Critical Review Form
Diagnostic Test

Sharp AL, Vinson DR, Alamshaw F, Handler J, Gould MK. An Age-Adjusted D-dimer Threshold for Emergency Department Patients With Suspected Pulmonary Embolus: Accuracy and Clinical Implications. Ann Emerg Med. 2016 Feb;67(2):249-57.

Objectives: **"to evaluate the sensitivity and specificity of an age-adjusted D-dimer threshold in detecting pulmonary embolism among patients older than 50 years." (p. 250)**

Methods: **This retrospective chart review was conducted using the Kaiser Permanente Southern California medical record system, which collects data from 14 community emergency departments (EDs). Patients older than 50 years with suspected PE presenting between 2008 and 2013, and who received a D-dimer test, were eligible for inclusion. Patients without continuous membership for 30 days following the ED encounter were excluded, as were those who received a D-dimer for reasons other than the evaluation for a possible acute PE and those with a prior diagnosis of PE in the preceding 90 days.**

The primary outcome was a diagnosis of acute PE at the initial ED encounter. 30-day mortality was assessed using Kaiser Permanente Southern California "clinical and administrative data," and the California death registry. Outcomes were assessed using an age-adjusted cutoff for D-dimer (age X 10), the standard D-dimer limit (500 ng/dL), and a higher limit of 1000 ng/dL. Patients who underwent imaging within 24 hours of ED arrival—including CTPA, V/Q scan, chest MRA, or pulmonary angiography—were identified.

For any patient with no diagnosis of PE and no imaging study during the initial encounter, but who received a diagnosis of PE within 30 days of the encounter, the charts were reviewed and it was determined by consensus whether or not it was likely that a PE was missed on the initial encounter (n = 12). Charts of patients with a diagnosis of PE at the initial encounter who did not undergo imaging at that time were also reviewed to identify patients who had a prior hx of PE, but did not have an acute PE (n = 7).

A total of 31,094 patients were identified; the mean age was 65 years and 61% were women. A total of 514 patients were determined to have an acute PE at the initial encounter, and 30,580 were found not to have a PE.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did clinicians face diagnostic uncertainty?**	Yes. This study included patients presenting to the ED with D-dimer testing and a chief complaint that the authors felt could possibly be "related to a possible pulmonary embolism, such as chest pain or dyspnea." (p. 251) The authors did not calculate a Well's score or modified Geneva score for these patients, so it is unclear what the distribution of risk was. The overall incidence of PE among enrolled patients was quite low (1.6%), suggesting an overuse of the D-dimer assay in a very low-risk population of patients.
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. Not all patients underwent the same gold standard testing, as the D-dimer result dictated whether or not confirmatory testing was performed at the time of the ED visit. This was a retrospective study, so neither the radiologists nor the clinicians were blinded to the D-dimer results at any time during the ED stay.
C.	**Did the results of the test being evaluated influence the decision to perform the gold standard? (Ascertainment Bias)**	Yes. In the large majority of cases, only patients with a positive D-dimer underwent confirmatory testing. There is a high probability that this would underestimate the number of false-negative results and hence overestimate the sensitivity (partial verification bias). 10.6% of patients who underwent imaging had a D-dimer below the standard cutoff, and 17.6% of patients who did not receive imaging had a D-dimer above the standard cutoff.
II.	**What are the results?**	
A.	**What likelihood ratios were associated with the range of possible test results?**	• See Table 1 (at bottom of last page) for test characteristics of D-dimer using the three cutoff values. • Using previously reported incidences of contrast-inducted nephropathy (CIN), renal failure, and death due to CIN of 11%, 0.9%, and 0.6%, the authors suggest that use of an age-adjusted D-dimer cutoff would have prevented 322 cases of CIN, 29 cases of renal failure, and 19 deaths due to CIN.
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**	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-

	setting?	Dimer Units (DDU) rather than Fibrinogen Equivalent Units (FEU). Additionally, the reported cutoff 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 cutoff.
B.	**Are the results applicable to the patients in my practice?**	Uncertain. The overall prevalence of PE in this study was very low (1.6%), suggesting an overuse of D-dimer and additional imaging. This prevalence is, in fact, below the recommended test threshold for additional testing of 1.8% as derived by Kline et al. The authors reported incidence of potential adverse outcomes related to CIN is therefore likely highly exaggerated, and would me much lower with a more judicious use of testing.
C.	**Will the results change my management strategy?**	No. This study demonstrates a low negative likelihood ratio of 0.11 with the use of an age-adjusted D-dimer cutoff, but does so in a population with a very low prevalence of disease. While prevalence itself should not influence sensitivity, specificity, or likelihood ratios, the spectrum of disease has been shown to affect these test characteristics, and invariably changes as the prevalence of disease changes in clinical studies (Brenner 1997).
D.	**Will patients be better off as a result of the test?**	Uncertain. The authors of this study likely greatly overestimate the reduction in adverse outcomes related to CIN by evaluating such a low-risk population. Combined with the retrospective nature of this study, it would be difficult to weigh the potential harm of missed diagnoses with the potential risks of overtesting.

Limitations:

1. **This was a retrospective chart review with poorly defined chart review methodology (Gilbert 1996 and Worster 2004).**

2. **The overall prevalence of PE among enrolled patients was quite low (1.6%), suggesting an overuse of the D-dimer assay in a very low-risk population of patients. The prevalence was already below the test threshold for PE previously derived by Kline et al.**

3. **Not all patients underwent confirmatory "gold standard" testing. A large majority of patients with a positive D-dimer underwent confirmatory testing, while the majority of patients with a negative D-dimer did not (partial verification bias).**

4. **The team that determined by consensus whether or not a PE had been missed on the index visited was NOT blinded to either the final diagnosis or, more importantly, the D-dimer test result (observer bias).**

Bottom Line:

This retrospective, observational study involving ED patients from 14 community EDs in the Kaiser Permanente Southern California system demonstrated a negative LR of 0.11 for an age-adjusted D-dimer in the evaluation of PE (95% CI 0.08-0.15). This study was limited by its retrospective nature, a high risk of partial verification bias, and a very low prevalence of disease. These limitations make it difficult to ascertain the clinical implications of using such a cutoff in practice.

Table 1. Test characteristics at varying thresholds (95% CI)

Cutoff	Sensitivity %	Specificity %	LR+[†]	LR-[†]
500 ng/dL	98.0 (96.4-84.2)	54.4 (53.9-55.0)	2.15 (2.11-2.19)	0.04 (0.02-0.07)
Age-adjusted	92.9 (90.3-95.0)	63.9 (63.4-64.5)	2.57 (2.50-2.65)	0.11 (0.08-0.15)
1000 ng/dL	84.2 (80.8-87.3)	75.4 (74.9-75.9)	3.43 (3.28-3.57)	0.21 (0.17-0.26)
† calculated using http://araw.mede.uic.edu/cgi-bin/testcalc.pl				