Suspected pulmonary embolism in the emergency department: over-, under- and/or mis-testing?

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The wide availability of CT scans for patients in emergency departments generally improves diagnostic pathways, but its increased use may also pose significant public health challenges that include the risk of cancer from cumulative radiation exposure, overdiagnosis and overtreatment of insignificant diseases, increased emergency department stay, and associated costs. Suspected pulmonary embolism (PE) is a prime example of these issues. The symptoms of PE are unspecific, leading clinicians to often consider it to avoid missing a potentially fatal condition. Since the 2000s, diagnostic algorithms involving clinical probability assessment, D-dimer levels, and CT pulmonary angiography (CTPA) have been shown to be reliable and safe.[1] Schematically, patients with a high clinical probability of PE according to validated clinical decision rules and those with a non-high clinical probability and elevated D-dimers levels must proceed to lung imaging. However, easy access to CTPA has increased its use in patients investigated for PE, with a consequent decrease in its diagnostic yield.[2] Furthermore, despite increasing diagnoses, this shift has not significantly impacted PE mortality.[3] Efforts to combat overtesting include estimating when clinically suspected PE may not need further investigation (PERC rule) and adapting D-dimer level thresholds to rule out PE in certain subpopulations (age-adjusted and clinical probability adjusted cutoffs).[4,5]

In this issue of *The Lancet Regional Health-Europe*, Falster et al. investigated the effect of a combined heart, lungs and proximal leg veins ultrasound exploration by emergency physicians on the need for further testing. In an open-label randomized trial of 150 patients, across 6 Danish hospitals, who would undergo lung imaging per current guidelines, they found that a multi-organ ultrasound exploration reduced the use of CTPA or lung scintigraphy by 45.2% (95% CI: 34.3–56.6, $p < 0.0001$).[6] If not for confirmatory CTPA after positive venous ultrasound results, which represented nine of eleven PE diagnoses obtained with ultrasonography, this reduction would have been even greater. Overall, these data support the high positive predictive value of ultrasound for diagnosing PE.

However, the performance of ultrasonography to exclude PE in this trial proved far from acceptable. The failure rate of the strategy, i.e., the proportion of patients who had PE ruled out by ultrasonography and remained untreated but then suffered PE during the 3-month follow-up was 6.7% (2 of 30 patients), with an upper limit of the 95% confidence interval (CI) reaching 21.3%. The failure rate in the control arm was 0% (0 of 51 patients). For the ultrasound-based strategy to be considered safe, the upper limit of the failure rate 95% CI should not have exceeded 2%.[7] Although the trial was not designed and powered to reliably assess safety, these results are concerning and will help reconsider the place of multi-organ ultrasound in future studies.

Improving the negative predictive value of the proposed strategy might involve applying it to a low prevalence population. The authors suggest using it only in patients with a low clinical probability of PE (prevalence 6%). However, the effectiveness of a diagnostic test depends on its place in the diagnostic strategy. In the PEGeD study, a low clinical probability corresponded to an initial pre-test probability of PE of 5%, but a D-dimer level >1000 ng/mL in this group meant a post D-dimer test probability, i.e., a pre-test probability for the next examination, of 18%.[5] Hence, the negative predictive value of ultrasound may still be insufficient for these patients. Also, the low sensitivity and imperfect specificity of lung ultrasonography for diagnosing PE might lead to reconsider its very place in the ultrasound strategy.[8]

Evaluating diagnostic strategies also requires assessing their practical applicability. Interventions to reduce over-testing add complexity to the diagnostic strategy for suspected PE. For example, integrating the PERC rule into the PEGeD strategy involves evaluating clinical probability three times (gestalt assessment to ensure that the PERC rule is applicable and, if positive, applying the Wells score) resulting in a significant risk of misapplication. Past research found that emergency physicians followed a guideline-conforming diagnostic approach in <50% of patients with suspected PE, and this nonconformity was a major independent risk factor for misdiagnosis.[9] More recent work indicates that non-

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adherence to a validated diagnostic strategy based on clinical probability estimation and D-dimer testing significantly contributes to CTPA overuse.[2,10] In this regard, ultrasound results could be used to alleviate difficulties in evaluating the subjective item of "alternative diagnosis less likely than PE" in the Wells score. Hence, ultrasonography, increasingly used in emergency medicine, may complement the clinical examination and, by supporting differential diagnoses without conclusively excluding PE, might nonetheless enhance the value of clinical probability estimation and optimize D-dimer use.

In conclusion, this study underscores the value of ultrasound in unexpected areas for patients with suspected PE: refining pre-test probability estimation before D-dimer testing, and confirming diagnoses by exploring proximal leg veins. The role of ultrasonography in reducing both overtesting and undertesting in this population certainly merits further exploration.

Contributors

PMR wrote the original draft, PG edited the draft, and both authors approved the final version.

Declaration of interests

The authors have no conflicts of interest to declare.

References

1 Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J*. 2019;54:1901647.

2 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:e005753.

3 Roussel M, Bloom B, Taalba M, et al. Temporal trends in the use of computed tomographic pulmonary angiography for suspected pulmonary embolism in the emergency department: a retrospective analysis. *Ann Intern Med*. 2023;176:761–768.

4 Freund Y, Cachanado M, Aubry A, et al. 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;319:559–566.

5 Kearon C, de Wit K, Parpia S, et al. Diagnosis of pulmonary embolism with d-dimer adjusted to clinical probability. *N Engl J Med*. 2019;381:2125–2134.

6 Falster C, Mørkenborg MD, Thrane M, et al. Utility of ultrasound in improving selection of patients with suspected pulmonary embolism for diagnostic imaging (the PRIME study): an open-label multicentre randomized controlled trial. *Lancet Reg Health Eur*. 2024. https://doi.org/10.1016/j.lanepe.2024.100941.

7 Dronkers CEA, van der Hulle T, Le Gal G, et al. Diagnostic variables in thrombotic D. Towards a tailored diagnostic standard for future diagnostic studies in pulmonary embolism: communication from the SSC of the ISTH. *J Thromb Haemost*. 2017;15:1040–1043.

8 Falster C, Jacobsen N, Coman KE, et al. Diagnostic accuracy of focused deep venous, lung, cardiac and multiorgan ultrasound in suspected pulmonary embolism: a systematic review and meta-analysis. *Thorax*. 2022;77:679–689.

9 Roy PM, Meyer G, Vielle B, et al. Appropriateness of diagnostic management and outcomes of suspected pulmonary embolism. *Ann Intern Med*. 2006;144:157–164.

10 Dhakal P, Iftikhar MH, Wang L, et al. Overutilisation of imaging studies for diagnosis of pulmonary embolism: are we following the guidelines? *Postgrad Med J*. 2019;95:420–424.