

AAEM Clinical Practice Statement: The Use of an Age-Adjusted D-Dimer

Can an Age-Adjusted D-Dimer be Used to Safely Rule Out Pulmonary Embolism in Emergency Department Patients?

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Answer: Yes, it appears that age-adjusted D-dimer (AADD) cut-off values, in combination with a non-high clinical probability, are safe and effective to essentially rule out pulmonary embolism in emergency department patients. Caution may be advised in patients older than 75 as they are slightly more likely to have a missed diagnosis of a clinically significant pulmonary embolism (PE).

Introduction: Pulmonary embolism (PE) is a serious, potentially fatal condition, but is difficult to safely rule out using only clinical features. Studies have demonstrated that a combination of risk-stratification and D-dimer testing can essentially rule-out PE. The prevalence of PE increases with age, but D-dimer levels also increase with age, which lowers D-dimer test specificity and reduces its utility in elderly patients.

We performed a systematic review using the AAEM CPC Statement on Protocols for literature search/grading process to identify articles that could answer the question: Can an age-adjusted D-dimer be used to safely rule-out pulmonary embolism in emergency department patients?

Review: We performed a structured review of the medical literature using PubMed. Based on this review, we identified 97 unique articles. After screening and author review, 21 were utilized for this clinical policy statement. Studies included for the final detailed review were limited to meta-analyses or prospective clinical trials evaluating the safety and utility of an AADD in ruling out PE.

Studies have demonstrated patients with a non-high probability of PE and a negative D-dimer test can safely avoid further testing. A “non-high” clinical probability of PE is the terminology used in most of the literature, and is defined by using any of the following: Well’s Score of 4 or less, a Revised Geneva Score of 10 or less (validated decision rules), or clinical “Gestalt” of <15% likelihood of PE. The traditional level for a negative D-dimer is 500 µg/l, however, as patients age, the likelihood of having a false positive D-dimer level above 500 µg/l increases. As older patients are more likely to have a false positive D-dimer, they are more likely to require further testing. Older patients are at increased risk of unnecessary treatment when exposed to avoidable testing. In patients above 50 years of age, the

use of AADD cut-off (D-dimer level below patient age multiplied by 10, in $\mu\text{g/L}$), in combination with non-high clinical probability of PE, might increase specificity without significantly decreasing sensitivity in ruling out PE. For example: If the patient is 50, cutoff for negative D-dimer is $50 \times 10 = 500$, or If the patient is 62, cutoff for negative D-dimer is $62 \times 10 = 620$.

In the meta-analyses we reviewed, there were more than 30,000 patients. There may be overlap as it is unclear if patients were included in more than one study. These studies consistently found improved sensitivity and similar specificity when compared to traditional D-dimer cut-off values. The inclusion criteria, tests used, and populations demonstrated some variability, but overall were at low risk of bias. Clinical suspicion of PE and a non-high clinical probability were required for entry into the studies. The studies define test efficiency as the percentage increase in patients that could be ruled out for PE by using the AADD. Throughout the meta-analyses, the test efficiency was about 5%, meaning that an additional 5% of patients could be ruled-out for PE and avoid further testing. From subgroup analysis in some studies, the test efficiency was higher in patients older than 75 and in patients with COPD. However, the false-negative rate gradually increased in patients above 75 years old.

The single prospective study published (Righini, ADJUST-PE) is consistent with the findings suggested by the meta-analyses. Using an age-adjusted D-dimer cut-off in combination with a non-high clinical probability increases the number of patients that can be ruled-out for PE by about 5%, and has a miss rate less than 3%. The efficiency is lower in patients with cancer and for inpatients. Again, the greatest improvement in efficiency is in the most elderly patients (75 or older), but this group is also the most likely to have false negatives. This study used 3 month symptomatic VTE as the endpoint; a patient centered outcome, but not the gold-standard.

There has been some preliminary work evaluating D-dimer assays that are reported in different units or have different cut-offs than the 500 $\mu\text{g/L}$. Unfortunately, there is not enough evidence to support age-adjustment for these other assays.

Conclusion: Based on multiple retrospective and one prospective study, it appears that age-adjusted D-dimer cut-off values (patient age in years $\times 10 =$ cut-off in $\mu\text{g/L}$) in combination with a non-high clinical probability is safe and effective to essentially rule out pulmonary embolism in emergency department patients. Caution may be advised in patients over 75 years old, as these patients are more likely to avoid unnecessary testing, but are also slightly more likely to have a missed diagnosis of a clinically significant PE.

