Current Diagnosis and Management of Acute Pulmonary Embolism: A Strategy for General Practitioners in Emergency Department

Joshua Eldad Frederich Lasanudin[1], Sidhi Laksono[2,3,*], Hillary Kusharsamita[4]

ABSTRACT

Pulmonary embolism (PE) is a disease with a relatively good prognosis when diagnosed and treated properly. This review aims to analyse available data and combine them into algorithms that physicians can use in the emergency department for quick decision-making in diagnosing and treating PE. The available data show that PE can be excluded through highly sensitive clinical decision rules, i.e. Pulmonary Embolism Rule-Out Criteria (PERC), Wells criteria, and Revised Geneva criteria, combined with D-dimer assessment. In cases where PE could not be excluded through the mentioned strategies, imaging modalities, such as compression ultrasonography (CUS), computed tomographic pulmonary angiography (CTPA), and planar ventilation/perfusion (V/Q) scan, are indicated for a definite diagnosis. Once a diagnosis has been made, treatment of PE depends on its mortality risk as patients are divided into low-, intermediate-, and high-risk cases. High-risk cases are treated for their hemodynamic instability, given parenteral or oral anticoagulant therapy, and are indicated for reperfusion therapy. Intermediate-risk PE is only given parenteral or oral anticoagulants and reperfusion is indicated when anticoagulants fail. Low-risk cases are given oral anticoagulants and based on the Hestia criteria, patients may be discharged and treated as outpatients.

KEYWORDS

pulmonary embolism; clinical decision rules; physicians

AUTHOR AFFILIATIONS

[1] Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
[2] Department of Cardiology and Vascular Medicine, Central Pertamina Hospital, Jakarta, Indonesia
[3] Faculty of Medicine, Universitas Muhammadiyah Prof Dr Hamka, Tangerang, Indonesia
[4] Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia
* Corresponding author: Fakultas Kedokteran Universtas Muhammadiyah Prof Dr Hamka, Jl. Raden Patah No.01, RT.002/RW.006, Parung Serab, Kec. Ciledug, Kota Tangerang, Banten 13460, Indonesia; e-mail: sidhilaksono@uhamka.ac.id

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INTRODUCTION

Pulmonary embolism is a blockage of the lung vasculature by embolic venous thrombi. The exact global incidence of pulmonary embolism is unknown, but large surveys within countries have estimated that, annually, pulmonary embolism occurs at approximately 1 in 1000 persons (1, 2). However, this true incidence of the disease may be larger as post-mortem studies have shown that pulmonary embolism is found as the mechanism of death in around 5–10% of cases (3–5). Furthermore, in many cases in which an autopsy reveals pulmonary embolism as the cause of death, the diagnosis was never made clinically (5–6). Hence, a high index of suspicion for the disease along with proper steps in diagnosing pulmonary embolism is needed.

Additionally, it should be noted that the overall prognosis of pulmonary embolism is good, with studies generally showing mortality rates of under 10% (7). However, such studies mostly assess diagnosed and, hence, treated pulmonary embolism cases. A review by Cohen et al. reveals that of all pulmonary embolism-related death, 59% were from undiagnosed and untreated cases, whereas only 7% were from those properly diagnosed and treated (8). These findings suggests that adequate treatment results in a better prognosis and further supports the need of a proper strategy in diagnosing and managing patients with pulmonary embolism.

DIAGNOSIS OF PULMONARY EMBOLISM

Diagnosing pulmonary embolism starts from the clinical signs and symptoms of the patient. A meta-analysis by West et al. shows that from clinical history, pulmonary embolism has a high likelihood ratio if the patient presents with syncope, current deep vein thrombosis (DVT), leg swelling, sudden dyspnea, active cancer, recent surgery, hemoptysis, or leg pain. On the other hand, rarely does a pulmonary embolism present without sudden dyspnea and tachypnea. A systematic review conducted by Stein, et al. found silent PE diagnosed in 1665 of 5233 patients (32%) with DVT. It was higher found in proximal DVT rather than distal DVT (9).

From physical examination, patients with shock have a high likelihood of pulmonary embolism (10). Moreover, the use of clinical features as a basis for judgement to rule in or rule out pulmonary embolism is made more sensitive and specific through scoring tools. Commonly used tools include the pulmonary embolism rule-out criteria (PERC), Wells score, Revised Geneva score, Simplified Geneva score, and the YEARS algorithm (11).

The American College of Physcians released guidelines for ruling out pulmonary embolism using said scoring methods as follow (12):

1. Should all physicians assest and decide probability of PE (low, intermediate, high) using either a clinical decision tool or gestalt.
2. Wells or Geneva Score are used to determine patient's risk for PE.
3. In low-risk probability of PE patient, PERC are reccomended. When the PERC scoring are negative, no further test is needed, and PE can be ruled out. When the PERC score are positive, do high-sensitivity plasma D-dimer test as initial test.
4. Patient with intermediate risk can underwent plasma D-dimer test, PERC are not necessary.
   a. Patient > 50 years use an age-adjusted threshold (age × 10ng/mL) as D-dimer increased with age.
   b. D-dimer lower than treshold no need further imaging test.
   c. Patient with raised D-dimer should do imaging test.
5. Patient with high risk of PE should skip the D-dimer test and underwent imaging studies.
   a. CTPA are reccomended when there is no contraindication.
   b. V/Q lung scanning can be used when CTPA is unavailable or contraindicated.

The Wells score assesses seven factors and associates each factor with a certain point (Table 1). There were 3 tier (low, moderate, or higher) or 2 tier (likely or unlikely) models that physician can use. In three tier model, score 0–1 are considered low, score 2–6 are considered moderated, while >6 are considered high. In two tier model otherwise, <4 score are unlikely, while ≥4 score are likely (13). A meta-analysis by Bass et al. reveals that the sensitivity and specificity of the criteria ranges from 60% to 70% and from 60% to 80% respectively (14, 15). Further, in the original study by Wells et al., the combination of a low probability Wells criteria alongside a negative D-dimer testing was found to have a negative predictive value of 99.5% (16). A meta-analysis supports the notion that combining Wells criteria and D-dimer testing increases sensitivity to 99.7%, although the specificity decreases dramatically (15). This indicates that performing Wells criteria alone is likely insufficient, which other scoring tools should be considered. ESC also recommending Wells score supported by D-dimer results to rule out PE (17).

The revised Geneva score is another clinical decision tool for the diagnostic workup of patients suspected with pulmonary embolism. It consists of nine variables, and each are given points accordingly (Table 2). If the accumulation of points results in 11 or higher, then the patient has a high probability of pulmonary embolism (18). The scoring was further simplified so that each item were given

Tab. 1 Wells score (11, 13).

Factors assessed	Points
An alternative diagnosis is less likely than pulmonary embolism	3.0
Clinical signs and symptoms of deep vein thrombosis (DVT)	3.0
Tachycardia (heart rate > 100 beats/min)	1.5
Immobilization or surgery in previous four weeks	1.5
Previous DVT or pulmonary embolism	1.5
Hemoptysis	1.0
Active malignancy	1.0

Tab. 2 Revised and simplified Geneva Score (11, 18, 19).

Factors assessed	Points (Revised)	Points (Simplified)
Age > 65 years	1	1
Previous DVT or pulmonary embolism	3	1
Surgery or fracture within 1 month	2	1
Active malignant condition	2	1
Unilateral lower limb pain	3	1
Hemoptysis	2	1
Heart rate of 75–94 beats/min	3	1
Heart rate of 95 beats/min or more	5	2
Pain on lower-limb deep venous palpation and unilateral edema	4	1

one point, excluding heart rate ≥ 95 beats/min which is given two points, and a result of more than and equal to five indicates a high probablity of pulmonary embolism. It was found that the simplification of the scoring system does not affect its diagnostic value (19). Further studies have shown that a revised Geneva score of 10 or less when combined with a negative D-dimer test have a sensitivity of nearly 100% (20, 21). Hence, exclusion of pulmonary embolism in such circumstances can be supported.

The PERC criteria comprises of an eight-item questionnaire, which are (22, 23):

1. Is the patient's age ≥ 50 years old?
2. Is the patient's heart rate ≥ 100 times per minute?
3. Is the pulse oxymetry reading < 95% while on room air?
4. Is there hemoptysis?
5. Is the patient taking exogenous estrogen?
6. Is there a prior history of venous thromboembolism diagnosis?
7. Has the patient had recent surgery or trauma within the last 4 weeks?
8. Does the patient have swelling in one leg?

If all questions are answered as 'no', it is regarded as PERC negative, whereas if one or more questions are answered as 'yes', it is regarded as PERC positive. A negative PERC criteria when combined with a low initial clinical suspicion of pulmonary embolism, i.e. a physician's implicit estimation of pulmonary embolism is less than 15%, reduces the probability of venous thromboembolism to less than 2% (22). Thus, pulmonary embolism can be ruled out in such cases.

The YEARS clinical decision rule combines both presenting clinical manifestations and D-dimer values. Patients are clinically assessed for the following items: clinical signs of DVT, the presence of hemoptysis, and whether pulmonary embolism is the most likely diagnosis. In patients with none of the abovementioned items and a D-dimer less than 1000 ng/mL, pulmonary embolism can be excluded. On the other hand, patients with one or more items, a D-dimer less than 500 ng/mL supports the exclusion of pulmonary embolism (24). A meta-analysis by Geersing et al. reveals that the sensitivity and specificity of the YEARS algorithm in primary healthcare is 98.2% and 60.55% respectively (25).

Tab. 3 D-dimer cut-offs (25).

D-dimer test	Defined as negative if D-dimer level is ...
Qualitative test	Shown negative on device
Fixed cut-off	< 500 ng/mL
Age-adjusted cut-off	Patients < 50 years old: < 500 ng/mL
	Patients ≥ 50 years old: < (age × 10) ng/mL
Pre-test-probability-adjusted cut-off	Wells criteria ≤ 4: < 1000 ng/mL Wells criteria ≤ 6: < 500 ng/mL
	Revised Geneva criteria ≤ 5: < 1000 ng/mL Revised Geneva criteria ≤ 10: < 500 ng/mL

As has been mentioned, the addition of D-dimer testing increases sensitivity. However, besides the YEARS algorithm, the other scoring systems do not explicitly state the recommended cut-off value for D-dimer. A study by Riley, et al. shows widely used D-dimer manufacturer have their own cut-off (mostly 200 ng/mL and 500 ng/mL). Physicians and laboratorians should pay attention on what D-dimer assay they uses (26). Geersing et al. includes studies that combine the Wells criteria with a qualitative D-dimer cut-off, a fixed cut-off, an age-adjusted cut-off, or pre-test-probability-adjusted cut-off. These cut-offs are also combined with the Revised Geneva criteria (25). The definition of the cut-offs are listed in (Table 3). In all of those combinations, it is found that the sensitivity remains high, ranging from 96% to 99% (25). Hence, any combination with the aforementioned cut-offs can be used to exclude pulmonary embolism.

In cases where pulmonary embolism could not be excluded through clinical decision rules and D-dimer assessment, further testing is required. According to the European Society of Cardiology (ESC) 2019 guideline for pulmonary embolism, several imaging techniques are available to accept or reject the diagnosis of pulmonary embolism (27). The recommended imaging modalities include computed tomographic pulmonary angiography (CTPA), planar ventilation/perfusion (V/Q) scan, and compression ultrasonography (CUS) (27).

A meta-analysis reveals that CTPA has a sensitivity of 94% and a specificity of 98% (28), thus making it an excellent diagnostic modality for pulmonary embolism. A similar high sensitivity and specificity is also found in V/Q scans (28). However, both of these modalities incorporate radiation and thus proposes a risk to the patient. On the other hand, proximal vein CUS does not use radiation. This tool is used to find evidence of deep vein thrombosis and can be used as an indirect tool to diagnose pulmonary embolism. This is due to the presumption that the majority of pulmonary embolism arises from DVT. A positive finding has a sensitivity of 49% and a specificity of 96% for diagnosing pulmonary embolism (28). Another study supports the notion that in suspected patients, either clinically or through positive D-dimer testing, a positive vein CUS has a specificity of 99% (29). Thus, in such cases, CUS can be used to rule-in pulmonary embolism. An overall algorithm to diagnose pulmonary embolism is presented on Figure 1.

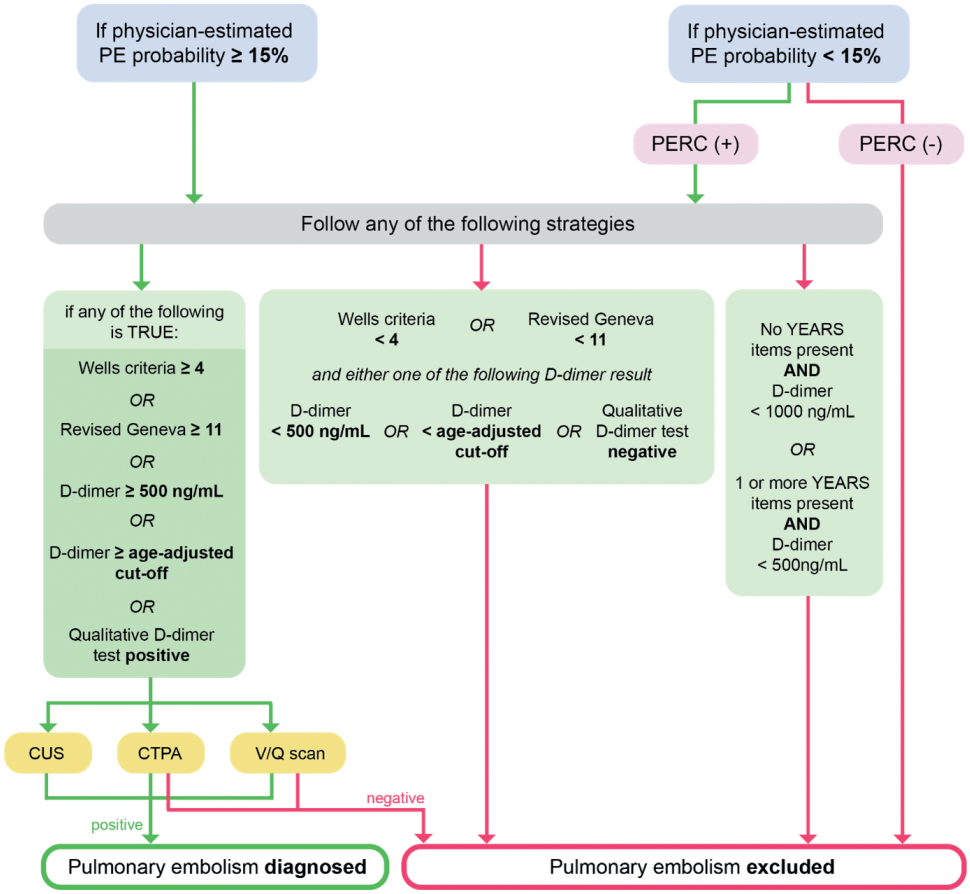

Fig. 1 Diagnostic algorithm for pulmonary embolism (11, 22, 25). Abbreviations: PE = pulmonary embolism; PERC = pulmonary embolism rule-out criteria; CUS = compression ultrasonography; CTPA = computed tomographic pulmonary angiography; V/Q scan = ventilation/perfusion scan.

MANAGEMENT OF PULMONARY EMBOLISM IN THE EMERGENCY DEPARTMENT

RISK STRATIFICATION

Pulmonary embolism management is guided by the severity of the case, which is divided into three risk categories: high, intermediate, and low. Further scoring systems have been developed to measure the prognosis of patients, the most commonly used are the Pulmonary Embolism Severity Index (PESI), which has later been simplified (27, 30, 31). These scoring assess multiple factors and each factor are coupled with a certain weighted point. Higher accumulation of points indicates more severe cases, i.e. a higher risk of death within 30 days (30, 31). Both the original and simplified versions of the PESI, along with their interpretations, can be found in (Table 4).

In stratifying patients into high-, intermediate-, and low-risk pulmonary embolism, a combination of the PESI or simplified PESI (sPESI) score, along with findings of hemodynamic instability, right ventricular dysfunction, and elevation of cardiac troponin levels are incorporated. Hemodynamic instability is defined as at least one of the following clinical presentation: (1) cardiac arrest, (2) obstructive shock (systolic blood pressure < 90 mmHg or requirement of vasopressors to maintain blood pressure ≥ 90 mmHg despite adequate filling status, along with findings of end-organ hypoperfusion), or (3) persistent hypotension (systolic blood pressure < 90 mmHg or systolic blood pressure drops by ≥ 40 mmHg, lasts > 15 minutes, and not caused by new-onset arrhythmia, sepsis, or hypovolemia). Right ventricular dysfunction can be detected through transthoracic echocardiography or CTPA (27).

A high-risk pulmonary embolism is characterised by hemodynamic instability. In intermediate-risk pulmonary embolism, the patient is hemodynamically stable, but PESI or sPESI are > 85 or ≥ 1, respectively. This can also be combined with findings of right ventricular dysfunction or elevated cardiac troponin levels. In low-risk pulmonary embolism, none of the above parameters are found (27). Table 5 provides a summary of the stratification of pulmonary embolism mortality risk.

MANAGEMENT OF HIGH-RISK PULMONARY EMBOLISM

Initial management for high-risk pulmonary embolism include respiratory support and hemodynamic correction. Respiratory support is indicated in patients with oxygen saturation less than 90%. Oxygen therapy can be given through high-flow nasal cannula (HFNC) or mechanical ventilation (27). The use of HFNC is found to increase oxygen saturation and decrease respiratory rate in a couple of hours after initiation (32, 33). Further, its use is found to be superior to that of conventional nasal cannula (32).

Tab. 4 Pulmonary Embolism Severity Index (30, 31).

Factor assessed	Original version	Simplified version
Age	Age in years = points	1 point (if > 80 years)
Male	+ 10 points	–
Cancer	+ 30 points	1 point
Chronic heart failure	+ 10 points	1 point
Chronic pulmonary disease	+ 10 points	
HR ≥ 110 beats/minute	+ 20 points	1 point
Systolic BP < 100 mmHg	+ 30 points	1 point
RR > 30 breaths/minute	+ 20 points	–
Temperature < 36 °C	+ 20 points	–
Altered mental status	+ 60 points	–
Arterial oxyhemoglobin saturation < 90%	+ 20 points	1 point
Interpretation	**Point accumulation**	**Point accumulation**
	• ≤ 65: very low 30-day mortality risk (0–1.6%) • 66–85: low 30-day mortality risk (1.7–3.5%) • 86–105: moderate 30-day mortality risk (3.2–7.1%) • 106–125: high 30-day mortality risk (4.0–11.4%) • > 125: very high 30-day mortality risk (10–24.5%)	• 0: 30-day mortality risk 1% • ≥ 1: 30-day mortality risk 10.9%

Abbreviations: HR = heart rate; RR = respiratory rate

Tab. 5 Stratification of pulmonary embolism severity (27).

Risk	Indicators			
	Hemodynamic instability	PESI > 85 *or* sPESI ≥ 1	RV dysfunction	Elevated cardiac troponin levels
High	+	+	+	+
Intermediate	–	+	+/–	+/–
Low	–	–	–	–

Abbreviations: PESI = Pulmonary Embolism Severity Index; sPESI = simplified Pulmonary Embolism Severity Index; RV = right ventricular.

Non-invasive mechanisms should be attempted first and intubation is reserved for refractory cases (27).

Hemodynamic instability due to acute right ventricular failure can be treated by increasing volume and/or the use of vasopressors. A ≤ 500 mL fluid challenge can be given in cases where central venous pressure is low (27, 34). However it should be noted that excessive fluid may cause further deterioration of right ventricular function as it increases wall stress and induces further ischemia (35). Pharmacological approach through vasopressors and inotropes can also be considered. The ESC guideline recommends the use of norepinephrine, 0.2–1.0 mcg/kg/minute, and/or dobutamine, 2–20 mcg/kg/minute (27). If dobutamine is used, it is recommended to also incorporate

Tab. 6 Hestia exclusion criteria (11, 27).

Questions
Is the patient haemodynamically unstable?
Is reperfusion therapy necessary?
Is there an active bleeding or high risk of bleeding?
Does the patient need > 24 hour of oxygen supply to maintain oxygen saturation > 90%?
Is pulmonary embolism diagnosed while patient is taking anticoagulant treatment?
Is there severe pain which needs intravenous pain medication for > 24 hours?
Medical or social reason for treatment in the hospital for >24 hours (infection, malignancy, or no support system)?
Does the patient have a creatinine clearance of <30 mL/min?
Does the patient have severe hepatic impairment?
Is the patient pregnant?
Is there a documented history of heparin-induced thrombocytopenia?

norepinephrine as dobutamine has a vasodilatory effect that could cause further hypotension (27, 36). On the other hand, norepinephrine can be given as a monotherapy (37).

Further, in patients with a high clinical probability of pulmonary embolism (refer to the Wells or Geneva mentioned on the previous section), initial anticoagulation can be administered even before the results of diagnostic tests. Parenteral anticoagulation is the recommended approach and patients are administered subcutaneous low-molecular weight heparin (LMWH; e.g., enoxaparin 1 mg/kg every 12 hours) or fondaparinux (7.5 mg once daily for patients weighing 50–100 kg) or intravenous unfractionated heparin (UFH) (27). Studies have found that LMWH and fondaparinux have a lower risk for bleeding compared to UFH (38–40). Moreover, the efficacy of LMWH and fondaparinux are similar to that of UFH (38–40). Other options that can be considered include non-vitamin K antagonist oral anticoagulants and vitamin K antagonists (27).

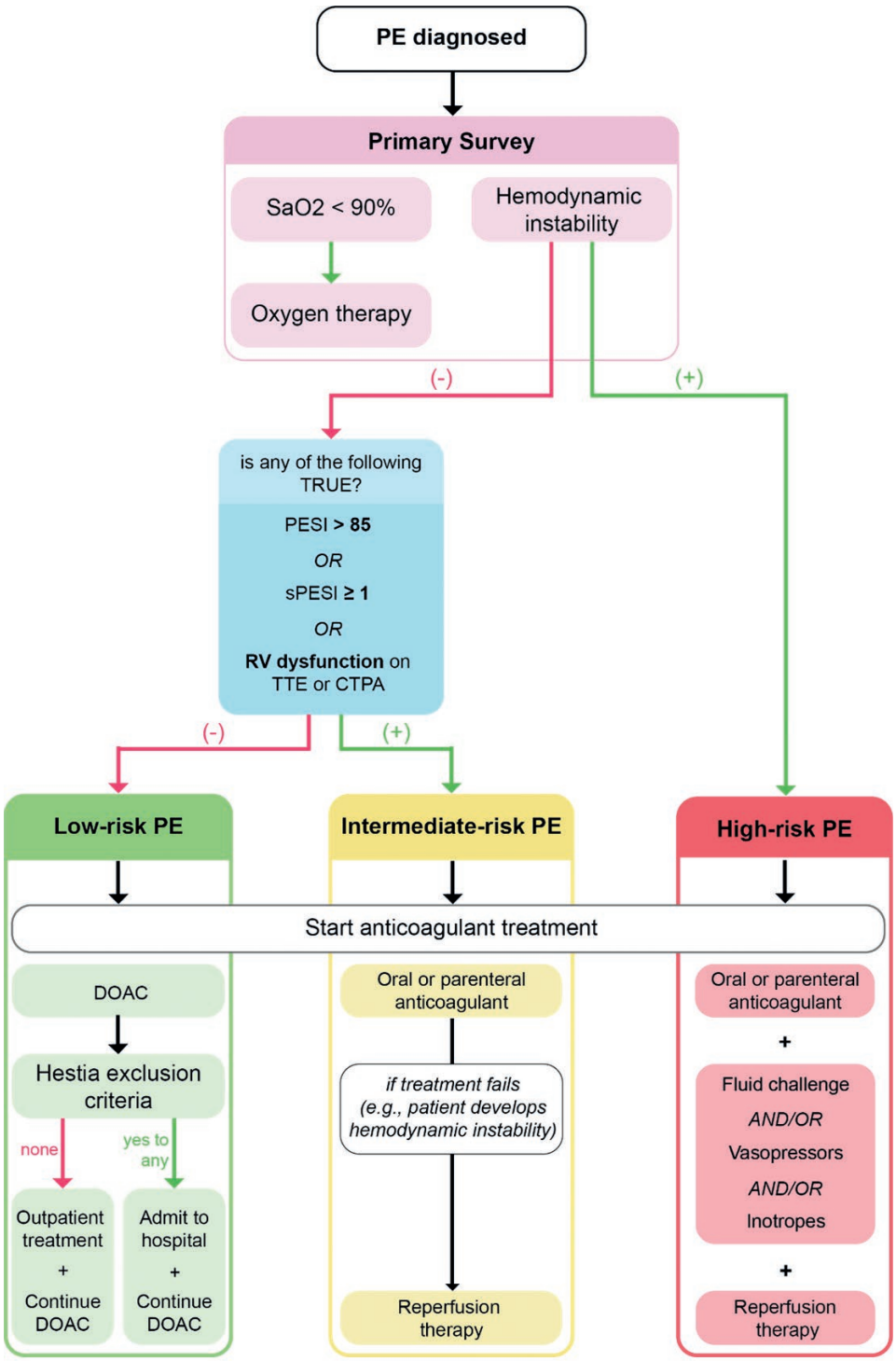

Fig. 2 Initial management of pulmonary embolism based on risk stratification (11, 27). Abbreviation: PE = pulmonary embolism; SaO2 = oxygen saturation; PESI = Pulmonary Embolism Severity Index; sPESI = simplified Pulmonary Embolism Severity Index; RV = right ventricular; DOAC = direct oral anticoagulant.

The primary treatment for high-risk pulmonary embolism is reperfusion. The mainstay of treatment is systemic thrombolysis. However, a percutaneous catheter approach and a surgical embolectomy are also viable options. A couple of meta-analyses found that, in acute pulmonary embolism which includes high-risk pulmonary embolisms, systemic thrombolysis was found to reduce mortality when compared to the use of UFH alone (41, 42). However, studies also found increased risk of major bleeding in patients who underwent systemic thrombolysis (41, 42).

Thrombolysis is optimally given within 48 hours post-onset, but can still be beneficial up to 2 weeks after onset of symptoms (27). Several approved thrombolytic regimens include recombinant tissue-type plasminogen activator (rtPA; 100 mg over 2 hours), streptokinase (250,000 IU loading dose for 30 minutes, continued by 100,000 IU/hour for 12–24 hours), and urokinase (4,400 IU/kg loading dose for 10 minutes, followed by 4,400 IU/kg/hour over 12–24 hours) (27). It should be noted that before undergoing systemic thrombolysis, contraindications must be assessed (e.g., active bleeding, history of stroke, intracranial neoplasm) (27, 43). Surgical pulmonary embolectomy and percutaneous catheter-directed treatment is reserved for cases where systemic thrombolysis is contraindicated or has failed (27).

MANAGEMENT OF INTERMEDIATE-RISK PULMONARY EMBOLISM

In intermediate-risk pulmonary embolism, anticoagulation treatment, whether orally or parenterally, along with hospitalisation for monitoring is usually sufficient (27). Routine thrombolytic therapy is not recommended and it is only performed in patients who develop hemodynamic instability (27). A trial by Meyer et al. shows that in intermediate-risk pulmonary embolism, thrombolytic therapy increases the risk of major bleeding and stroke when compared to treatment with anticoagulation alone (44). However, other studies have also shown that catheter-directed thrombolysis are as safe as anticoagulation treatment only and is able to improve patients' condition (marked by improvement of hemodynamic parameters) (45–47). Nonetheless, in the long term, no difference in mortality between catheter-directed thrombolysis and anticoagulation treatment alone is found (45).

MANAGEMENT OF LOW-RISK PULMONARY EMBOLISM

Low-risk pulmonary embolism are treated by administration of direct oral anticoagulant therapy (11, 27). A further decision that needs to be made in low-risk populations is whether hospitalization is necessary or if patients can be discharged early (27). Several studies have shown that low-risk patients can be safely and effectively treated as outpatients using direct oral anticoagulants (48, 49). However, it is recommended to further stratify low-risk patients using the Hestia exclusion criteria, which consists of 11 criterion (Table 6). If any of the questions asked is answered 'yes', then the patient should be hospitalised (27, 50).

MANAGEMENT IN SPECIFIC POPULATION

In pregnant patient, CUS can be considered in order to avoid radiation. Perfusion scintigraphy in pregnant patient with normal chest X-ray to rule out PE. LMWH are recommended during pregnancy without shock or hypotension. For patient with cancer who diagnosed with PE, subcutaneous LMWH are recommended for first 3–6 month, except for high-risk PE. After then, LMWH still can be continued, switched to VKA, or discontinued. This decision should be made carefully after considering the success of anti-cancer therapy, risk of recurrence of VTE, bleeding risk, and patient's preference (17).

CONCLUSION

Patients with pulmonary embolism that comes into the emergency department, when diagnosed and treated in a timely manner, have a good prognosis. There is a breadth of clinical manifestations related to the disease which has further been simplified into scoring systems, i.e. PERC, Wells criteria, or Revised Geneva criteria, that can be utilised to exclude and diagnose pulmonary embolism. The initial supporting test needed is D-dimer, whereas imaging modalities are reserved in cases where pulmonary embolism still can't be excluded after clinical and D-dimer tests. Treatment of pulmonary embolism is based on risk stratification into high-, intermediate-, and low-risk cases. Hemodynamic status along with oxygen saturation should be corrected and anticoagulants are given to every case. Reperfusion therapy is only mandated in high-risk cases and are given in other risk groups only if anticoagulants fail or contraindicated. In low-risk cases, consider early discharge for patients that fulfil the Hestia criteria.

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