EDITORIAL

Diagnostic Strategies for Suspected Pulmonary Embolism

Marcel Levi, MD, PhD; Nick van Es, MD, PhD

Pulmonary embolism is a serious and potentially life-threatening condition. However, after a timely and accurate diagnosis and initiation of appropriate treatment, patients usually quickly recover and most will have an excellent prognosis.

The diagnosis of pulmonary embolism can be difficult because patients may present with nonspecific clinical manifestations and typical signs and symptoms frequently are absent.[1] In the past few decades, a rapid and reliable diagnosis of pulmonary embolism has been made easier with the availability of high-resolution computed tomography (CT) pulmonary angiography (PA). However, because many patients with clinically suspected pulmonary embolism have alternative diagnoses, such as pulmonary infections, cardiac conditions, pleural disease, or musculoskeletal problems, much effort has been devoted to develop triage protocols to identify the right patients who need CTPA to avoid unnecessary scanning, contrast-induced nephropathy, radiation exposure, cost, and overdiagnosis of small subsegmental clots, of which the clinical relevance is controversial.[2,3] This is becoming more important as the threshold of physicians to consider the diagnosis of pulmonary embolism is currently much lower, as illustrated by a decreasing pulmonary embolism prevalence in diagnostic management studies. In some studies, pulmonary embolism was confirmed in less than 10% of patients in whom the diagnosis was initially suspected.[4,5]

Related article page 2141

The absence of elevated levels of D-dimer, a blood test that indicates clot formation and degradation, has been shown to reliably exclude pulmonary embolism in patients with a low probability of pulmonary embolism on clinical grounds. To operationalize and standardize the assessment of clinical probability, simple and straightforward clinical decision rules have been developed, using parameters such as age, heart rate, oxygen saturation, recent trauma or surgery, cancer, signs of deep vein thrombosis, or previous venous thromboembolism.[6,7] For example, the YEARS algorithm combines only 3 clinical parameters (clinical signs of deep vein thrombosis, hemoptysis, and pulmonary embolism as the most likely diagnosis) and, depending on the presence of one of those, a high (1000 µg/L) or low (500 µg/L) cutoff value for D-dimer is applied.[4] A prospective validation cohort study involving 3465 patients confirmed that a negative YEARS rule safely excluded pulmonary embolism without the need for CTPA in 46% of patients.[8]

In this issue of *JAMA*, Freund et al[9] present a further refinement of these diagnostic algorithms for suspected pulmonary embolism. In a cluster-randomized noninferiority trial, the authors investigated a diagnostic strategy in which patients were first selected as at intermediate risk for pulmonary embolism using a first subjective clinical impression ("gestalt") in combination with the pulmonary embolism rule-out criteria (PERC) rule (which consist of age ≥50 years, pulse rate of ≥100/min, arterial oxygen saturation of ≤94%, unilateral leg swelling, hemoptysis, recent trauma or surgery, prior pulmonary embolism or deep venous thrombosis, and exogenous estrogen use). Patients were then assessed using the YEARS rule with an age-adjusted D-dimer threshold (rather than a fixed normal value) among those without clinical items (intervention group). This strategy was compared with a more usual diagnostic workup, ie, D-dimer testing in all patients with chest imaging for those with levels above an age-adjusted threshold (control group). The primary end point was venous thromboembolism at 3 months.

Among the 1414 patients enrolled at 18 emergency departments in France and Spain, including 1217 (86%) analyzed in the per-protocol analysis, pulmonary embolism was diagnosed in 100 patients (7.1%). During 3-month follow-up, the failure rate was very low in both the intervention group (1 patient; 0.15%) and control group (5 patients; 0.80%) (adjusted difference, 0.64% [1-sided 97.5% CI, −∞ to 0.21%]), which met criteria for noninferiority compared with the YEARS rule (according to a predefined noninferiority margin of 1.35%). Chest imaging was performed in a significantly lower proportion of patients of the intervention group (30.4%) than in the control group (40.0%), and emergency department length of stay was 1.6 hours shorter in the intervention group than the control group.

The robust data from this methodologically sound trial underscore the safety of both investigated approaches for the exclusion of pulmonary embolism without imaging. It is helpful that the diagnostic strategies were evaluated in a randomized design with a control group (albeit based on cluster randomization and not individual patient randomization) instead of the more common single-group management studies in the literature. The largest advantage of the new algorithm is probably a reduction of 10% in chest imaging (defined as CT angiography or ventilation/perfusion scanning) in the diagnostic workup (or exclusion) of pulmonary embolism.

However, several factors should be considered in the interpretation of the study findings. Although the algorithms used in this study were not particularly complex, the multistep process presented in this trial could complicate the approach for evaluating suspected pulmonary embolism by busy emergency department physicians who evaluate and treat patients with myriad clinical conditions. A diagnostic sequence that requires a first clinical impression followed by calculating the PERC rule in patients judged to be at low risk, then another scoring system (YEARS) for PERC-positive patients or those judged to be at intermediate risk, which is ultimately

combined with D-dimer testing using a differential threshold, might not be the most practical and easy-to-remember approach in a busy clinical setting. Moreover, the proposed approach was only studied in a cohort of patients with a subjective low or intermediate risk of pulmonary embolism, which likely explains the rather low pulmonary embolism prevalence (about 7%) in this study. The safety of these diagnostic workups for a group with an a priori higher suspicion of pulmonary embolism was not validated in this study, but this subtlety may be easily forgotten in routine clinical practice. It could be argued that in clinical emergency medicine practice a simpler approach might be preferred to avoid confusion or even possible errors.

In addition, patients do not regularly present to the emergency department just to establish or rule out a diagnosis of pulmonary embolism. Instead, they present to the hospital because of chest symptoms (eg, pain), shortness of breath, or feeling unwell. Pulmonary embolism is often just one of many possibilities in the differential diagnosis. While this study shows that 10% fewer CTPAs were performed, it does not report all other imaging modalities that might have been used in the patients to establish or rule out alternative diagnoses. Hence, from a patient perspective, the benefit of this reduction in diagnostic imaging may be more modest than reported in this study.

CT scans are particularly useful (and more sensitive than chest x-rays) in the diagnosis of chest infections, pleural disease, pneumothorax, aortic dissection, and even some cardiac conditions, such as pericarditis. Thus, a chest CT scan that does not show a pulmonary embolism may still be highly valuable in the diagnostic workup of the patient's presenting symptoms. The study by Freund et al[9] (like many other studies that have focused on the diagnostic workup of pulmonary embolism) does not mention alternative diagnoses and the usefulness of CT scans and other imaging modalities in the overall diagnostic approach to determine an explanation of a patient's symptoms and signs.

Overburdening physicians with algorithms that drive clinical decision-making is becoming more and more customary. While algorithms can be helpful and may generate a more objective and standardized approach to clinical decisions, they are also associated with potential disadvantages. Blindly applying algorithms to every patient may be less appropriate or even undesirable in specific situations in which deviation from the rules on clinical grounds is indicated. For example, results of the present study should not be applied to pregnant or critically ill patients or those already using therapeutic anticoagulation as they were excluded. Hence, the use of algorithms should never obscure (or even prohibit) the use of common clinical sense and deviation from diagnostic rules in specific clinical conditions.

Taken together, there is a role for efficient diagnostic algorithms to decrease the use of CTPA in patients with clinically suspected pulmonary embolism. The elegant study by Freund et al[9] shows that this can be achieved by a combination of clinician gestalt, PERC rule, clinical YEARS items, and D-dimer testing with a differential threshold (age-adjusted or fixed high cutoff). However, in the acute clinical setting of emergency medicine, which is usually busy or even hectic, such a rather complex approach toward triage for CTPA is not only time consuming, but may also prove challenging. A simple diagnostic approach based on the YEARS algorithm combined with age-adjusted D-dimer testing in all patients might have been just as efficient and safe overall, while less burdensome. Further, from a patient perspective, a negative diagnostic algorithm for pulmonary embolism does not diminish the physician's obligation to consider other diagnoses that explain the symptoms, for which chest CT scans may still be needed and helpful.

ARTICLE INFORMATION

Author Affiliations: Department of Vascular Medicine, Amsterdam Cardiovascular Sciences, Amsterdam University Medical Center, Amsterdam, the Netherlands (Levi, van Es); Department of Medicine, University College London Hospitals NHS Foundation Trust, London, United Kingdom (Levi); Cardiometabolic Programme-NIHR UCLH/UCL BRC, London, United Kingdom (Levi).

Corresponding Author: Marcel Levi, MD, Department of Vascular Medicine–AMC D3, Meibergdreef 9, 1105AZ Amsterdam, the Netherlands (m.m.levi@amsterdamumc.nl).

Conflict of Interest Disclosures: None reported.

REFERENCES

1. Pollack CV, Schreiber D, Goldhaber SZ, et al. Clinical characteristics, management, and outcomes of patients diagnosed with acute pulmonary embolism in the emergency department: initial report of EMPEROR (Multicenter Emergency Medicine Pulmonary Embolism in the Real World Registry). *J Am Coll Cardiol*. 2011;57(6):700-706. doi:10.1016/j.jacc.2010.05.071

2. Raja AS, Ip IK, Prevedello LM, et al. Effect of computerized clinical decision support on the use and yield of CT pulmonary angiography in the emergency department. *Radiology*. 2012;262(2):468-474. doi:10.1148/radiol.11110951

3. Fernandes A, Connors JM, Carrier M. Anticoagulation for subsegmental pulmonary embolism. *N Engl J Med*. 2019;381(12):1171-1174. doi:10.1056/NEJMclde1907665

4. Kearon C, de Wit K, Parpia S, et al; PEGeD Study Investigators. Diagnosis of pulmonary embolism with D-dimer adjusted to clinical probability. *N Engl J Med*. 2019;381(22):2125-2134. doi:10.1056/NEJMoa1909159

5. Kline JA, Garrett JS, Sarmiento EJ, Strachan CC, Courtney DM. Over-testing for suspected pulmonary embolism in American emergency departments: the continuing epidemic. *Circ Cardiovasc Qual Outcomes*. 2020;13(1):e005753. doi:10.1161/CIRCOUTCOMES.119.005753

6. Kline JA, Courtney DM, Kabrhel C, et al. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. *J Thromb Haemost*. 2008;6(5):772-780. doi:10.1111/j.1538-7836.2008.02944.x

7. Freund Y, Cachanado M, Aubry A, et al; PROPER Investigator Group. Effect of the pulmonary embolism rule-out criteria on subsequent thromboembolic events among low-risk emergency department patients: the PROPER randomized clinical trial. *JAMA*. 2018;319(6):559-566. doi:10.1001/jama.2017.21904

8. van der Hulle T, Cheung WY, Kooij S, et al; YEARS study group. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. *Lancet*. 2017;390(10091):289-297. doi:10.1016/S0140-6736(17)30885-1

9. Freund Y, Chauvin A, Jimenez S, et al. Effect of a diagnostic strategy using an elevated and age-adjusted D-dimer threshold on thromboembolic events in emergency department patients with suspected pulmonary embolism: a randomized clinical trial. *JAMA*. Published December 7, 2021. doi:10.1001/jama.2021.20750