REVIEW ARTICLE

# How to predict prognosis in patients with acute pulmonary embolism? Recent advances

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## ABSTRACT

Pulmonary embolism (PE) is the third most frequent cardiovascular disease, characterized by a wide range of presentations and clinical courses. Prognostic assessment is a cornerstone of PE management as it determines the choice of both diagnostic and therapeutic strategies. During the previous decades significant efforts have been made to safely select patients for early discharge or home treatment, but appropriate risk stratification, particularly of intermediate-risk patients, remains challenging. In addition to the guideline-recommended clinical prediction rules, such as Pulmonary Embolism Severity Index (PESI), simplified PESI (sPESI), and/or Hestia criteria, a multimodality approach based also on biomarkers and cardiac imaging is crucial for risk-stratification and for selecting appropriate management of patients. In this review article, we discuss the current methods for predicting short and long-term prognosis in PE patients, focusing on the current guidelines, but also on the most recently proposed clinical prediction rules, biomarkers, and imaging parameters.

**Key words:** mortality, pulmonary embolism, prognosis, risk stratification, venous thromboembolism

## INTRODUCTION

Pulmonary embolism (PE) is the third most frequent cardiovascular disease, accounting for approximately 300 000 deaths in Europe every year [1, 2]. It has various presentations, ranging from an asymptomatic incidental finding to circulatory collapse.

In the past, PE patients were traditionally hospitalized for the indication of intravenously anticoagulation and concerns about a high risk of death [3]. Since oral anticoagulants demonstrated their efficacy and safety, PE can nowadays often be treated on an outpatient basis. However, appropriate patient selection remains debatable. Risk stratification is a cornerstone in managing several conditions, including PE. It determines the need for urgent reperfusion therapy in high-risk patients and identifies low-risk patients that can be safely treated at home. The major challenge in managing PE patients is for the remaining group of intermediate-risk patients, which is highly heterogeneous. Although most of those patients experience favorable outcomes, a small, albeit significant, proportion will need rescue reperfusion [4].

In this article, we discuss the current models for predicting short- and long-term prognosis for PE patients and the decision-making process for PE management, particularly regarding the decision on inpatient vs. outpatient treatment.

## INSTRUMENTS USED FOR PROGNOSIS ASSESSMENT IN PE

### *Clinical scores*

The Pulmonary Embolism Severity Index (PESI) and Geneva score were the first to be proposed and validated for acute PE risk stratification.

The Geneva prediction rule was developed to identify PE patients who are at low risk of

**Table 1.** Summary of prognostic clinical scores for pulmonary embolism

| Geneva [5] | PESI [6] | Simplified PESI [7] | Hestia criteria [9] |
|---|---|---|---|
| Cancer<br>Heart failure<br>Previous DVT<br>Documented DVT<br>SBP <100 mm Hg<br>Arterial $PaO_2$ <60 mm Hg (8 kPa) | Cancer<br>Chronic heart failure<br>Chronic obstructive pulmonary disease<br>Male sex<br>SBP <100 mm Hg<br>Arterial oxyhemoglobin saturation <90%<br>Respiratory rate >30 bpm<br>Pulse rate ≥110 bpm<br>Temperature <36° C<br>Altered mental status<br>Age in years | Cancer<br>Chronic heart failure or chronic pulmonary disease<br>Pulse rate ≥110 bpm<br>SBP <100 mm Hg<br>Arterial oxyhemoglobin saturation <90%<br>Age >80 years | Hemodynamic instability<br>Need for thrombolysis or embolectomy<br>Active bleeding or high bleeding risk<br>Oxygen supply to maintain oxygen >90% for >24 hours<br>PE diagnosed during anticoagulant treatment<br>Severe pain needing IV medication >24 hours<br>Medical or social reasons for hospital treatment<br>Creatinine clearance <30 ml/min<br>Severe liver impairment or disease<br>Pregnancy<br>Documented history of HIT |

Abbreviations: DVP, deep vein thrombosis; HIT, heparin-induced thrombocytopenia; IV, intravenous; PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index; SBP, systolic blood pressure

death, recurrent venous thromboembolism (VTE), or major bleeding at three months [5]. This score is based on 6 predictors, including cancer, heart failure, previous deep vein thrombosis (DVT), documented DVT, systolic blood pressure (SBP) <100 mm Hg, and arterial $PaO_2$ <60 mm Hg (8 kPa). About two-thirds of patients achieve a score of two or less, which is associated with a 2% risk of adverse outcomes.

The Pulmonary Embolism Severity Index (PESI) comprises 11 clinical variables and stratifies patients into five severity classes [6]. A simplified PESI score (sPESI) version includes only six variables and two risk classes [7]. A PESI risk of I or II indicates a low-risk population (as does a simplified PESI [sPESI] of zero), with a 30-day mortality rate of less than 3%. According to a meta-analysis including 50 021 patients, the area under the curve (AUC) of sPESI was 0.79 for all-cause mortality with pooled sensitivity and specificity of 0.92 and 0.38, respectively, which was similar to the original PESI score [8]. That study documented pooled mortality of 2% in patients with PESI class I or II, and 1.8% in patients with 0 points on sPESI [8].

The Hestia criteria represent an alternative approach to identifying low-risk patients and selecting those who can be safely treated at home [9]. This approach consists of eleven criteria on the patient's clinical presentation, comorbidities, and familial and social factors. In a prospective study, 90-day mortality was 1% for patients with acute PE and no Hestia criteria for hospitalization who were managed as outpatients.

Table 1 summarizes the most frequently used clinical prognostic scores.

To re-stratify patients with intermediate risk, several scores have been developed. One of the most often used is the BOVA score, which includes parameters such as heart rate (HR), SBP, biomarkers, and transthoracic echocardiography (TTE) [10]. The primary composite outcome was PE-related death, hemodynamic collapse, or recurrent PE at 30 days. Thirty-day complications differed significantly across categories of the model (0–2 points: 4%; 3–4 points: 11%; >4 points: 29%), with an AUC of 0.73 (95% confidence interval [CI], 0.68–0.77). Other scores, such as TELOS, CAPE, and SHIeLD scores, were also developed for additional risk stratification in normotensive patients [11–13]. The variables comprised in those scores are summarized in Table 2.

The shock index (SI) includes information about the patient's HR and SBP (shock index = HR/SBP) to assess hemodynamic status. A SI ≥0.9 indicates a high-risk population. The shock index was demonstrated to be an independent predictor of 30-day mortality, and it performed better than SBP alone for discrimination of low-risk patients [14]. However, while the SI had higher sensitivity compared to SBP (31% vs. 14% for SBP <100 mm Hg and 8% for SBP <90 mm Hg, respectively), it was associated with lower specificity (86% vs. 93 and 97%, respectively) [15]. The sPESI was demonstrated to outperform the SI in predicting 30-day mortality [16].

## Biomarkers

Biomarkers were traditionally included as part of the risk stratification of PE patients. Although in initial studies, elevated troponin was associated with poor outcomes, including mortality, subsequent studies have questioned its predictive value. Nowadays, the recommendation is that it should be combined with other prognostic markers [17, 18]. The prognostic value of natriuretic peptides has also been demonstrated, and it seems to have an additive predictive value when combined with troponin measurements. In the PROTECT study, a combination of sPESI with troponin and N-terminal prohormone B-type natriuretic peptide (NT-proBNP) measures had a higher positive predictive value for adverse outcomes than the sPESI alone [19]. The current guidelines recommend employing NT-proBNP to identify normotensive patients with an expected benign disease course.

Elevated plasma lactate signalizes patients with organ dysfunction and is associated with increased mortality in patients with acute PE [13, 20]. The FAST score is a clinical predicting rule that includes heart fatty acid-binding protein (H-FABP), syncope, and HR. The positive predictive value was 20.5%, and the AUC was 0.85 (95% CI, 0.75–0.95). A meta-analysis of 9 studies including 1680 patients found that elevated H-FABP levels were associated with 30-day PE-related mortality [21]. Although a promising biomarker, H-FABP is not routinely available. Other biomarkers,

**Table 2.** Summary of prognostic clinical scores for normotensive patients with pulmonary embolism

| BOVA score [10] | CAPE score [12] | TELOS score [40] | SHIELD [11] |
|---|---|---|---|
| SBP 90–100 mm Hg | SBP 90–100 mm Hg | Elevated lactate[d] | Lactate[f] |
| HR ≥100 bpm | HR ≥100 bpm | HR ≥100 bpm | Shock index ≥1.0 |
| RV dysfunction[a] | Right-to-left ventricular ratio 1.5[c] | RV dysfunction[e] | Cardiovascular dysfunction[g] |
| Cardiac troponin elevation[b] | Presence of central pulmonary artery clot | | Hypoxaemia ($PaO_2/FiO_2$ ratio) |

[a]RV dysfunction defined as echocardiographic assessment RV/LV >0.9, systolic pulmonary artery pressure >30 mm Hg, RV end-diastolic diameter >30 mm, RV dilatation or RV free-wall hypokinesis; or on CT scan as an RV/LV ratio >1 [10]. [b]Based on standard manufacturer assays and cut-off values [10]. [c]Evaluated on cardiac CT [12]. [d]Elevated plasma lactate is defined as plasma lactate levels ≥2 mmol/l [40]. [e]RV dysfunction defined as the presence of at least one of the following: (1) RV dilatation (end-diastolic diameter >30 mm or right-to-left ventricular end-diastolic diameter ≥1 mm in apical four-chamber view); (2) pulmonary hypertension (estimated RV-right atrial gradient over 30 mm Hg); (3) Hypokinesis of the RV free wall [40]. [f]Absolute value in mmol/l [11]. [g]Cardiovascular dysfunction is defined as the cumulative presence of elevated troponin, elevated NT-proBNP, and an RV/LV ratio ≥1.0 [11]

Abbreviations: CT, computed tomography; HR, heart rate; LV, left ventricle; RV, right ventricle; SBP, systolic blood pressure

such as copeptin, have also been studied but are less extensively validated and not readily available in clinical practice [22–24].

## Cardiac imaging

Right ventricular (RV) dysfunction has been associated with increased risk of death [4]. Computed tomography pulmonary angiography (CTPA) has the advantage of combining both diagnostic and prognostic features at once [4]. CTPA signs of RV dysfunction include septal bulging, pulmonary artery enlargement, elevated right-to-left ventricular end-diastolic diameter ratio, and retrograde contrast reflux into the vena cava [4]. CTPA also assesses PE extension, and due to high sensitivity, it contributes to an increased incidence of subsegmental PE diagnosis. The clinical significance of subsegmental PE remains uncertain, and recommendations are extrapolated mainly from historical ventilation-perfusion lung scan trials. In the PIOPED study, 17% of patients had defects isolated to the subsegmental pulmonary arteries [25]. A systematic review and meta-analysis showed no difference between patients with subsegmental PE treated with anticoagulation and those not treated, with regard to the pooled outcomes of a 3-month incidence of recurrent VTE and all-cause mortality [26]. Thus, the indication of anticoagulation should be individualized in patients with incidentally diagnosed PE who have no additional risk factors such as cancer.

TTE is a readily available examination that can be easily performed at the patient's bedside. Although according to the European Society of Cardiology (ESC) guidelines on PE, TTE is not a mandatory part of the routine diagnostic workup in hemodynamically stable patients, several parameters have been proposed for risk stratification [4]. Prognostic markers include an increased right-to-left ventricular ratio, ratio of tricuspid annular plane systolic excursion (TAPSE) to pulmonary arterial systolic pressure, 60/60 sign, and RV wall hypokinesis (including McConnell's sign) [27]. Considering that TAPSE cannot be measured in some patients, subcostal echocardiographic assessment of tricuspid annular kick (SEATAK) was demonstrated to be an accurate alternative, reflecting RV systolic function and demonstrating a prognostic value [28].

A clot in transit, defined as a free-floating thrombus within cardiac chambers, represents a potential source of recurrent embolism and is associated with higher short-term all-cause mortality and PE-related mortality [29]. The prevalence of TTE detection of right heart thrombi was 3.1% (95% CI, 2.8–3.4) [29]. Besides the prognostic value, there was no significant difference in outcomes between treatment with anticoagulation alone or reperfusion strategy in these patients [30]. A multicenter prospective cohort study including 490 normotensive PE patients managed according to the current ESC guidelines proposed an optimal definition of RV dysfunction for prognostic assessment. In this study, the multivariable analysis identified SBP, right-to-left ventricular ratio, and TAPSE as independent predictors of adverse outcomes or rescue thrombolysis within the first 30 days [21].

New echocardiographic parameters have reinforced the role of TTE in risk assessment of acute PE. Right ventricular outflow tract velocity time integral <9.5 cm was associated with increased PE-related mortality [31]. RV strain assessed with speckle-tracking echocardiography is an independent prognostic marker for in-hospital events in patients with acute non-massive PE [31]. The ratio of tricuspid annular plane systolic excursion to pulmonary arterial systolic pressure (TAPSE/PASP) predicts adverse outcomes in PE better than each measurement individually [31]. Pulmonary artery systolic pressure/left ventricular stroke volume (PASP/LVSV) performs better compared to BOVA and PESI in predicting adverse events in intermediate risk of PE [32].

Although markers of RV dysfunction have a consistent association with short-term mortality, they have poor diagnostic performance when used as a stand-alone test, requiring combination with other parameters [33]. In some patients with suspected acute PE, TTE and CTPA may be useful tools to identify pre-existing chronic thromboembolism pulmonary hypertension [4].

## Electrocardiogram

The electrocardiogram (ECG) is a quickly interpretable, low-cost, and widely available tool that could be used for prognostic stratification of PE patients. The Daniel score was developed as a scoring system for the severity of pulmonary hypertension in PE patients. However, since

its publication, several studies have investigated the use of ECG as a risk-stratification tool for PE. A systematic review and meta-analysis identified S1Q3T3, complete right bundle branch block, and right axis deviation as the best predictors for in-hospital mortality [15]. T wave inversion and atrial fibrillation were also identified as predictors of negative outcomes [15].

## RISK-STRATIFICATION IN PE PATIENTS

### *Identification of high-risk patients*

Identifying a high risk of mortality in patients should be the first step in PE risk stratification. According to the ESC criteria, high-risk patients include those who present with cardiac arrest, hemodynamic instability (defined as SBP less than 90 mm Hg for more than 15 minutes in the absence of other explanation), and/or the need for vasopressors in combination with end-organ hypoperfusion, or persistent hypotension not caused by new-onset arrhythmia, hypovolemia, or sepsis [4]. This subgroup of patients corresponds to 4% of PE patients, with documented short-term mortality of 16% to 19% [34, 35]. These patients' management relies on organ support and prompt reperfusion with thrombolytic therapies or thrombectomy.

In a hemodynamically compromised patient with suspected PE, if immediate CTPA is not possible, bedside TTE echocardiography is the most useful test to evaluate signs of RV pressure overload. Some specific TTE findings (60/60 sign, McConnell's sign, or right-heart thrombi) justify emergency reperfusion treatment for PE, without further tests.

### *Identification of low-risk patients*

Low-risk PE corresponds to about 40% of acute PE patients [36]. Although historically, all patients with acute PE were admitted to the hospital, in the last decades, several prediction rules have been developed to identify patients that can be safely treated as outpatients [3]. Home treatment seems feasible in approximately 30% of normotensive patients with acute PE [37].

The safety of these scoring systems was further investigated in the HOME-PE (Hospitalization or Out-treatment Management of PE) study, which directly compared the sPESI and Hestia criteria. This study demonstrated that both strategies had similar safety and effectiveness and may be used for PE risk stratification. In that study, Hestia criteria identified a lower proportion of patient candidates for home treatment compared to the sPESI (39.4% vs. 48.4%). Still, the proportion of patients managed at home was similar in the two-triaging group (38.4% vs. 36.3% in the Hestia and sPESI groups, respectively) [37]. The incidence of recurrent VTE, major bleeding, or death in patients who were qualified for home treatment by the Hestia or sPESI strategy and were treated at home was as low as 1.3% and 1.1%, respectively. Thirty-day mortality was 0.27% and 0.28%, respectively [37]. The HOT-PE (Home Treatment of Patients with Low-risk PE with the Oral Factor Xa inhibitor Rivaroxaban) trial investigated the safety and efficacy of home treatment of PE using rivaroxaban in low-risk patients, defined by the adapted Hestia criteria and the absence of RV enlargement or dysfunction, and of free-floating thrombi on TTE or CTPA. From the reported initial population of 2854 patients with objectively confirmed PE, 300 patients had either RV dysfunction or free-floating thrombi despite not meeting any of the Hestia criteria. A recent meta-analysis of 3295 patients from 21 studies showed that RV dysfunction, primarily defined by RV pressure overload assessed on imaging tests, alternatively by elevated cardiac biomarkers, may have a significant impact on the early prognosis of patients classified as low-risk based on PESI, sPESI, or Hestia criteria [21]. Thus, outpatient treatment appears to be safe for truly low-risk patients identified by PESI, sPESI, or Hestia criteria combined with the exclusion of RV dysfunction by either imaging studies or cardiac biomarkers. Data show that these instruments are similarly reliable in identifying low-risk patients in terms of prognosis [38].

### *Re-stratifying intermediate-risk patients*

The intermediate-risk patients represent a highly heterogenous group of patients, with a 30-day mortality risk varying between 5% and 15% [6, 7]. Data from the FLASH (FlowTriever All-Comer Registry for Patient Safety and Hemodynamic) registry showed that over one-third of these patients were in normotensive shock, described as the presence of SBP higher than 90 mm Hg in patients with a cardiac index ≤2.2 l/min/m$^2$ (invasive evaluation). This subgroup of patients is at higher risk of hemodynamic deterioration and in-hospital mortality. For this reason, in the last decade, efforts have been made to identify the subgroup of patients at higher risk who mainly benefit from close in-hospital monitoring. Several markers have been investigated as potential tools to stratify intermediate-risk patients, such as troponin and natriuretic peptides and detection of RV dysfunction. However, when considered in isolatation, none of those markers exceeded specificity of 70% (ranging from 56% for CT-documented RV dysfunction to 70% for natriuretic peptides) [3]. Based on expert opinions, the current guidelines proposed a subdivision into intermediate-high and intermediate-low-risk patients, as the first represents a high 30-day mortality risk subgroup (10% vs. 4%) [39]. Normotensive patients with an sPESI <1 or PESI II-II are considered low-risk patients without further risk stratification; those with an sPESI ≥1 or those with either RV dysfunction or elevated cardiac biomarkers are considered intermediate-low-risk patients; and those with sPESI ≥1 and both RV dysfunction and elevated cardiac biomarkers are considered intermediate-high risk patients. However, the currently available tools for the stratification of this subgroup of patients still have some limitations. The PESI and sPESI scores have a high negative predictive value but a low positive predictive value.

They do not adequately identify those normotensive patients who are at a higher risk and require intensive monitoring [3, 26]. For this purpose, alternative scores such as the BOVA, TELOS, and CAPE scores seem more appropriate [26].

The TELOS score was derived from a prospective cohort of 496 patients and includes RV dysfunction, troponin, and plasma lactate elevation as predictors of death or hemodynamic collapse at 7 days. In a prospective validation of this score, 5.9% of patients were assigned to the intermediate-high-risk category, with a cumulative incidence of death or hemodynamic collapse at 7 days of 21% [3, 40].

The CAPE (Calgary Acute Pulmonary Embolism) score consists of a simple four-variable risk score (comprising computed tomography right-to-left ventricular ratio ≥1.5, presence of central clot, HR ≥100 beats per minute, and SBP <90–100 mm Hg), and demonstrated high predictive value for adverse outcomes in normotensive patients [12].

The SHIeLD score was created and validated to predict 30-days PE-related mortality and/or rescue thrombolysis and comprises four prognostic factors: a shock index ≥1, hypoxemia, lactate, and cardiovascular dysfunction (defined as elevated troponin and NT-proBNP and right-to-left ventricular ratio >1) [11].

Furthermore, both biomarkers and cardiac imaging can be useful for additional risk stratification [12]. In a cohort of 688 normotensive patients with acute PE, NT-proBNP, and echocardiography had a prognostic impact in addition to the sPESI. The risk of adverse outcomes in patients with an sPESI ≥1 with normal NT-proBNP and normal echocardiography was 2.5%, while the risk increased to 5.8% and 5.6% in patients with either NT-proBNP elevation or evidence of RV dysfunction, respectively. For those with both elevated NT-proBNP and RV dysfunction, the risk increases to 10.8%. In the PROTECT study, in normotensive patients with sPESI ≥1, the risk of adverse events was 6.1% in patients with normal biomarkers, 13.8% in patients with elevated BNP, and 20.4% in patients with both elevated troponin and natriuretic peptides [19].

Despite current advances, re-stratification of intermediate-risk patients remains a challenging and important area of research as it may impact not only treatment decisions but also decisions about in- or out-of-hospital care. The use of systemic thrombolysis in normotensive patients considered as being at high risk of decompensation has been evaluated in several trials. The European Pulmonary Embolism Thrombolysis (PEITHO) trial included 1005 patients with intermediate-high risk PE, defined by the evidence of myocardial injury (documented by elevated troponin) and RV dysfunction on imaging. It demonstrated that the incidence of hemodynamic collapse or death within one week was substantially lower in patients in whom tenecteplase plus unfractionated heparin (UFH) was administered compared to those who received UFH alone (2.6% vs. 5.6%; $P = 0.02$). However, this benefit was mainly driven by reducing the risk of hemodynamic decompensation, while mortality did not significantly differ. In addition, the risk of major bleeding was significantly higher in patients who had thrombolysis. Based on these findings, bleeding risks seem to outweigh potential benefits of full-dose systemic thrombolysis, which highlights that more refined strategies are necessary to re-stratify patients at higher risk. The ongoing PEITHOS-3 trial will evaluate whether a reduced dosage of alteplase may be superior to heparin without excessive risk of major bleeding in these patients [41].

One possibly safer alternative to systemic thrombolysis in intermediate-risk PE patients may be catheter-directed PE treatment using lower thrombolytic doses, which has been the focus of recently published small randomized and cohort studies. The results are promising, although only surrogate endpoints were used [42–45]. A larger randomized ongoing ultrasound-facilitated catheter-directed thrombolysis vs. anticoagulation alone for acute-intermediate-high-risk pulmonary embolism (HI-PEITHO) study will evaluate catheter-directed treatment (CDT), and particularly ultrasound-assisted CDT vs. isolated anticoagulation in selected patients with intermediate-high risk acute PE [46]. In this trial, the investigators are using the National Early Warning Score (NEWS), an objective assessment and monitoring of each patient's vital status to enable early detection of patients who may benefit from prompt initiation of rescue therapy before hemodynamic collapse occurs.

### *Bleeding risk as an additional prognostic factor*

Aside from the thrombotic risk, bleeding risk also impacts the prognostics for PE patients. Major bleeding was identified as a predictor of short and midterm mortality in the Rejestr ZATorowósci plucnej w POLsce (ZATPOL) and as a predictor of 1-year mortality in the Registro Inormatizado Enfermedad TromboEmbolica (RIETE). The VTE-BLEED score was developed in the dabigatran arms of the pooled RE-COVER studies and identified six variables as predictors of major bleeding in VTE patients on stable oral anticoagulation: active cancer, males with uncontrolled hypertension, anemia, history of bleeding, age ≥60 years, and renal dysfunction. This score was externally validated in HOKUSAI-VTE, and its prognostic value was further demonstrated in a real-world prospective cohort study [47].

A systematic review evaluated the ability of different bleeding risk tools to predict major bleeding. Most scores showed a moderate ability to predict major bleeding events in VTE patients. The VTE-BLEED score was the most sensitive in forecasting major bleeding events in patients treated with direct oral anticoagulants [48].

### *Specific populations: Patients with cancer*

Venous thromboembolism is a frequent complication in cancer patients and represents the second cause of death after cancer itself. Pulmonary embolism attributable to neoplasia is associated with 3-fold increased mortality compared to a non-neoplastic condition [49, 50]. Approximately 80% of patients with acute PE attributable to cancer died after 1 year of follow-up [49]. Although it is associated with significant

mortality, there is considerable heterogeneity in prognosis, and prognostic tools adapted to this population are lacking.

The most frequently used non-cancer-specific prediction rules, such as the PESI, sPESI, and Geneva score, include cancer as a relevant predictor of mortality, even though these patients may be at low risk and successfully treated as outpatients [26]. Those prediction rules fail to account for cancer-specific disease characteristics by including cancer as a generic variable. Particularly, sPESI automatically classifies all cancer patients as high-risk individuals, limiting its usefulness in this setting. Previous studies have demonstrated that the performance of those non-cancer-specific clinical prediction rules could not be relied on to predict 30-day mortality in cancer patients with acute PE [51]. Recognizing that the existing clinical prediction rules likely require modification in cancer patients, Carmona-Bayonas et al. [51] adapted the commonly used Hestia, PESI, and sPESI by replacing the typical "history of cancer" variable with "metastatic cancer". While these score adaptations demonstrated acceptable predictive accuracy, these rules categorize only a small portion of patients at low risk [51, 52].

As an alternative to the generic risk scores, there are two cancer-specific risk-stratification rules: the RIETE and POMPE-C scores. The RIETE score uses 6 variables (age >80 years, HR ≥110/min, SBP <100 mm Hg, weight <60 kg, immobilization, and presence of metastases) [7]. The POMPE-C calculates the probability of death based on respiratory rate, $O_2$ saturation, weight, pulse, altered mental status, respiratory distress, do-not-resuscitate status, and unilateral limb swelling [53]. In their original studies, both rules classified 22% to 38% of patients as low risk with sensitivity >95%. When cancer-specific risk-stratification tools were compared to cancer-adapted generic prediction rules (adapted PESI and sPESI), RIETE and POMPE-C demonstrated better discriminatory ability [51].

A meta-analysis performed to assess the prognostic accuracy of clinical prediction rules for mortality in patients with cancer and PE concluded that the highest sensitivity was observed with Hestia criteria (98.1%; 95% CI, 75.6%–99.9%) [54]. Other clinical prediction rules, such as POMPE-C, PESI, sPESI, modified PESI, and RIETE, displayed sensitivity between 87.8% and 93.8% [54]. Considering all the clinical prediction rules with sensitivity equal to or higher than 95%, all had specificity lower than 33% [54]. Thus, further studies are necessary to define specific predictors of mortality in this heterogenous group of patients.

## LONG TERM PROGNOSIS

In addition to minimizing short-term mortality, PE management should focus on long-term prognosis and reducing the risk of VTE recurrence. Although the risk of recurrence is low during anticoagulant treatment, it increases after interruption of anticoagulation to as much as 10% in the first year and more than 30% within 5 years. Currently, most guidelines recommend balancing the risk of bleeding with the risk of recurrence after an initial treatment period of three to six months based on the etiology and presence of modifiable risk factors. The provoked (e.g., by a transient risk factor such as major surgery) or unprovoked nature of PE also impacts prognosis, as patients with unprovoked PE are at higher risk of recurrence and represent a heterogenous subgroup of patients, in which further risk-stratification is needed.

Previous studies have suggested that D-dimer testing after three to six months of treatment can help identify patients with unprovoked PE with low risk of VTE recurrence. The PROLONG study demonstrated that patients with elevated D-dimer levels after an initial treatment period who had stopped using anticoagulation had an annualized PE recurrence of 11%. In comparison, the rate was 2% among patients who resumed treatment [55].

The Vienna model is a prediction model for assessing the risk of recurrence in patients with unprovoked VTE; it comprises male sex and the absolute D-dimer level as predictors. Based on this score, the expected rate of recurrent VTE at one year is below 5%, 5%–10%, and > 10% for patients with low, moderate, or high risk, respectively [56].

## USE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence (AI) is having a significant impact on healthcare. In the past few years, investigation of new AI-based PE tools has focused on diagnosis, using deep-learning models to improve time and diagnostic accuracy based on CTPA and also ECG-signals [57–59]. Few studies are available regarding the use of AI models for risk stratification, although they demonstrate that machine learning models have notable potential for PE prediction [21]. Based on the knowledge that the clot burden is related to the prognosis of acute PE, Liu la et al. [21] developed a deep framework based on U-Net to conduct pulmonary emboli segmentation and quantification on CTPA. Thus, artificial intelligence is taking the first steps aiming at new applicability in the future, but it has already shown promising results in this field.

## CONCLUSION

The management of patients with acute PE requires accurate step-by-step risk stratification. Hemodynamic instability allows identifying high-risk patients who will benefit from thrombolytic therapy, while the clinical prediction rules such as PESI, sPESI, and Hestia criteria will enable identifying low-risk patients who can safely be treated as outpatients. The approach to intermediate-risk patients could be most challenging, and no single parameter could be recommended. In these patients, a multimodal approach should be encouraged based on PESI, sPESI or Hesta criteria, biomarkers, and cardiac imaging.

## Article information

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