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Perspectives on the use of Adjusted D-dimer Cutoffs to Rule Out Pulmonary Embolism

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Perspective

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ABOUT THE STUDY

Pulmonary Embolism (PE) is a potentially life threatening condition that requires prompt and accurate diagnosis for effective management. The modern diagnostic strategies rely on sequential evaluation of clinical probability, measurement of plasma D-dimer levels and Computed Tomography Pulmonary Angiography (CTPA). D-dimer testing is a commonly used and widely evaluated diagnostic tool to exclude PE in patients with low or intermediate clinical probability. However, the specificity of this test is limited (35%-40%), especially in some clinical situations, leading to unnecessary imaging tests. In a recently published article in the journal of clinical medicine [1], the efficiency and safety of age-adjusted and clinical probability-adapted D-dimer cutoffs were reported, providing a narrative review of relevant clinical trials. This review highlighted the potential benefits of D-dimer adjustment in improving the diagnostic management of PE by reducing unnecessary thoracic imaging.

Age adjusted D-dimer cutoff

The concept of age-adjusted D-dimer thresholds arose from the need to address a significant diagnostic challenge: The test's specificity decreases with age. Historically, a fixed threshold of 500 ng/mL was used in all patients, resulting in a high number of patients needed to test to exclude one PE in the elderly Number Needed to Treat (NNT) of 20 in patients>80 years old, compared to 3 in the general population) and thus in a high proportion of elderly patients undergoing CTPA. Adjusting the D-dimer threshold to age using a progressive cutoff of (patient's age × 10) in ng/mL for patients over 50 years old has been shown to improve specificity without compromising sensitivity [2].

The acute deep vein thrombosis: A Diagnostic and Therapeutic Strategies for Pulmonary Embolism (ADJUST-PE) study showed that age-adjusted cutoff provided a 5 fold increase in the proportion of patients >75 years (from 6% to 30%) in whom PE can be excluded without imaging while maintaining diagnostic safety [3].

The Rapid Evaluation of Large Pulmonary Embolism (RELAX-PE) study further confirmed the safety of the age-adjusted D-dimer cutoff, with a 3-month Venous Thromboembolism (VTE) risk after a negative D-dimer of 0.07% (95% CI .01%-0.40%). Interestingly, 67% of patient's ≥ 75 years who had PE excluded by negative D-dimer had a D-dimer level above 500 but below their age-adjusted cutoff and 33% a D-dimer level <500 ng/mL. Finally, age-adjusted D-dimer cutoff could help reduce emergency department wait times and costs associated with PE diagnostic workups [4].

Clinical probability-adapted D-dimer cutoffs

Another strategy explored to increase the yield of D-dimer is the use of cutoffs adapted to pre-test clinical probability. The first model uses three items from the wells score clinical signs of deep vein thrombosis, hemoptysis and whether PE is the most likely diagnosis identified by post-hoc derivation and validation studies as the most predictive for PE [5]. In the Years of Experience in Assessing Risk Score model (YEARS), the D-dimer threshold was 500 ng/mL when one or more items were present and 1000 ng/mL when none was present [6]. The second probability-adapted model Pulmonary Embolism (PE) in General and Diverse Populations (PEGeD) assessed a 500 ng/mL cutoff for patients with intermediate clinical probability and 1000 ng/mL for patients with low clinical probability using the Wells score with modified cutoffs [7].

Both clinical probability-adapted D-dimer cutoff models were shown as

- To be safe to exclude PE, with a 3-month VTE risk of 0.61 (95% CI 0.3%-0.96%) and 0.05 (95% CI 0.01%-0.3%), respectively.
- To provide an absolute reduction in the use of CTPA of 14% and 17.6%, respectively compared to the conventional 500 ng/mL cutoff in all patients.

External validation studies however suggest that these algorithms, although more efficient (i.e. allowing to exclude PE in a higher proportion of patients) may lack safety in a population of patients with a higher PE prevalence [8,9]. Clinician education and awareness regarding these adapted cutoffs and their use in their given population of patients will contribute to prevent both over diagnosis and under diagnosis of PE.

Perspectives and clinical implications

In clinical practice, any physician should be aware of the approximate PE prevalence in patients with clinical suspicion of PE to whom the person is exposed. Geographical differences in PE prevalence among suspected patients have been consistently described over time. In the studies mentioned above, PE prevalence was 19% in the ADJUST-PE (European Study), 13% in the years study (Dutch study) and only 7% in the North American (PEGeD) study [3,6,7]. A clinical setting with an expected prevalence between 10% - 20% is better suited to an age-adjusted cutoff for safety reasons. However clinical settings with a PE prevalence less than 10% might well be better served by a clinical probability-adapted cutoff, due to its higher efficiency. Diagnostic performance of D-dimer also differs across healthcare setting [10]. These issues are discussed in detail in the narrative review [1].

Another important issue is the type of D-dimer test used. All recent studies used high-sensitivity D-dimer tests by the Enzyme-Linked Immunosorbent Assay (ELISA) technique or quantitative latex methods in their diagnostic algorithms. The clinician facing a patient with suspected PE should be aware of the test they are prescribing, as the negative predictive value will be affected by the test's intrinsic performance characteristics in addition to PE prevalence. A post-hoc analysis of six different high sensitivity D-dimer assays used in the ADJUST-PE study has been performed [11] and the manuscript will be published soon.

CONCLUSION

Two strategies of D-dimer cutoff adjustment have been validated in large scale prospective outcome studies to reduce the proportion of patients with clinically suspected PE who will eventually need thoracic imaging, with different trade-offs between safety (i.e. the diagnostic failure rate) and efficiency (i.e. the proportion of patients who can have PE excluded without imaging). Overall, the important message to bear in mind is that age-adjusted cutoff is safer but less efficient in ruling out PE, whereas clinical probability-adapted cutoffs are less safe but more efficient.

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