Critical Review Form
Diagnostic Test

PGY-4

Douma RA, le Gal G, Söhne M, et al. Potential of an age adjusted D-dimer cut-off value to improve the exclusion of pulmonary embolism in older patients: a retrospective analysis of three large cohorts. BMJ. 2010 Mar 30;340:c1475.

Objectives: **To derive and analyze the safety and efficacy of an age dependent D-dimer cutoff value in combination with clinical probability assessment in two large prospective cohort studies of patients with suspected pulmonary embolism (PE), and to validate the outcome in two other large management studies.**

Methods: **Data from two previously reported prospective cohort studies, both conducted in Switzerland and France, both including consecutive patients admitted to the emergency department (ED) with a clinical suspicion of PE were gathered. These studies comprised a total of 1721 patients. Patients underwent sequential testing, including plasma D-dimer measurement and Geneva score clinical probability assessment. In the first study, PE was ruled out by D-dimer < 500 µg/l alone, while the second study only allowed PE to be ruled out by negative D-dimer alone in patients with a non-high clinical probability on the Geneva score. In both studies, patients with an elevated D-dimer (and in the second study those with high-risk clinical probability) then underwent additional sequential testing in the form of lower extremity venous compression ultrasonography, helical CT, V/Q scanning, and pulmonary angiography. A positive result on any of these tests was deemed a positive diagnosis of PE. Patients were followed by study coordinators for 3 months.**

Two additional studies were then used as validation sets. The first of these comprised 3306 patients enrolled at 12 hospitals in the Netherlands, used a dichotomized Well's score, D-dimer testing, and CT to evaluate for PE. The second validation study included 1812 patients enrolled in 6 hospitals in France, Belgium, and Switzerland and included a clinical probability calculation using the Geneva score, D-dimer testing, and randomization to either CT alone or compression ultrasonography followed by CT.

Patients in the combined derivation set and the first validation study were classified as unlikely or likely to have a PE based on a calculated Well's score. Patients in the second validation set were classified as high or non-high risk based on the Geneva score. Using receiver operating characteristic (ROC) curves and linear regression analysis, the authors then derived the regression coefficient that provided high sensitivity for each age group for D-dimer cutoff. The regression coefficient calculated was 11.2, but this was rounded down to 10 for ease of calculation. Accordingly, the new formula for age-adjusted cutoff for D-dimer based on these calculations was 500 µg/l plus the number of years over 50 multiplied by 10.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did clinicians face diagnostic uncertainty?**	Yes. All studies included patients presenting to EDs with symptoms concerning for PE, in whom the diagnosis was not yet certain.
B.	**Was there a blind comparison with an independent gold standard applied similarly to the treatment group and to the control group? (Confirmation Bias)**	No. In all 4 studies included in the derivation and validation sets, patients with non-high clinical probability (based on Well's or Geneva scores) and a negative D-dimer based on a cutoff of 500 µg/l did NOT undergo additional confirmatory testing (partial verification bias). Additionally, patients in two of these studies underwent sequential testing, with a positive lower extremity compression ultrasound resulting in a positive diagnosis of PE without CT/VQ/angiography (differential verification bias).
C.	**Did the results of the test being evaluated influence the decision to perform the gold standard? (Ascertainment Bias)**	Yes. As noted above, a negative D-dimer test in patients without high clinical probability of disease resulted in no further testing in all 4 studies included in this paper.
II.	**What are the results?**	
A.	**What likelihood ratios were associated with the range of possible test results?**	In the derivation set: • Using an age-adjusted cut-off, D-dimer was negative in 615 of 1712 patients (46.2%). • This resulted in a 20.1% (95% CI 16.9-23.8%) relative increase in the number of patients with a normal D-dimer compared to a traditional cutoff, with a false negative rate of 0.8% (95% CI 0.4-1.9%). • Among 1331 patients with an unlikely clinical probability, an age-adjusted cutoff resulted in a 17.4% (95% CI 14.3-21.1%) increase in the number of patients with a negative D-dimer, with a false negative rate of 0.2% (95% CI 0-1.0%). In validation set #1: • Using the traditional cutoff, 983 patients had a negative D-dimer, of whom 2 (0.2%, 95% CI 0.1-0.7%) had PE during follow-up. • Using the age-adjusted cutoff, 1093 patients had a negative D-dimer, of whom 7 (0.6%, 95% CI 0.3-1.3%) had PE during follow-up. • Use of an age-adjusted cutoff resulted in an 11.2% (95% CI 9.3-13.3%) increase in the number of patients with a negative D-dimer. In validation set #2: • Using the traditional cutoff, 561 patients with a non-high clinical probability had a negative D-

		dimer, of whom 0 (0%, 95% CI 0-0.7%) had PE during follow-up. • Using the age-adjusted cutoff, 663 patients had a negative D-dimer, of whom 2 (0.3%, 95% CI 0.1-1.1%) had PE during follow-up. • Use of an age-adjusted cutoff resulted in an 18.2% (95% CI 15-21.4%) increase in the number of patients with a negative D-dimer.
III.	**How can I apply the results to patient care?**	
A.	**Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?**	Yes. D-dimer is not a new test, and has been used extensively in the work-up of pulmonary embolism for over a decade. Unfortunately, the assay used at our institution is different in that our lab reports values in D-Dimer Units (DDU) rather than Fibrinogen Equivalent Units (FEU). Additionally, the reported cut-off in our system is 230 ng/mL, rather than the typically suggested 250, making it difficult to devise a formula for the calculation of an age-adjusted cut-off.
B.	**Are the results applicable to the patients in my practice?**	Yes. We frequently see older patients (>50 years of age) with a suspicion of PE, in whom D-dimer testing is employed. The ability to use an age-adjusted cut-off would be a valuable tool to reduce the use of unnecessary testing in these patients.
C.	**Will the results change my management strategy?**	Uncertain based on this study alone. These results do suggest that use of an age-adjusted D-dimer will significantly increase the number of patients with a negative D-dimer and hence decrease the need for additional testing, such as PE-protocol CT. However, this study used only previously collected datasets to retrospectively derive and validate the age-adjusted formula. Additional prospective studies will need to verify and further quantify the safety and efficacy of such an approach, and will need to demonstrate a reduction in unnecessary testing when put into practice.
D.	**Will patients be better off as a result of the test?**	Yes. The use of CT to evaluate PE is not without risks, including the risk of allergy/anaphylaxis due to IV contrast, the risk of contrast-induced nephropathy, and the risk of overdiagnosis and false positive reporting.

Limitations:

1. **The cohorts were evaluated for PE using very different algorithms, including measurement of pre-test probability and confirmatory testing, making it difficulty to generalize these results.**

2. **In all 4 cohorts, patients with non-high clinical probability (based on Well's or Geneva scores) and a negative D-dimer based on a cutoff of 500 µg/l did NOT undergo additional confirmatory testing (partial verification bias).**

3. **All of the included cohorts were used retrospectively to derive and validate the proposed age-adjusted cutoff. Further studies should seek to prospectively validate this cutoff and demonstrate both safety and decreased imaging with its use.**

4. **All 4 cohorts come from Western European countries with largely Caucasian populations. Further studies should seek to validate the results in other more heterogeneous populations.**

Bottom Line:

This article was able to derive and validate an age-adjusted cutoff of D-dimer using the formula age times 10 for patients over 50 years of age. This resulted in a significant increase in the number of patients with a negative D-dimer (who would hence not need to undergo further testing), with a small increase in the number of cases of missed PE. These results should be validated prospectively in diverse populations to demonstrate both safety and efficacy.