Thrombosis Research xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Thrombosis Research

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

Full Length Article

# Pulmonary embolism severity assessment and prognostication

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ARTICLE INFO

*Keywords:*
Pulmonary embolism
Prognosis
Mortality
Survival

ABSTRACT

For patients who have acute symptomatic pulmonary embolism (**PE**), risk of short-term death and adverse outcomes should drive the initial treatment decisions. Practice guidelines recommend that patients who have a *high-risk* of PE-related death and adverse outcomes, determined by the presence of haemodynamic instability (i.e., shock or hypotension), should receive systemically administered thrombolytic therapy. *Intermediate-high risk* patients might benefit from close observation, and some should undergo escalation of therapy beyond standard anticoagulation, particularly if haemodynamic deterioration occurs. *Low-risk* for adverse outcomes should lead to early hospital discharge or full treatment at home. Validated prognostic tools (i.e., clinical prognostic scoring systems, imaging studies, and cardiac laboratory biomarkers) assist with risk classification of patients who have acute symptomatic PE.

## 1. Introduction

Over the past two decades, technological and clinical research methods advances have improved acute pulmonary embolism (**PE**) diagnostic accuracy, risk stratification, and treatment. Contemporary multinational observational data showed temporal changes in patient management that were associated with reductions in all-cause and PE-related mortality [1,2].

The clinical presentation of acute PE ranges from mild symptoms to sustained hypotension or shock [3]. Depending on the estimated risk of an adverse outcome, admission to an intensive care unit (**ICU**) and early recanalization (i.e., thrombolysis, catheter or surgical embolectomy) may be indicated for patients deemed *high-risk* for developing complications associated with PE [4,5]. Alternatively, early hospital discharge or home treatment may be considered for patients who have a negligible short-term risk of complications [6].

## 2. Identification of patients who have PE and a low risk for early adverse outcomes

*A previously healthy 43-year-old man presented with right-sided aching chest pain that worsened with deep inspiration. On physical examination, the patient had a blood pressure of 120/85 mm Hg, a heart rate of 80 beats per minute, and a pulse oximetry oxygen saturation of 97% while breathing ambient air. A contrast-enhanced computed tomography pulmonary angiogram showed an isolated right lower lobe segmental PE (Fig. 1).*

Most clinicians would consider this patient as having a *low-risk* for short-term adverse outcomes. These *low-risk* patients lack significant signs of acute cardiopulmonary compromise (e.g., hypotension, marked hypoxemia) and have a low short-term risk of developing complications that include all-cause mortality, recurrent venous thromboembolism (**VTE**), and major bleeding. Since cardiac biomarkers and cardiac imaging results have poor predictive values for these adverse outcomes in patients who have acute PE, guidelines suggest the use of clinical prognostic scores to identify *low-risk* PE patients [7,8].

The most frequently used prognostic scoring systems in clinical practice for patients who have acute symptomatic PE are the Pulmonary Embolism Severity Index (**PESI**) [9], its simplified version (**sPESI**) [10], and the Hestia criteria [11] (Tables 1–3). In a recent open-label, non-inferiority, randomized, controlled trial of inpatient versus outpatient (discharged from the emergency department [**ED**] within 24 h of randomization) initial subcutaneous twice-daily enoxaparin therapy in patients who had acute PE and a *low-risk* of short-term adverse outcomes according to the PESI, one (0.6%) of 171 outpatients compared with none of 168 inpatients (0%, 95% upper confidence limit [**UCL**] 2.7%; non-inferiority $P = 0.011$) developed recurrent VTE within 90 days [12]. Only one (0.6%) patient in each treatment group died within 90 days (95% UCL 2.1%; $P = 0.005$), and two (1.2%) of 171 outpatients and no inpatients had major bleeding within 14 days (95% UCL 3.6%; $P = 0.031$) These results supported use of the PESI for the identification of *low-risk* PE patients who can safely undergo home PE management. Of note, in addition to basing eligibility on a low PESI score, the study used numerous additional criteria (e.g., no hypotension, hypoxemia, high bleeding risk, and barriers to treatment and

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http://dx.doi.org/10.1016/j.thromres.2017.09.007
Received 26 February 2017; Received in revised form 4 July 2017; Accepted 4 September 2017

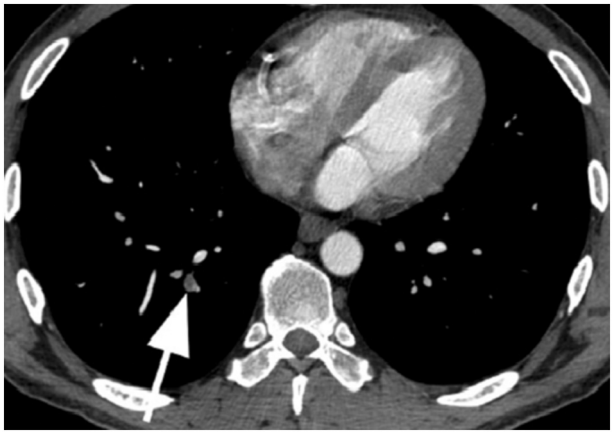

**Fig. 1.** PE-protocol chest computed tomography showing a right lower lobe segmental pulmonary embolism (arrow).

**Table 1**
Pulmonary Embolism Severity Index.

| Predictor variable | Points |
|---|---|
| Age | Years |
| Male sex | + 10 |
| History of cancer | + 30 |
| History of heart failure | + 10 |
| History of chronic lung disease | + 10 |
| Pulse ≥ 110 beats/min | + 20 |
| Systolic blood pressure < 100 mm Hg | + 30 |
| Respiratory rate ≥ 30 breaths/min | + 20 |
| Temperature < 36 °C | + 20 |
| Altered mental status | + 60 |
| Arterial oxyhemoglobin saturation ($SaO_2$) < 90% | + 20 |

A total point score for a given patient is obtained by summing the patient's age in years and the points for each predictor variable when present. The score corresponds with the following risk classes: ≤ 65 class I; 66–85 class II; 86–105 class III; 106–125 class IV; and > 125 class V. Patients in risk classes I and II are defined as low-risk.

**Table 2**
Simplified Pulmonary Embolism Severity Index.

| Variable | Points |
|---|---|
| Age > 80 years | 1 |
| History of cancer | 1 |
| History of chronic cardiopulmonary disease | 1 |
| Pulse ≥ 110 beats/min | 1 |
| Systolic blood pressure < 100 mm Hg | 1 |
| Arterial oxyhemoglobin saturation ($SaO_2$) < 90% | 1 |

Sum the variable points to produce the total point score. The score corresponds with the following risk classes: 0, low risk; ≥ 1, high risk.

follow-up adherence) to determine eligibility. Multiple retrospective and prospective studies have validated the prognostic accuracy of the simplified version of the PESI, the sPESI [13–15], but it has not been used in a PE management study or in a randomized trial of inpatient versus immediate outpatient therapy of acute PE.

The HESTIA criteria for determining eligibility for outpatient PE therapy address a broad range of issues that include risk for bleeding, clotting, dying, and inability to successfully receive home PE therapy. A single-arm, multicenter, prospective, management cohort study used the Hestia criteria to select patients for home once-daily subcutaneous nadroparin treatment within 24 h of PE diagnosis. Of the 297 (51% [297/581] of those screened) enrolled patients, 6 (2.0%, 95% confidence interval [**CI**], 0.8–4.3%) patients had recurrent VTE (five PE [1.7%] and one DVT [0.3%]), while only two (0.7%; 95% CI, 0.1–2.4%) patients had major bleeding and three (1.0%; 95% CI, 0.2–2.9%)

**Table 3**
Hestia criteria.

| Variable |
|---|
| Hemodynamically unstable?[a] |
| Thrombolysis or embolectomy necessary? |
| Active bleeding or high risk of bleeding?[b] |
| Oxygen supply to maintain oxygen saturation > 90% for > 24 h? |
| Pulmonary embolism diagnosed during anticoagulant treatment? |
| Intravenous pain medication > 24 h? |
| Medical or social reason for treatment in the hospital > 24 h? |
| Creatinine clearance of < 30 mL/min?[c] |
| Severe liver impairment?[d] |
| Pregnant? |
| Documented history of heparin-induced thrombocytopenia? |

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

[a] Include the following criteria, but are left to the discretion of the investigator: systolic blood pressure < 100 mm Hg with heart rate > 100 beats per minute; condition requiring admission to an intensive care unit.

[b] Gastrointestinal bleeding in the preceding 14 days, recent stroke (< 4 weeks ago), recent operation (< 2 weeks ago), bleeding disorder or thrombocytopenia (platelet count < 75 × $10^9$/L), uncontrolled hypertension (systolic blood pressure > 180 mm Hg or diastolic blood pressure > 110 mm Hg).

[c] Calculated creatinine clearance according to the Cockcroft-Gault formula.

[d] Left to the discretion of the physician.

patients died (one of the major bleeding [intracranial] events; none due to PE) during 3 months of follow-up [11]. This study provided evidence that HESTIA can identify reasonably low-risk patients for initial outpatient PE therapy.

Some studies have evaluated the benefit of adding cardiac biomarkers and/or imaging testing to clinical prognostic scores for identification of patients with acute PE at low risk for short-term complications. The PROgnosTic valuE of Computed Tomography scan in haemodynamically stable patients with acute symptomatic PE (**PROTECT**) study prospectively assessed the prognostic value of right ventricular (**RV**) dysfunction assessed by multidetector computed tomography pulmonary angiography (**CTPA**) [16]. The PROTECT investigators elucidated whether the addition of CTPA and/or echocardiography prognostic information to the sPESI model improved the identification of patients at *low-risk* for adverse outcomes [17]. Of the 143 (17% of the entire study population) patients deemed *low-risk* according to sPESI (i.e., 0 points) who also had a negative CTPA for RV dysfunction, 3 (2.1%; 95% CI, 0.4–6.0%) experienced a complicated course during the study period, and none died. In contrast, 1.2% (95% CI, 0.1–4.2%) of patients who had a low risk sPESI and CTPA-assessed RV dysfunction had a complicated course and 1 patient (0.6%; 95% CI, 0–3.2%) died. In the subgroup of patients who had a low-risk sPESI and no RV dysfunction on CTPA, the addition of echocardiographic prognostic information did not significantly modify the probability of an adverse outcome [17]. This study questioned the additional prognostic information gained by assessing RV function on CTPA in patients who have a low-risk PESI, and it provided evidence that echocardiography does not assist with short-term prognostication in the setting of a low-risk PESI and a lack of RV dysfunction on CTPA.

Regarding blood test cardiac biomarkers, the PROTECT study also showed that the combination of the sPESI and brain natriuretic peptide (**BNP**) testing had a negative predictive value (**NPV**) for a complicated course of 99.1% and 100% in derivation and validation cohorts, respectively [18]. In contrast, the recent VESTA randomized controlled trial did not demonstrate the additive prognostic value of cardiac biomarkers to the HESTIA prognostic score for identifying *low-risk* patients with acute PE [19]. The study enrolled 550 patients who had *low-risk* PE according to the Hestia criteria: 275 patients were randomly assigned to direct discharge from the ED, and 275 were assigned to a prognostic strategy involving the measurement of NT-proBNP levels [19]. Investigators only discharged the latter patients from the ED if NT-proBNP was ≤ 500 ng/L (88% of patients). Otherwise, they