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Clinical Review

RAPID SYSTEMATIC REVIEW: AGE-ADJUSTED D-DIMER FOR RULING OUT PULMONARY EMBOLISM

Bradley E. Barth, MD, FAAEM,* Grzegorz Waligora, MD, PHD, FAAEM,† and Gary M. Gaddis, MD, PHD, FAAEM‡

*University of Kansas Medical Center, Kansas City, Kansas, †Torbay and South Devon NHS Foundation Trust, Torbay Hospital, Torquay, Devon, United Kingdom, and ‡Division of Emergency Medicine, Washington University in Saint Louis School of Medicine, St. Louis, Missouri
Corresponding Address: Bradley E. Barth, MD, FAAEM, University of Kansas Medical Center, 3901 Rainbow Boulevard, Mailstop 1019, Kansas City, KS 66160

☐ **Abstract—Background: Pulmonary embolism (PE) is a disease diagnosed relatively frequently in emergency departments (EDs). Evidence suggests that improved decision making may decrease inappropriate testing, unnecessary radiation exposure, and non-beneficial treatment. Several studies have looked at the utility and safety of age-adjusting the D-dimer levels used to safely rule out PE. Objective: This rapid systematic review sought to answer the question: Can an age-adjusted D-dimer be used to safely rule out PE in patients over 50 years old? Methods: We performed a structured review of PubMed from January 2012 to January 2018 limited to reports involving human subjects and written in the English language and containing relevant keywords. The highest-quality studies were then reviewed in a structured format. Results: One hundred and eleven papers were identified for further review. Eight articles were determined to be appropriate for inclusion in this summary. These studies all used patient age (in years over 50) × 10 μg/L (fibrinogen equivalent units) as their definition of an age-adjusted D-dimer. Conclusions: Age-adjusted D-dimer cutoff values, in combination with a non-high clinical probability, is safe and effective to essentially rule out PE in ED patients.** © **2018 Elsevier Inc. All rights reserved.**

☐ **Keywords—age factors; D-dimer; pulmonary embolism**

Reprints are not available.

INTRODUCTION

Pulmonary embolism (PE) is a disease diagnosed relatively frequently in emergency departments (EDs). Mortality of PE is highly variable based on the clinical presentation: 25% of patients with PE present with sudden death, and mortality in patients that present hemodynamically unstable is 58% (1–4). However, patients with more favorable presentations have a mortality rate of < 1%. More PEs are being diagnosed with the advent of multi-slice computed tomography pulmonary angiography (CTPA) and quantitative D-dimer testing. Interestingly, the number of deaths from PE has not changed significantly when comparing the pre-CTPA era (pre-1998) with later data (1998–2006) (5,6). Evidence suggests that improved decision making may decrease inappropriate testing, unnecessary radiation exposure, and non-beneficial treatment (7–11).

D-dimer testing is highly sensitive but lacks specificity for the diagnosis of PE. The use of D-dimer in the diagnostic pathway can be preceded by calculation of pretest probability of disease. Clinical prediction rules, such as revised Geneva score or Wells score, are useful to provide these estimates. These estimates, or clinical gestalt, combined with D-dimer testing, can safely rule out PE (2). PE is "ruled out" when the likelihood that the patient has the disease and will suffer adversely from it, is equivalent to the risk of harm from further diagnostic efforts or potential treatments.

D-dimer levels increase almost linearly with age, thereby decreasing the specificity of the un-adjusted D-dimer test and limiting its usefulness in ruling out PE in older patients. Several studies have looked at the utility and safety of age-adjusting the D-dimer cutoff levels used to safely rule out PE. This rapid systematic review seeks to answer the question: Can an age-adjusted D-dimer (AADD) be used to safely rule out PE in patients over 50 years old?

MATERIALS AND METHODS

We performed a structured review of the medical literature using the American Academy of Emergency Medicine Clinical Practice Committee Protocols. We reviewed PubMed using inclusion criteria of reports involving human subjects and written in the English language and containing the following keywords: (Age AND D-Dimer) AND Systematic Review; and a second search using the keywords: (Age-adjusted AND D-Dimer) AND limited to January 2012–January 2018. We also screened references of selected articles for potential additional studies. The abstracts of the articles found in this search were assessed independently by two of the authors, to determine which papers should be pulled for more detailed review based on their suspected relevance to the clinical question. Any difference of opinion was resolved by consensus and author agreement. Studies included for the final detailed review were limited to meta-analyses, systematic reviews, or clinical trials evaluating the safety and utility of an AADD in ruling out PE. Selected studies related to AADD and venous thromboembolism (VTE) were also reviewed. Clinical guidelines, recommendations, and conference proceedings were reviewed, but not included for analysis. There were no randomized controlled studies. General review articles, case reports, and abstracts presented at conferences were not included for formal review.

Each author reviewed the selected articles in detail. The articles were assigned an Evidence Grade, a Quality Ranking, and a Recommendation for inclusion in the review as described previously (Tables 1 and 2). Finally, we made recommendations based on our review of the literature using the levels described in Table 3 (12).

Table 1. The Definitions of the Grades of Evidence of the Articles

Grade	Definition
A	Randomized clinical trials or meta-analyses (i.e., multiple clinical trials) or randomized clinical trials (i.e., smaller trials), directly addressing the review issue
B	Randomized clinical trials or meta-analyses (i.e., multiple clinical trials) or randomized clinical trials (i.e., smaller trials), indirectly addressing the review issue
C	Prospective, controlled, nonrandomized, cohort studies
D	Retrospective, nonrandomized, cohort, or case-control studies
E	Case series, animal/model scientific investigations, theoretical analyses, or case reports
F	Rational conjecture, extrapolations, unreferenced opinion in literature, or common practice

RESULTS

Using these search strategies, we identified 70 unique papers. References of the articles revealed an additional 41 articles that were screened for inclusion. After screening and author review, 27 papers were included for detailed review. A total of 8 articles were determined to be of the grade, quality, and relevance according to our methodology for inclusion in this summary (Table 4). All eight of these studies used age adjustment of age × 10 (e.g., D-dimer cutoff for a 64-year-old is 64 × 10 = 640 μg/L) as their definition of AADD.

Of the eight high-quality articles that address our question, the "Adjust PE" study by Righini et al. was the only prospective study (19). They included a large number of patients (>3000), and provided excellent short-term follow-up for clinically relevant outcomes, chiefly mortality. Patients were evaluated using revised Geneva or 2-Level Wells score and an AADD. If patients were non-high risk and AADD-negative, they were not imaged. Patients were followed for 3 months. The rate of missed VTE was 0.1%–1.7% (95% confidence interval [CI]). Their patient population had a higher prevalence of PE (19% [95% CI 17.7%–20.4%]) than in typical cohorts based exclusively in the United States. This could be expected to lead to an even more reliable test performance in a typical ED population than that reported for their subjects by Righini et al. Their a priori safety level was a failure rate no higher than 3%. This level was selected because studies have shown that a negative CTPA has a similar 3% failure rate at 3-month follow-up. They had no failures in the diagnostic strategy for patients over 75 years old (0.0% [95% CI 0.0%–1.9%]). This study concluded that combining a clinical risk prediction tool and an AADD were safe and effective to rule out clinically important PE, in that short-term mortality did not occur in any of the 343 patients who had an "abnormal" D-dimer level but a normal AADD. The rate of "missed" PE was well below the 3% threshold, and the clinical relevance of these few "missed" events is debatable. This study did not address the questions of whether or not all PE should be treated with anticoagulants, or what should be done for small, sub-segmental PE. This remains an area of controversy.

Of the seven other studies included in our review, six were determined to support our recommendation. Four of these studies were systematic reviews and meta-analyses (13,15–17). Together these studies had >