Which age-adjusted d-dimer cut-off performs best?

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D-dimer testing is used to determine the need for advanced imaging (e.g. CTPA) in low probability patients with suspected pulmonary embolism (PE). While d-dimer testing is highly sensitive for PE, its specificity reduces with advancing age (especially age over 50) resulting in increased rates of advanced imaging carrying both risk (radiation, contrast nephropathy) and inconvenience for patients. Recently three age-adjusted cut-offs for d-dimer assay in patients aged over 50 have been proposed – age in years times 10^1 , age in years times 16^2 and a decade-specific levels with cut-offs of 500 $\mu\text{g/L}$ for age < 60 years, 600 $\mu\text{g/L}$ for age 61-70 years and 700 $\mu\text{g/L}$ for age 71-80 years.³ To test the diagnostic performance of these, we conducted a retrospective cohort study by medical records review of patients having both d-dimer and CT pulmonary angiography (CTPA) for investigation of suspected PE. This planned sub-study had the additional eligibility criteria of age ≥ 50 and assessment as low risk by the simplified Wells' score⁴ Our rationale for this was that this is the group in whom advanced imaging may be able to be avoided if the adjusted cut-offs were adopted. D-dimer level was measured in fibrinogen equivalent units using the Siemens INNOVANCE® D-Dimer assay measured on the Siemens/Sysmex CA-1500 (Siemens/Sysmex, Japan). The study was approved by the institutional ethics panel.

404 patients were eligible for inclusion. The prevalence of PE was 7% (28 PE, 95% CI 5-10%). Diagnostic performance of each of the proposed cut-offs is shown in Table 1.

There was no statistically significant difference in sensitivity or negative predictive value between cut-offs, largely due to the lower than expected PE rate. The single PE missed by the decade-specific and age x 10 cut-offs was in an 81 year old woman who was shown to have a sub-segmental PE and an undiagnosed lung neoplasm. Half of the PE missed by the age x 16 cut-off were also sub-segmental. All age-specific cut offs would

have avoided a clinically significant proportion of the CTPA scans however, they also would have missed additional PEs when compared to the conventional cut off; concerning more so for the age x16 cut-off. A significant proportion of the missed PE were sub-segmental. There are varying opinions regarding the clinical significance and treatment of these. Unanswered questions remain. Is the reduction in risk from avoided scans in balance with the small number of additional missed PEs? What missed PE rate is acceptable to patients and clinicians? Our data support previous evidence that the use of age-specific D-dimer cut-offs could reduce imaging for suspected PE in patients aged over 50 years. The decade-specific and age x 10 methods seem to have the best balance of avoided imaging and missed PE. In terms of feasibility, the age x 10 is probably the easiest method to remember and apply in practice.

This data adds to the mounting evidence, reflected in recent clinical practice guidelines,⁵ that age-adjusted d-dimer cut-offs should be used in low risk patients to guide investigation strategy.

Table 1: Diagnostic performance of proposed age-adjusted d-dimer cut-offs

Cut-off	Sensitivity	Specificity	Negative predictive value	Advanced imaging avoided	PE missed
Conventional (500 µg/L)	100%	10%	100%	*	0
Decade-specific	96%	24%	99%	44 (15%)	1
Age x10	96%	30%	99%	78 (21%)	1
Age x16	86%	61%	98%	199 (54%)	4

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