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REVIEW ARTICLE

Current strategies for the diagnosis of pulmonary embolism

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ABSTRACT

The diagnosis of symptomatic acute pulmonary embolism (PE) should be considered in any patient presenting with new-onset dyspnea, worsening of usual dyspnea, chest pain, syncope, or hypotension without an alternative explanation, particularly when basic complementary tests (chest X-ray, electrocardiogram, and arterial blood gas analysis) rule out other differential diagnoses. PE, therefore, represents a condition with a broad spectrum of clinical manifestations, with varying prognosis and treatment. This generally renders the diagnostic management of patients with suspected PE complex, which could be detrimental to patient survival given its potential lethality. This review addresses how to assess the clinical probability of PE, the diagnostic value of basic readily accessible tests, diagnostic tests, and their integration into validated algorithms, as well as the most current diagnostic strategies validated in PE.

Keywords: Computed tomography. Diagnosis. Diagnostic algorithm pregnancy. Pulmonary angiography. Pulmonary embolism.

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CLINICAL SUSPICION

The clinical spectrum of pulmonary embolism (PE) is broad, encompassing patients who are asymptomatic and have an incidental diagnosis of PE, as well as those who present with hemodynamically unstable conditions and an imminent risk of mortality. Although PE may be asymptomatic and incidental, in most patients, PE is suspected in the presence of symptoms such as dyspnea, chest pain, syncope or presyncope, and hemoptysis. Other, less frequent, symptoms are orthopnea, anginal chest pain, cough (usually irritative), or palpitations. Additionally, a variable percentage of patients may have a fever. However, the clinical suspicion of PE should be considered not only in the presence of acute symptoms but also in patients with respiratory symptoms of prolonged evolution or in those with a history of cardiorespiratory disease, where the only warning sign may be a worsening of their usual dyspnea[1].

On physical examination, tachypnea and tachycardia are the most frequent findings. In addition, reinforcement of the fourth and second tones, jugular ingurgitation, and right gallop are frequent in pulmonary thromboembolism (PTE) with hemodynamic repercussion[2]. Pulmonary auscultation is usually normal, with crepitations and a decrease in the vesicular murmur as the most frequent alterations.

The clinical presentation and course of PE are determined by three fundamental factors: the extent of pulmonary arterial embolic obstruction, the severity of preexisting cardiopulmonary pathology, and recurrent embolic episodes. The combination of symptoms and signs allows establishing the suspicion of PE, but the clinical variability of PE is so nonspecific that predictive scales are required to determine the use of diagnostic resources.

Basic complementary examinations

The role of complementary tests such as standard laboratory analysis, chest X-ray, electrocardiography, and arterial blood gas analysis is merely orientative in the diagnosis of PE[1].

ARTERIAL BLOOD GAS ANALYSIS

Arterial hypoxemia is a common alteration in PE. It is often associated with hypocapnia, respiratory alkalosis, and an increased alveolar-arterial oxygen difference. However, a normal partial pressure of oxygen (PO_2) does not rule out the diagnosis.

ELECTROCARDIOGRAM

Electrocardiogram (ECG) alterations are common in patients with PE. Most of them reveal nonspecific ST segment or T wave changes (T wave inversion in leads DIII, aVF, and from V1 to V4), supraventricular arrhythmias, P pulmonale wave, right ventricular hypertrophy, right axis deviation, or complete or incomplete right bundle branch block. Most show right ventricular overload. The distinctive pattern of an S wave in DI, combined with a Q wave and negative T wave in DIII (S1Q3T3, McGinn-White sign), occurs in only 15–26% of cases. With appropriate clinical suspicion, ECG alterations strongly support the diagnosis of PE. The early reversibility of these anomalies is associated with a satisfactory response to treatment and a favorable prognosis.

CHEST X-RAY

Even when the diagnosis is suspected clinically and confirmed by angiography, chest X-ray shows no specific features in approximately 10–15% of cases. Changes associated with thromboembolic episodes include peripheral oligemia, alterations of the pulmonary arteries, such as enlargement of a major pulmonary artery or abrupt narrowing of the obstructed blood vessel in the distal direction, elevation of the hemidiaphragm, parenchymal consolidation and volume loss, subsegmental atelectasis, and pleural effusion. The main utility of this technique is the possibility of ruling out other diseases that can simulate this pathology and correlating the results obtained with lung scintigraphy.

Assessment of clinical probability (pretest)

The combination of symptoms and signs, along with the presence of predisposing factors for venous thromboembolism (VTE), allows us to classify patients with suspected PE into different clinical categories or pretest probabilities, which correspond to different prevalences of PE. These pretest assessments are the first step in all PE diagnostic algorithms.

Clinical probability for conditions such as VTE is effectively determined by the Wells score[3] or the revised Geneva score[4]. These scales integrate risk factors for VTE as well as the signs and symptoms of PE (Table 1). Originally conceived as three-tier scales (low, intermediate, or high clinical probability), they have since been adapted to a dichotomous model, categorizing patients as either probable/high probability or improbable/low probability for PE.

IMAGING TESTS

Computed tomography pulmonary angiography

Computed tomography pulmonary angiography (CTPA) has surpassed other diagnostic methods and is currently the standard for diagnosing PE. This test also facilitates the identification of alternative diagnoses when PE is absent. Globally, the sensitivity and specificity of CTPA range from 57 to 100% and 78 to 100%, respectively; although it exhibits above 95% sensitivity and specificity when diagnosing PE in the main and lobar pulmonary arteries.

The advent of multidetector CTPA revolutionized PE diagnosis. Its introduction offers rapid diagnosis, reduced contrast administration, fewer imaging artifacts due to multiplanar imaging, and improved precision with a slice thickness of 0.5 mm, thus reducing interobserver variability. The primary

Table 1. Clinical probability assessment for PE

Well's score		Revised Geneva score	
Variables	Points	Variables	Points
Symptoms and signs of DVT	3.0	Age > 65 years	1
First diagnostic possibility of PE	3.0	History of DVT or PE	3
Tachycardia > 100 /min	1.5	Surgery under general anesthesia or fractures ≤ one month	2
Immobilization for at least 3 days or surgery within the previous 4 weeks	1.5	Active solid or hematologic cancer or cured ≤ one year	2
History of PE or DVT	1.5	Unilateral pain in the lower extremities	3
Hemoptysis	1.0	Hemoptysis	2
Neoplasm (under treatment, treated within the past 6 months, or in palliative care)	1.0	Heart rate 75–94/min	3
Low probability: < 2 points Moderate probability: adds between 2–6 points (inclusive) High probability: > 6 points Unlikely: < or = 4 Likely: > 4		Heart rate ≥ 95 /min	5
		Tenderness on LES and unilateral edema	4
		Low probability: 0–3 points Moderate probability: 4–10 points High probability: ≥ 11 points Unlikely: 0–5 Likely: > 6	

DVT: deep vein thrombosis; LES: lower extremity swelling; PE: pulmonary embolism.

advantage is its enhanced capability to visualize subsegmental pulmonary artery filling defects[5]. Over the past decade, MDCTPA technology has significantly improved, with current systems equipped with up to 320 detectors, reducing acquisition time and radiation dose to the patient. These systems allow for multiplanar reconstructions and postprocessing for enhanced visualization of the vascular tree, improving detection of subsegmental thrombi and reducing interobserver variability. Currently, images can be acquired with cardiac synchronization. In these protocols with retrospective reconstruction, radiation is emitted throughout the cardiac cycle, allowing image reconstruction at any point in the cycle and enabling the calculation of both right and left cardiac function[6,7].

Advanced tomographic techniques, such as iodine mapping, provide information on pulmonary perfusion that shows excellent correlation with ventilation/perfusion (V/Q) scintigraphy images[8].

The disadvantages of CTPA include radiation exposure, which was previously a significant limitation, particularly in pregnant patients, the use of contrast medium which limits its application in severe renal insufficiency (creatinine clearance <30 mL/min), and the necessity of specialized personnel for interpretation. However, ongoing advancements have significantly reduced patient exposure time and radiation, making CTPA the diagnostic technique of choice even during pregnancy. Consequently, CTPA is now considered the "gold standard" for PE diagnosis, having replaced invasive pulmonary angiography.

Lung scintigraphy

Lung scintigraphy has been the chosen first-line screening procedure for over 20 years[9]. It is a safe, noninvasive method for evaluating regional ventilation and perfusion. The radiopharmaceuticals of choice for perfusion scintigraphy are human albumin microaggregates or microspheres labeled with Tc-99m. There are no absolute contraindications for this test; however, severe pulmonary hypertension is a relative contraindication requiring individual assessment in each case. This technique is sensitive but not sufficiently specific, as all diseases of the pulmonary parenchyma and some affecting the airways will cause a decrease in arterial blood flow to the affected area. Hence, V/Q scintigraphy is recommended in specific cases, as conditions affecting the pulmonary parenchyma will cause combined ventilation and perfusion defects in the same area, whereas embolic disease shows preserved ventilation with perfusion abnormalities.

For ventilation scintigraphy, radioactive gases such as xenon-133 or aerosols like 99mTc-DTPA can be used. Ventilation scintigraphy should precede the perfusion study. Diagnosis is based on the presence of a discrepancy between ventilation and perfusion: ventilation presence in the absence of perfusion distal to an obstructive embolus. Findings are classified into several groups in terms of the gammagraphic probability of suffering a PE[10]: high, intermediate, low probability, and a fourth group with normal scintigraphy (of these, less than 4% will have positive angiography). Scintigraphy is primarily used as an alternative in patients with a history of adverse reactions to contrast agents or with renal insufficiency.

Magnetic resonance angiography

Magnetic resonance angiography (MRA) remains infrequently used in diagnosing PE. Its principal advantages include being a radiation-free modality, its multiplanar capabilities, and precise assessment of ventricular function. However, it requires careful patient selection, is unavailable in emergency settings, and yields a high number of indeterminate or nondiagnostic studies, particularly in peripheral areas. Currently, MRA is reserved for patients suspected of having PE where neither MDCT nor V/Q scintigraphy is feasible. Recent progress in MRA technology suggests an improvement in diagnostic sensitivity and specificity, advocating for its future potential as an alternative to CTPA[11].

Pulmonary angiography

The gold-standard status of pulmonary angiography is debatable, given that CTPA has similar or superior diagnostic capacity[12]. This involves radiographic visualization of the pulmonary vascular tree postintravenous contrast injection. Digital subtraction angiography offers the benefit of eliminating structural overlaps, enhancing the visibility of pulmonary blood vessels. It reduces the required contrast material by 25%, lowers costs, shortens procedure time, and provides results equal to or better than conventional angiography. The hallmark sign for diagnosing PE is the filling defect identified as persistent, central, or marginal intraluminal radiolucency without complete blood flow obstruction or residual intraluminal radiolucency coinciding with total downstream blood flow obstruction. Secondary signs require cautious interpretation due to various conditions affecting circulation and associated nonuniform arterial perfusion.

Single photon emission computed tomography

Single photon emission computed tomography (SPECT) imaging, possibly combined with low-dose computed tomography (CT), has been shown to reduce indeterminate assessments to 0–5%[13]. Most studies, however, are retrospective or of questionable quality, with only one study using a validated diagnostic algorithm[14]. Moreover, an optimal scan technique is undefined[15] (e.g., perfusion SPECT, V/Q SPECT, perfusion SPECT with noncontrast CT), with scant extensive outcome data. Hence, SPECT currently lacks utility and necessitates vast prospective studies for validation.

Transthoracic echocardiography

Transthoracic echocardiography generally lacks utility in the diagnostic algorithm for suspected PE patients, employed only in hemodynamically unstable patients unmovable to radiology for CTPA. The absence of right ventricular dysfunction or overload in critical patients rules out PE as a cause of hemodynamic instability.

Evaluation of deep venous system in PE assessment

Notably, most PEs originate from deep vein thrombosis (DVT) in the lower limbs. Approximately one-third of PE patients exhibit DVT symptoms[16,17]. In a study by Righini and colleagues[18], 1819 suspected PE patients were randomized into two groups: the first evaluated clinical probability followed by D-Dimer or CTPA; the second utilized D-Dimer, then lower limb compression ultrasound, and if this was a negative result, then performed thoracic CTPA. Both groups showed an identical 20.6% PE incidence, with 9% in the second group avoiding CTPA via DVT diagnosis. Similar 3-month VTE incidences affirmed both strategies' safety, and ultrasound could aid patients contraindicated for CTPA.

DIAGNOSTIC ALGORITHMS IN PE

The primary challenge in PE diagnosis is accurate and rapid identification of patients who require urgent treatment to avoid complications. The diagnosis of PTE, based on clinical manifestations alone, is unreliable because the signs and symptoms are very non-specific[19]. The clinical spectrum of PTE requires different diagnostic algorithms depending on the patient's hemodynamic involvement.

Diagnostic algorithm in hemodynamically stable PE patients

For stable patients, diagnostic algorithms relying on clinical probability evaluation and D-Dimer testing help determine imaging test suitability (see Fig. 1). The first step of the diagnostic strategy is an estimation of the pre-test clinical probability of PE as low, moderate, or high. The prevalence of PE within these three categories varies according to the different clinical prediction rules but is approximately less than 15%, 15–40%, and greater than 40%, respectively[20,21].

The two most widely used classical scales, validated and included in diagnostic algorithms, are the Wells scale[22] and the revised Geneva scale[23] (Table 1). The clinical probability classification determines the usefulness of D-dimer testing, which, in patients with low or intermediate clinical probability, can safely rule out PTE without imaging tests when the D-dimer is negative, that is, below the laboratory-determined cut-off point (usually <500 ng/mL)[24]. In patients with high clinical probability, D-dimer testing is not performed, but diagnostic imaging (CTPA) is performed directly. The high prevalence of PTE in this group leads to a lower negative predictive value of D-dimer, which in turn may increase the risk of false negative[25,26].

Diagnostic algorithm in hemodynamically unstable PE patients

For unstable patients who cannot undergo CTPA, transthoracic echocardiography is preferred as the first step in the algorithm (Fig. 2). The differential diagnosis usually includes cardiac tamponade, acute coronary syndrome, aortic dissection, acute valvular dysfunction, and hypovolemia.

The absence of right ventricular overload excludes PE in hemodynamic compromise. Hemodynamic instability involves systolic blood pressure <90 mmHg or a drop >40 mmHg for >15 min, not due to new arrhythmias, hypovolemia, or sepsis (Goldhaber). In very unstable patients, echocardiographic evidence of right ventricular dysfunction is sufficient to proceed immediately to reperfusion therapy, without waiting for further testing[1].

For patients with suspected recurrent PE, CTPA is the imaging test of choice[27]. Other imaging tests have been evaluated for the diagnosis of PE, such as magnetic resonance imaging[28] and SPECT, but direct comparison data with CTPA are scarce, and therefore these modalities should be considered in the experimental setting

D-dimer adjusted cut-off diagnostic algorithms

To reduce unnecessary CTPA use safely while enhancing diagnostic precision, new strategies employ adjusted D-Dimer cut-offs. These strategies effectively reduce

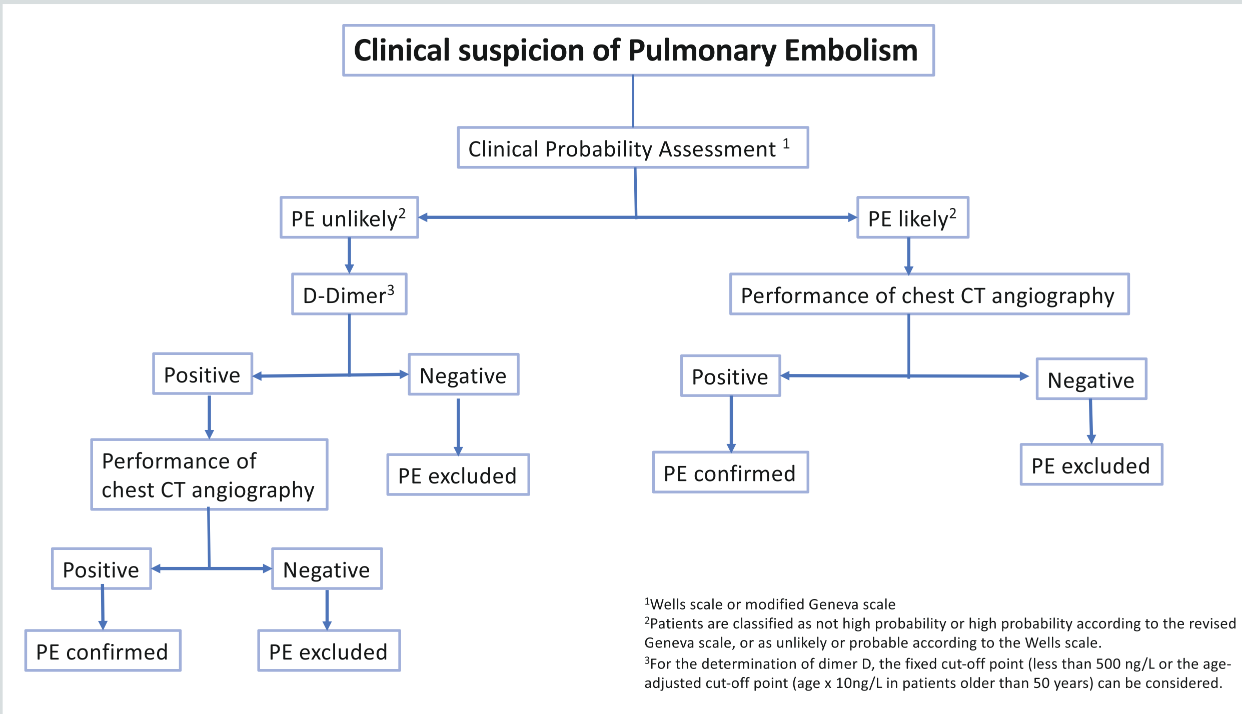

Figure 1. Diagnostic algorithms for hemodynamically stable PE patients. CT: computed tomography; PE: pulmonary embolism.

confirmatory imaging (mainly CTPA), adjusting D-Dimer cut-offs based on:

1. Adjustment for patient age

2. Adjustment for clinical probability:
   – YEARS strategy

   – Pulmonary embolism graduated D-dimer (PEGeD) strategy

   – 4-level pulmonary embolism probability strategy (4PEPS)

   – Modified diagnostic strategy (MODS)

The first strategy to reduce the use of CTPA is to raise the D-dimer threshold. Given the patient's age-adapted strategy, D-Dimer thresholds elevation to age * 10 ng/mL over 50 years of age[29]. This is about a 12% reduction in the number of CTPAs needed to rule out PE. However, this age adjustment is obviously only useful for patients over 50 years of age.

Among the strategies based on clinical probability, YEARS and PEGeD are the most evaluated and widespread in recent years. YEARS and PEGeD strategies, tested extensively, raise D-Dimer levels to 1,000 ng/mL for low PE probability.

The **YEARS strategy** allows the D-dimer threshold to be raised to 1,000 if none of its clinical items are present. It consists of using

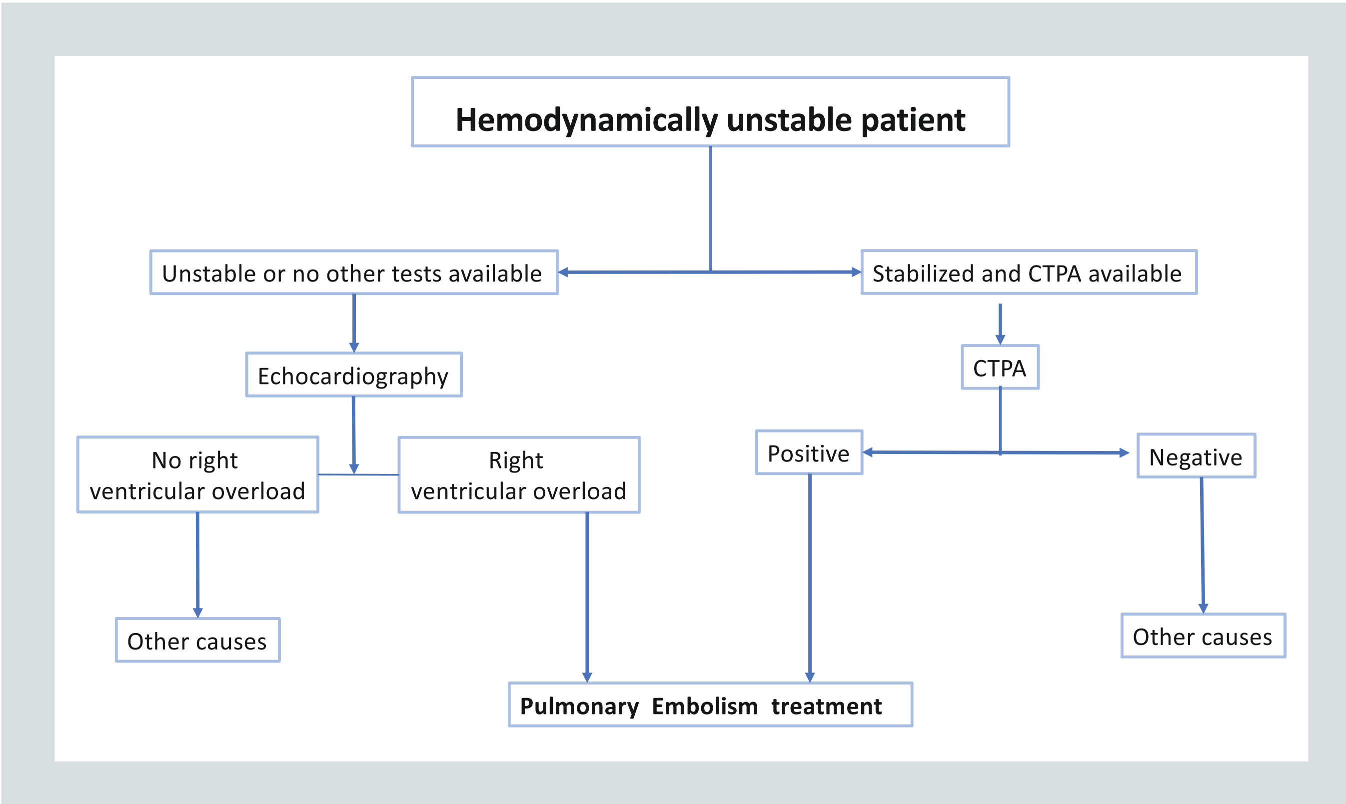

Figure 2. Diagnostic algorithms for hemodynamically unstable PE patients. CTPA: computed tomography pulmonary angiography; PE: pulmonary embolism.

a D-dimer cut-off point of 1,000 ng/mL in patients with none of the following criteria: (1) symptoms or signs of DVT, (2) hemoptysis, and (3) PE as the most likely diagnosis.

For patients with one or more of the criteria, the D-Dimer cut-off is set at 500 ng/mL (Fig. 3)[30,31]. The YEARS strategy combined with age-adjusted D-dimer in patients with PERC >0 was evaluated in a crossover, noninferiority, cluster-randomized clinical trial in 18 emergency departments in France and Spain (MODIGLIANI study). 1,414 patients with a low clinical risk of PE not excluded by the PERC rule or an intermediate subjective clinical risk of PE were included. In the intervention period (726 patients), PE was excluded without imaging in patients without YEARS criteria and a D-dimer level below 1,000 ng/mL and in patients with one or more YEARS criteria and a D-dimer level below the age-adjusted cut-off point (500 ng/mL if age <50 years or age in years × 10 in patients >50 years). In the control period (688 patients), PE was excluded without imaging if the D-dimer level was below the age-adjusted threshold. Finally, 1,217 (86%) were analyzed in the per-protocol analysis. PE was diagnosed in the emergency department in 100 patients (7.1%). At 3 months, VTE was diagnosed in one patient in the intervention group (0.15% [95% confidence interval CI 0.0–0.86%]) versus 5 patients in the control group (0.80% [95% CI 0.26–1.86%]) (adjusted difference, –0.64% [one-sided 97.5% CI –0.21%], within the noninferiority margin).

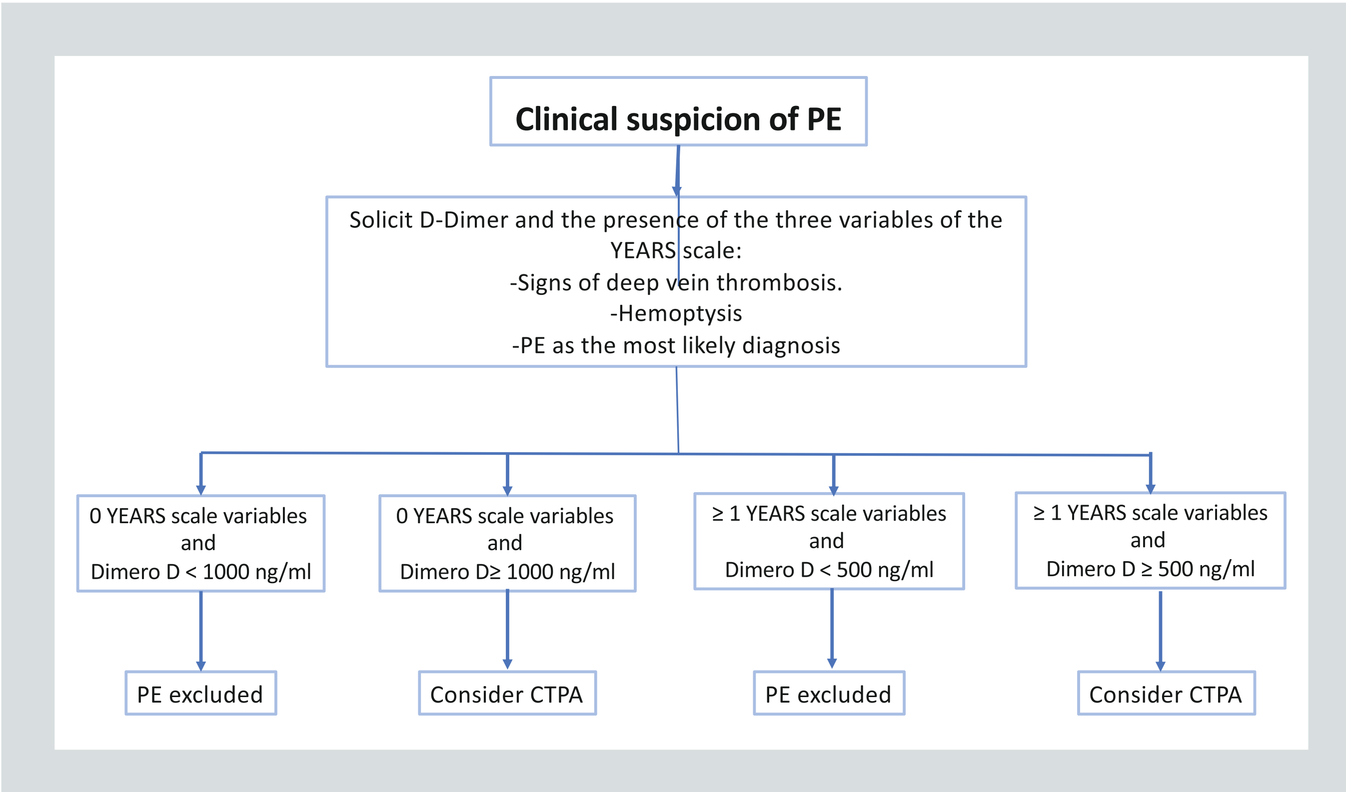

FIGURE 3. YEARS strategy for PE diagnosis. CTPA: computed tomography pulmonary angiography; PE: pulmonary embolism.

Imaging to rule out PE was significantly reduced by 9.6% (30.4% vs. 40.0%; adjusted difference, –8.7% [95% CI, –13.8% to –3.5%]) and mean length of stay in the emergency department[31].

The **PEGeD rule** consists of using a D-dimer cut-off point of 1,000 ng/mL in patients with a low pre-test clinical probability of PE (Wells score less than 4.5); and 500 ng/mL in those with a moderate clinical probability (Wells score greater than 4.5) (Fig. 3)[32]. These rules have been prospectively validated and can be safely used to rule out PE without imaging tests[31].

The **4PEPS strategy** was derived and validated in a study published in 2021 from several international prospective cohorts of consecutive outpatients with suspected PE from US and European emergency departments[33]. A total of 11,114 patients were included with an overall prevalence of PE of 11%. For the referral cohort, 5,588 patients were included. The 4PEPS comprises 13 clinical variables scored from –2 to 5. It results in the following classification:

1. very low probability of PE if 4PEPS is less than 0: PE ruled out;

2. low probability of PE if 4PEPS is 0 to 5: PE ruled out if the D-dimer level is less than 1.0 µg/mL;

3. moderate probability of PTE if 4PEPS is 6 to 12: PE ruled out if the D-dimer level is less than the age-adjusted cut-off value;

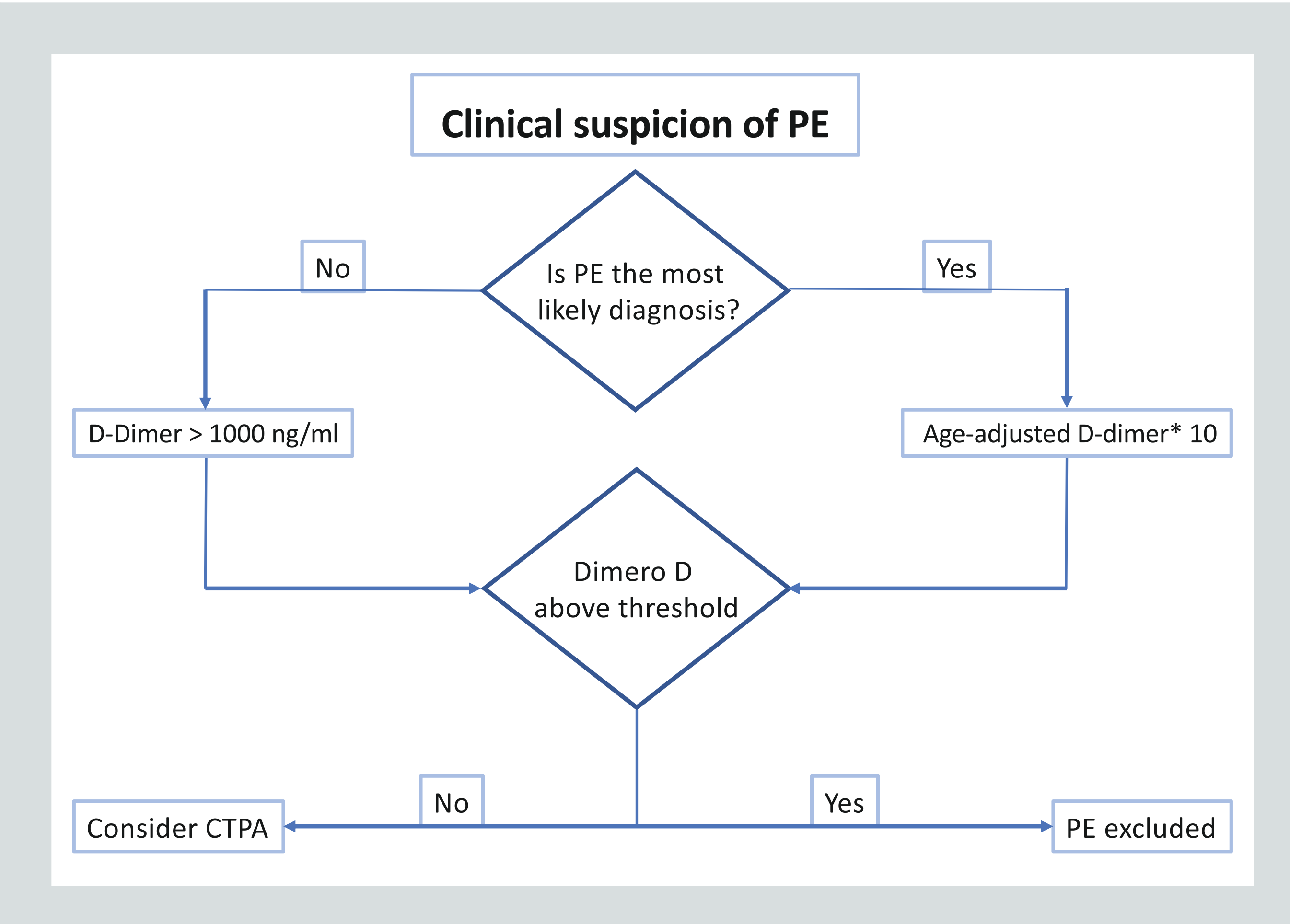

Figure 4. MODS strategy for the diagnosis of PE patients. CTPA: computed tomography pulmonary angiography; PE: pulmonary embolism.

4. high probability of PE if 4PEPS is greater than 12: PE ruled out by imaging studies without prior D-dimer testing.

External validation was performed in two independent cohorts: The first with a high PE prevalence (n = 1,548; prevalence, 21.5%) and the second with a moderate PE prevalence (n = 1,669; prevalence, 11.7%). In the first and second external validation cohorts, the area under the receiver operator characteristic curves was 0.79 (95% CI, 0.76 to 0.82) and 0.78 (95% CI, 0.74 to 0.81), respectively, and the absolute reductions in imaging tests were -22% (95% CI, –26 to –19) and –19% (95% CI, –22 to –16), respectively[34] .

The **MODS strategy** determines "probable PE" by the physician's implicit estimation of whether PE is the most likely diagnosis, and the D-dimer cut-off point of 1,000 ng/mL, and can safely rule out PTE in patients in whom PTE was not the most likely diagnosis and D-dimer <1,000 ng/mL (Fig. 4). The advantage of the MODS strategy is the applicability in routine clinical practice in the emergency department, as it only requires assessment of whether "PTE is the most likely diagnosis" and applying the D-dimer cut-off point at 1,000 ng/mL for

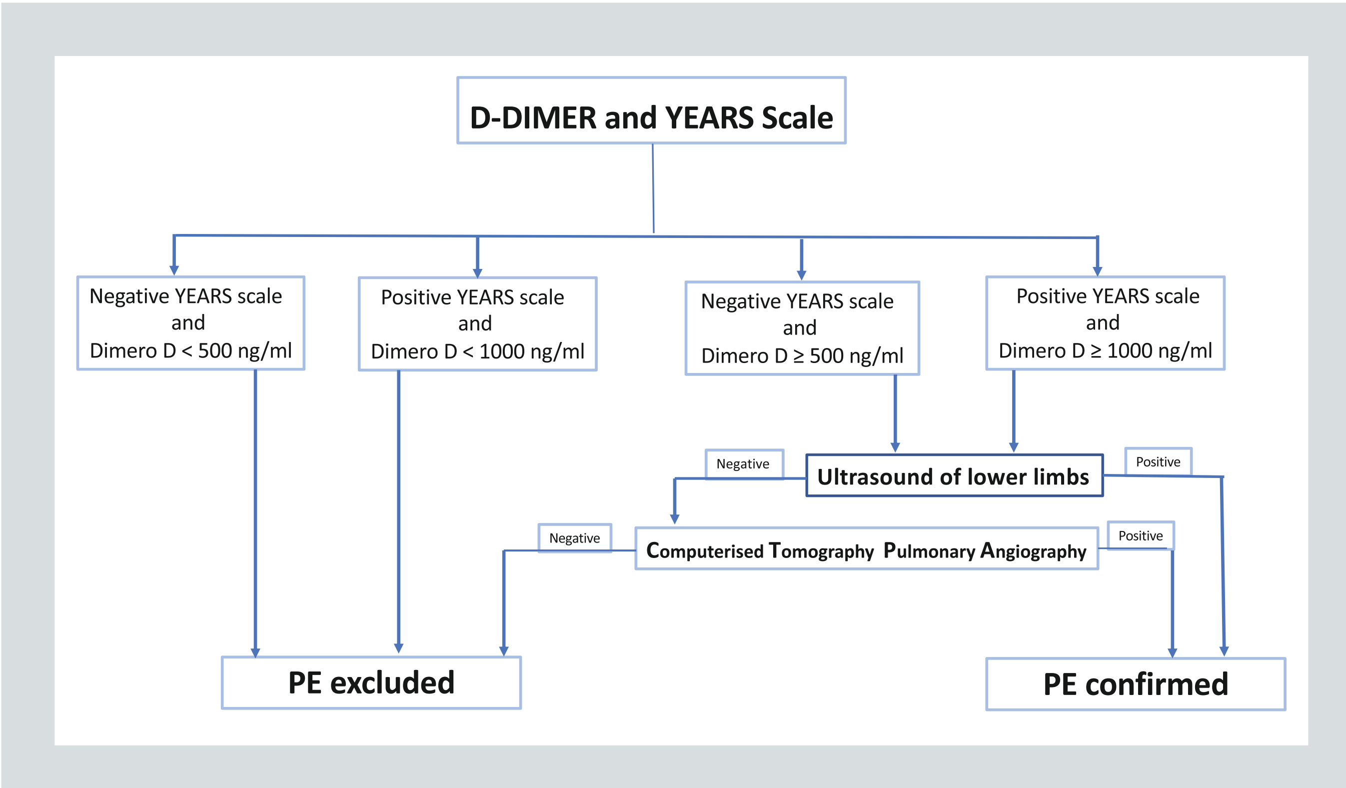

Figure 5. YEARS strategy for the management of pregnant patients with suspected PE. YEARS scale: (1) clinical signs of DVT; (2) hemoptysis; (3) PTE as most likely diagnosis. Negative: all criteria absent. Positive: one or more criteria present. PE: pulmonary embolism; PTE: pulmonary thromboembolism.

those who answer "no," or the age-adjusted cut-off point when the answer is "yes." Simplification of the MODS strategy would allow emergency department physician adherence to recommended practices. However, it requires well-designed studies to confirm its efficacy and safety in the diagnostic evaluation of patients with suspected PE in the emergency department.

DIAGNOSTIC ALGORITHMS FOR SUSPECTED PE IN PREGNANCY

Studies like CT-PE Preg and Assessment of the role of the YEARS algorithm in the diagnostic management of suspected PE in pregnancy (ARTEMIS) assess diagnostic strategies in pregnant women, demonstrating efficiency[35-37]. The CT-PE pregnancy study evaluated the combination of low or intermediate pretest clinical probability according to the revised Geneva scale and negative D-dimer result to rule out PE. 395 pregnant women with suspected PE were included. The rate of symptomatic venous thromboembolic events was 0.0% (95% CI 0.0–1.0%) among untreated women after exclusion of PE[35].

The ARTEMIS study evaluated the YEARS strategy adapted to pregnancy and included 498 pregnant women. Twenty patients (4.0%) were diagnosed with PTE at baseline. The YEARS strategy was evaluated, with the difference of performing lower extremity venous ultrasound in those patients with

DVT symptoms as a first step. CTPA was not indicated and therefore avoided in 195 patients (39%; 95% CI 35–44%)[36]. Efficiency of the algorithm (Fig. 5) was highest during the first trimester of pregnancy and lowest during the third trimester; CTPA was avoided in 65% of patients who started the study in the first trimester and in 32% who started the study in the third trimester.

In conclusion, validated and clinically recommended strategies like the YEARS and Geneva score combined with D-Dimer level estimation can effectively manage suspected PE in pregnant patients.

ETHICAL DISCLOSURES

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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