TAKE-HOME MESSAGE

Patients with a low pretest probability for pulmonary embolism according to a structured clinical prediction rule and a negative D-dimer result are unlikely to have pulmonary embolism, particularly among those younger than 65 years.

Update: D-dimer Test for Excluding the Diagnosis of Pulmonary Embolism

EBEM Commentators
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METHODS

DATA SOURCES

The authors searched the following databases through December 12, 2013: MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature, Latin American and Caribbean Health Science Information Database, Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database in the Cochrane Library, Institute for Scientific Information Conference Proceedings Citation Index, British Library Zetoc, and MEDLINE. The following trial databases were also searched for information: World Health Organization International Clinical Trials Registry Platform, clinicaltrials.gov, and Current Controlled Trials.

STUDY SELECTION

Studies were screened to ensure that the following criteria were met: provision of a 2×2 contingency table (or allowed data to be back-calculated), all patients in an outpatient or an acute care setting and with a calculated pretest probability based on an accepted clinical prediction rule, and the use of ventilation/perfusion scanning, pulmonary angiography, computed tomography (CT) pulmonary angiography, or magnetic resonance pulmonary angiography as the reference standard.

Results

Summary of study results that included 95% CIs.

Clinical Prediction Rule*	D-dimer Sensitivity (95% CI), %	D-dimer Specificity (95% CI), %
Geneva[1]	Low PTP: 100 (61–100) Intermediate PTP: 100 (82–100) High PTP: 80 (38–96)	Low PTP: 25 (20–31) Intermediate PTP: 33 (28–38) High PTP: 37 (15–65)
Wells low PTP[6]	91 (81–97)	63 (52–73)
Wells nonhigh PTP[5]	<65 y: 100 (97–100) 65–75 y: 100 (85–100) >75 y: 100 (86–100)	<65 y: 50 (45–55) 65–75 y: 31 (20–44) >75 y: 23 (12–38)

PTP, Pretest probability.
*Raviv and Israelit[2] not included in the table because of lack of data on 95% CIs.

The titles and abstracts of 4,870 reports were screened by 2 review authors. Of these, only 4 studies met the inclusion criteria; these 4 studies were determined to be at low or unclear risk of bias and included a total of 1,585 patients with quantitative D-dimer test results and used 3 different clinical prediction rules. A low pretest probability was defined as low for a Geneva score of 0 to 3,[1] defined as nonhigh risk if the Wells score is less than or equal to 4,[2] and defined as low for a modified Wells score less than or equal to 1.[3] Across all ages, the 4 studies consistently reported high sensitivity (ranging from 91% to 100%) but low and variable specificity (ranging from 25% to 63%) for D-dimer testing.

Commentary

In this systematic review, up to 25% of patients who presented with symptoms of concern for pulmonary embolism ultimately received a diagnosis of this condition. This highlights the need for rapid and accurate identification methods.[4] Among patients with a low pretest probability, D-dimer had a high sensitivity but low specificity for the diagnosis of pulmonary

DATA EXTRACTION AND SYNTHESIS

Two investigators independently extracted data that included study design and patient population. Additionally, the authors collected data on the specific D-dimer tests and reference standards from each study, which were used to construct 2×2 contingency tables to assess accuracy. Details about clinical prediction rules, mortality, adverse events, and the administration of anticoagulants to patients awaiting reference standard tests were also extracted. The risk of bias and applicability of the study were evaluated with the Quality Assessment of Diagnostic Accuracy Studies–2. Study heterogeneity was unable to be investigated because of an insufficient number of studies.

embolism. Only the study by Gupta et al[1] included low (0 to 3 points), intermediate (4 to 10 points), and high pretest probability groups (≥11 points) when the Geneva clinical prediction rule was used. This study reported sensitivities of 100%, 100%, and 80% and specificities of 25%, 33%, and 37% in the low-, intermediate-, and high-probability groups, respectively[1]; however, these point estimates were imprecise, with wide 95% confidence intervals (CIs).

D-dimer values may be affected by several factors, including age.[2,5] Sohne et al[5] reported 100% sensitivity for D-dimer across all age groups; however, the point estimates were precise only for the group younger than 65 years (95% CI 97% to 100%), whereas the lower limits for the 95% CI were 85% to 86% for the 2 older age groups. This study also demonstrated diminishing specificity with increasing age: 50% for patients younger than 65 years, 31% for patients aged 65 to 75 years, and only 23% for patients older than 75 years.[5] Investigators have addressed this age-related specificity problem by using age-adjusted D-dimer cutoffs.[2]

There are several factors that limit this systematic review. Despite a large volume of literature on this topic, only 4 studies met the strict criteria. The authors restricted studies to those using imaging as the reference standard instead of using a combination of imaging and clinical follow-up. Even the strict imaging reference standard was not uniform because the authors did not account for the variety of CT slice scanners available and also included magnetic resonance angiography. Even among this select group of studies that met the strict inclusion criteria, the clinical heterogeneity among the 4 studies (eg, type and threshold of D-dimer test, clinical prediction rule used) did not allow meta-analysis, which limits the inferences that can be made. Although emergency providers routinely use D-dimer in clinical practice, application of this review requires use of a structured pretest probability calculation. In clinical practice, it is unknown whether emergency providers routinely use a formal prediction rule or rely on clinical gestalt before ordering a D-dimer test. Finally, the review is not able to answer questions about the ability of D-dimer to assess for pulmonary embolism in pregnant patients.

Appropriate use of advanced radiographic imaging has been highlighted through national efforts such as the Choosing Wisely campaign, which aims to improve patient care by avoiding wasteful or unnecessary medical tests, treatments, and procedures.[3] Using a negative D-dimer test result for patients with low pretest probability based on a clinical decision rule appears to be safe because of its high sensitivity; however, the poor specificity continues to subject a large proportion of patients with false-positive D-dimer test results to unnecessary radiation exposure.

Editor's Note: This is a clinical synopsis, a regular feature of the *Annals'* Systematic Review Snapshot (SRS) series. The source for this systematic review snapshot is: **Crawford F, Andras A, Welch K, et al. D-dimer test for excluding the diagnosis of pulmonary embolism. *Cochrane Database Syst Rev.* 2016;(8):CD010864.**

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