, and multidisciplinary collaboration help guide the way we treat our patients. We must use all of the tools at our disposal to judiciously diagnose, classify, and treat these patients. Several models have shown their ability to assess risk and identify patients outlining the appropriate patient-based treatment. Measurements of hemodynamic status, clot burden, and RV dysfunction are just a few of the possible ways

we can continue to identify those patients at risk of PE-related adverse outcomes. In 2012, Massachusetts General Hospital implemented the first *pulmonary embolism response teams* (*PERT*), in which a group of multidisciplinary providers were charged with providing rapid diagnosis and possible therapeutic options based on individual patient scenario.[23] Over the last decade, PERT have provided quicker access to advanced therapeutic options as well as better outcomes in massive PE patients.[23,24] Awareness of different clinical guidelines can help identify and classify patients based on their risk for harm with the goal of providing the best possible patient care.

Authors' Contribution

Sibu Saha contributed to the conception and design of the review. Suresh Keshavamurthy and Cody Russell contributed to the acquisition, analysis, and interpretation of the data. Cody Russell drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript

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Conflicts of Interest

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