Assessment of the Safety and Efficiency of Using an Age-Adjusted D-dimer Threshold to Exclude Suspected Pulmonary Embolism

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BACKGROUND: D-dimer levels increase with age, and research has suggested that using an age-adjusted D-dimer threshold may improve diagnostic efficiency without compromising safety. The objective of this study was to assess the safety of using an age-adjusted D-dimer threshold in the workup of patients with suspected pulmonary embolism (PE).

METHODS: We report the outcomes of 923 patients aged ≥ 50 years presenting to our ED with suspected PE, a calculated Revised Geneva Score (RGS), and a D-dimer test. All patients underwent CT pulmonary angiography (CTPA). We compared the false-negative rate for PE of a conventional D-dimer threshold with an age-adjusted D-dimer threshold and report the proportion of patients for whom an age-adjusted D-dimer threshold would obviate the need for CTPA.

RESULTS: Among 104 patients with a negative conventional D-dimer test result and an RGS ≤ 10, no PE was observed within 90 days (false-negative rate, 0%; 95% CI, 0%-2.8%). Among 273 patients with a negative age-adjusted D-dimer result and an RGS ≤ 10, four PEs were observed within 90 days (false-negative rate, 1.5%; 95% CI, 0.4%-3.7%). We observed an 18.3% (95% CI, 15.9%-21.0%) absolute reduction in the proportion of patients aged > 50 years who would merit CTPA by using an age-adjusted D-dimer threshold compared with a conventional D-dimer threshold.

CONCLUSIONS: Use of an age-adjusted D-dimer threshold reduces imaging among patients aged ≥ 50 years with an RGS ≤ 10. Although the adoption of an age-adjusted D-dimer threshold is probably safe, the CIs surrounding the additional 1.5% of PEs missed necessitate prospective study before this practice can be adopted into routine clinical care.
The clinical presentation of pulmonary embolism (PE) is highly variable. Use of a formalized pretest probability clinical decision rule that characterizes patient risk for PE in conjunction with a simple blood test, the D-dimer, is prospectively validated and recommended to evaluate the suspected diagnosis of PE.\textsuperscript{1-4} This is possible in large part because of the high sensitivity of D-dimer for VTE. However, the specificity of D-dimer is low, and, therefore, many patients with an elevated D-dimer level require imaging (CT pulmonary angiography [CTPA]) to confirm or exclude PE. D-dimer levels increase with age\textsuperscript{5,6} and lead to a proportional increased use of CTPA to exclude PE in elderly patients. Derivation and validation analyses\textsuperscript{7} and retrospective studies\textsuperscript{8-10} suggested that the use of a D-dimer threshold based on age will exclude PE among a greater proportion of patients. Initial reports of using an age-adjusted D-dimer threshold to exclude a greater proportion of elderly patients with suspected PE are promising,\textsuperscript{11} and a prospective clinical study in North America is under way.\textsuperscript{12} Yet, the safety of broadly adopting an age-adjusted D-dimer threshold remains uncertain. We report the safety and efficiency of applying an age-adjusted D-dimer threshold among 923 consecutive patients aged \textgreater{} 50 years with suspected PE and a Revised Geneva Score (RGS) \textless{}= 10 who presented to our ED.

Materials and Methods

A summary of the methods from our previous study are published elsewhere.\textsuperscript{13} The study methodology was a retrospective review of records of patients who underwent CTPA, from which those with suspected PE and low RGS were identified, and D-dimer level was obtained (Fig 1). In brief, we reviewed an electronic medical record to identify consecutive patients who had a CTPA ordered in the ED of LDS Hospital or Intermountain Medical Center to investigate suspected PE. The emergency physician’s report was reviewed manually by one investigator (D. M. A.) who used a data abstraction form to verify that each CTPA was performed to investigate suspected PE and capture elements necessary to calculate the RGS. Among the 3,500 consecutive CTPAs ordered to evaluate clinically suspected PE, 1,745 had a pretest probability of PE unlikely defined as an RGS \textless{} 10,\textsuperscript{4} and all had a D-dimer level obtained. Of these 1,745 encounters, 923 were among patients aged \textgreater{} 50 years, who comprised the study cohort (Fig 1).

Pretest probability for PE was assessed with the RGS. Prior VTE information was collected through a computer program developed at Intermountain Healthcare with high sensitivity and specificity for the identification of prior VTE.\textsuperscript{14,15} Recent surgery was extracted from the Operating Room Management Information System. Recent fracture and cancer were identified by International Classification of Diseases, Ninth Revision (ICD-9) codes. These electronically identified elements were verified during manual record review and were included if present in the medical record but not collected electronically. Unilateral leg pain and hemoptysis were recorded manually from the emergency physician’s report. If these were not described in the emergency physician’s report, we concluded that they were absent by using a strategy previously

\textsuperscript{5220} consecutive chest CT examinations performed 22 May 2009-30 June 2010

\textsuperscript{2500} consecutive CTPAs for the investigation of PE

RGS Calculated from Electronic Health Record

“PE Unlikely”
RGS \textless{} 10
n=3333

No d-dimer
n=1588

“PE Unlikely” and d-dimer
n=1745

Age \textless{} 50 years
n=822

STUDY COHORT: Age \textgreater{} 50 years
n=923

“PE Likely”
RGS \textless{} 10
n=167

1720 either not CTPA or not for the investigation of PE

Figure 1 – CONSORT (Consolidated Standards of Reporting Trials) diagram of the study design. CTPA = CT pulmonary angiography; PE = pulmonary embolism; RGS = Revised Geneva Score.
described to address missing clinical data in the derivation of a PE risk assessment tool. Heart rate was defined as the highest recorded value from the vital signs before CTPA. Pain on palpation of the deep veins of the leg and unilateral edema (also accepted was the physician’s interpretation that findings were consistent with DVT) were recorded from the physical examination component of the physician’s note, and if they were not recorded, they were considered absent.

All CTPAs were performed with a 64-row multidetector CT scanner using the protocol we previously reported. Every CTPA was interpreted by an in-house board-certified radiologist. Participating EDs uniformly used a high-sensitivity D-dimer test (Stago latex agglutination; Diagnostica Stago Inc.). (The mini-VIDAS [bioMérieux SA] assay is run fewer than one patient weekly at all Intermountain Healthcare institutions combined and only on highly lipemic samples.)

We multiplied the patient’s age by 10 ng/mL to calculate the age-adjusted D-dimer threshold for all 923 patients aged > 50 years with an RGS ≤ 10 and a D-dimer test. We excluded a priori patients aged < 50 years to avoid overestimating the safety of age adjustment to D-dimer level. To report the safety of using an age-adjusted D-dimer level, we compared the false-negative rate of using a conventional D-dimer threshold with an age-adjusted D-dimer threshold. We defined the false-negative rate as that of PE among patients for whom the D-dimer finding was negative yet PE was identified upon initial CTPA or within 90 days. To identify PE within 90 days of the index evaluation, we performed an electronic interrogation of our systemwide electronic medical record using (1) natural language processing for all radiology reports of CTPA and ventilation/perfusion lung scans as previously described and (2) the presence of an ICD-9 code (673.2x, 415.1, 415.19, 415.11) indicating a diagnosis of PE occurring within 3 months of patient presentation to the ED. A manual chart review was then performed for all records with evidence of PE within 90 days by one investigator (V.T.A.) to verify or refute acute PE. Subsequent individual chart reviews and adjudication of PE by three authors (S.C.W., D.M.A., V.T.A.) was performed. If a patient had more than one ED encounter, then 3-month follow-up was performed after each visit. If a patient was found to have a PE on a subsequent follow-up visit, the PE was attributed to the ED encounter immediately before the diagnosis of PE and counted only once to calculate the false-negative rate. To report efficiency, we calculated the proportion of patients for whom an age-adjusted D-dimer finding would be considered negative and compared this with the proportion of patients for whom a conventional D-dimer threshold would be considered negative.

**Statistical Methods**

The significance of the rates was tested by using exact binomial tests, and the CIs were constructed by using a highest posterior density with a binomial likelihood and a uniform prior on the proportion. Two-sample t tests were used to compare numerical variables, and χ² tests were used to compare proportions between groups.

### Results

The baseline patient characteristics are shown in Table 1. Safety was assessed by measuring the 90-day rate of PE among patients aged > 50 years who had an RGS ≤ 10 and a negative age-adjusted D-dimer test. We excluded a priori patients aged < 50 years to avoid overestimating the safety of age adjustment to D-dimer level. To report the safety of using an age-adjusted D-dimer level, we compared the false-negative rate of using a conventional D-dimer threshold with an age-adjusted D-dimer threshold. We defined the false-negative rate as that of PE among patients for whom the D-dimer finding was negative yet PE was identified upon initial CTPA or within 90 days. To identify PE within 90 days of the index evaluation, we performed an electronic interrogation of our systemwide electronic medical record using (1) natural language processing for all radiology reports of CTPA and ventilation/perfusion lung scans as previously described and (2) the presence of an ICD-9 code (673.2x, 415.1, 415.19, 415.11) indicating a diagnosis of PE occurring within 3 months of patient presentation to the ED. A manual chart review was then performed for all records with evidence of PE within 90 days by one investigator (V.T.A.) to verify or refute acute PE. Subsequent individual chart reviews and adjudication of PE by three authors (S.C.W., D.M.A., V.T.A.) was performed. If a patient had more than one ED encounter, then 3-month follow-up was performed after each visit. If a patient was found to have a PE on a subsequent follow-up visit, the PE was attributed to the ED encounter immediately before the diagnosis of PE and counted only once to calculate the false-negative rate. To report efficiency, we calculated the proportion of patients for whom an age-adjusted D-dimer finding would be considered negative and compared this with the proportion of patients for whom a conventional D-dimer threshold would be considered negative.

![](image-url)

**Table 1**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Conventional D-dimer Threshold (&lt;500 ng/mL)</th>
<th>Age-Adjusted D-dimer Threshold (Patient Age×10 ng/mL)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>D-dimer Positive</td>
<td>D-dimer Negative</td>
<td>D-dimer Positive</td>
</tr>
<tr>
<td>No. patients</td>
<td>923</td>
<td>819</td>
<td>104</td>
<td>650</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td>67 ± 11.5</td>
<td>67 ± 11.6</td>
<td>63 ± 9.0</td>
</tr>
<tr>
<td>Female sex</td>
<td>566</td>
<td>61.3</td>
<td>566 (61.3)</td>
<td>498 (60.8)</td>
</tr>
<tr>
<td>Prior VTE</td>
<td>118</td>
<td>12.8</td>
<td>99 (12.1)</td>
<td>19 (18.3)</td>
</tr>
<tr>
<td>Surgery</td>
<td>57</td>
<td>6.2</td>
<td>56 (6.8)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Fracture</td>
<td>9</td>
<td>1.0</td>
<td>9 (1.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Trauma</td>
<td>14</td>
<td>1.5</td>
<td>14 (1.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Cancer</td>
<td>46</td>
<td>5.0</td>
<td>41 (5.0)</td>
<td>5 (4.8)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>8</td>
<td>0.9</td>
<td>7 (0.9)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Leg pain</td>
<td>31</td>
<td>3.4</td>
<td>25 (3.1)</td>
<td>6 (5.8)</td>
</tr>
<tr>
<td>Leg edema</td>
<td>24</td>
<td>2.6</td>
<td>21 (2.6)</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>89.5</td>
<td>20.7</td>
<td>90.1 ± 21.1</td>
<td>84.4 ± 17.3</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or No. (%). CTPA = CT pulmonary angiography; RGS = Revised Geneva Score.

*Within 30 d.

**Currently treated or cured <1 y.**

![Chest logo]
D-dimer test by conventional threshold was 0 (95% CI not calculable) compared with the negative likelihood ratio of 0.07 (95% CI 0.02-0.29) observed among patients aged >50 years with a negative D-dimer test by age-adjusted threshold (Table 3).

Among 923 patients aged >50 years with an RGS <= 10, the use of an age-adjusted D-dimer threshold resulted in 273 negative D-dimer tests (29.6%), whereas use of a conventional D-dimer threshold yielded 104 negative D-dimer tests (11.3%). Adoption of an age-adjusted D-dimer reduced the percentage of patients who would be subject to further imaging for suspected PE by an absolute value of 18.3% (15.9%-21.0%) (Table 3). Among patients aged 51 to 65, 66 to 74, and ≥75 years, the rate of a negative D-dimer tests between conventional and age-adjusted thresholds was 14.8% vs 27.1%, 10.8% vs 35.5%, and
and 5.1% vs 30%, respectively (Table 3). The diagnostic yield of CTPA for PE was 10.3% (84 of 819; 95% CI, 8.3%-12.5%) by conventional D-dimer threshold and 12.6% (82 of 650; 95% CI, 10.2%-15.4%) by age-adjusted D-dimer threshold.

Discussion

Among 923 patients aged >50 years with an RGS ≤ 10 and a negative age-adjusted D-dimer test, we observed a 90-day failure rate for the detection of PE (false-negative rate) of 1.5%, with a upper limit of the 95% CI exceeding what is broadly considered safe (3%).\(^{1,17-19}\) By comparison, use of a conventional D-dimer threshold was associated with a 90-day false-negative rate of 0% (95% CI, 0%-2.8%). The age-adjusted D-dimer false-negative rate was associated with a negative likelihood ratio of 0.07, the upper limit of the 95% CI for which was 0.29. Several studies have demonstrated that an approach to the diagnosis of PE that yields a negative likelihood ratio of 0.8 to 0.13 among patients without a high pretest probability for PE has demonstrated that the use of an age-adjusted D-dimer threshold is probably safe should these events be attributed to a new PE finding during the follow-up period rather than false-negative results. Patient 3 experienced a PE 32 days after initial CTPA, whereas patient 4 experienced a PE 63 days after the initial evaluation. Neither patient had evidence on medical record review of any interim surgery, procedure, illness, or hospitalization.

A strength of the present study is that all patients underwent CTPA (even those for whom an age-adjusted D-dimer would have precluded imaging) in addition to 90-day follow-up. Another strength was the decision to exclude a priori those patients aged <50 years from analysis. We did so to explicitly avoid including patients for whom age adjustment would not influence the D-dimer threshold and inadvertently lead to an overestimate of the safety of age adjustment to D-dimer threshold. We used manual chart review to identify and include consecutive patients having CTPA performed expressly for the indication of suspected PE. We also used a rigorous approach to identify PE within 90 days to calculate the false-negative rate.

The prevalence of suspected PE among patients presenting to the ED varies greatly between Europe and the United States. We observed a prevalence rate of 10.6%, approximating that seen in a US cohort reported by Penaloza et al (5.1%),\(^9\) but in contrast to the prevalence in European cohorts reported by Penaloza et al (28%), Douma et al (24%), Jaffrelot et al (31%), and van Es et al (27%). Although a recent prospective management study demonstrated that the use of an age-adjusted D-dimer threshold among patients presenting to EDs in Europe with suspected PE and without a high pretest probability had a low 90-day rate of PE (0.3%),\(^{11}\) we emphasize the importance of prospective validation of adopting an age-adjusted D-dimer threshold in a population where the prevalence of PE is low. We highlight that even in the present cohort where the prevalence of PE was comparatively low, use of an age-adjusted D-dimer resulted in additional missed cases of PE.

This study has several limitations, including those attributable to its retrospective nature, the use of ICD-9 codes to ascertain certain patient characteristics, and our approach to calculating the RGS retrospectively from manual chart review as we previously described.\(^{13}\)
Because we considered clinical symptoms of unilateral lower-limb pain, pain on lower-limb palpation, or unilateral edema and hemoptysis as absent if not recorded, we acknowledge a risk of misclassification bias in our calculation of the RGS. However, in the present study cohort, a similar proportion of patients with pain on palpation and unilateral edema was observed as reported by us previously (6.6%)\textsuperscript{13} and by Douma et al\textsuperscript{21} (5.8%) and van Belle et al\textsuperscript{22} (5.7%) in which a clinical decision rule was prospectively determined. We did observe a lower rate of hemoptysis (2%) than that reported by us previously (6.6%)\textsuperscript{13} and by Douma et al\textsuperscript{21} (5.8%)

The study population comprised only patients for whom CTPA was ordered. Although this allowed us to calculate the performance of D-dimer testing against the reference of immediate CTPA, it also confers the limitation that the study population did not include patients for whom CTPA was not performed. It is, therefore, likely that the study population differs from an unselected population of all consecutive patients presenting to the ED with suspected PE, with the present patients probably at a higher risk for PE. However, we report a prevalence of PE among patients undergoing CTPA that differs little from that observed by others in the United States.\textsuperscript{9}

Our observations are subject to a type of selection bias (partial verification bias) as may occur when only a select sample of patients who underwent the index test (D-dimer) is verified by the reference standard (CTPA), and that sample depends on the results of the test. However, because the study compares members of the same group (all patients had a D-dimer test—we are only choosing variable cut points), we believe that the observations are valid.

We acknowledge that individual patient risk as perceived by the physician in certain clinical circumstances (eg, in the setting of known malignancy or recent surgery, fracture, or trauma) may lead the physician to refrain from obtaining a D-dimer level. To better understand why a D-dimer test was ordered among some patients but not others, we present patient characteristics demonstrating that D-dimer was not randomly missing (e-Table 1). Rather, we observed that D-dimer testing was absent in a fashion that would be expected in routine clinical care where the physician refrained from obtaining a D-dimer test disproportionately among patients who would be perceived to be at high risk for PE (higher RGS) or have a clinical history suggestive of D-dimer not being clinically useful (history of malignancy, recent surgery, recent fracture, recent trauma, prior VTE). The dataset did not include all patients with suspected PE because we sampled only patients undergoing CTPA. Because we report outcomes based on clinical practice and because our perception was that most cases of suspected PE at our institution are evaluated with imaging, we believed it unlikely that a significant selection bias was introduced. However, we performed an additional analysis to explore this. We retrospectively identified all patients during the study period who underwent D-dimer testing but had no CTPA performed. Next, we randomly selected patients from this group and performed manual chart review until we found 100 patients aged > 50 years for whom suspicion of PE was documented. We then calculated the RGS and the age-adjusted D-dimer threshold for each and determined the 90-day rate of PE. Among the 100 randomly selected patients, there were no PE events when the RGS was ≤ 10. Characteristics of this group are detailed in e-Table 2. Although patients who did not undergo CTPA were significantly younger than those in the study cohort (63 years vs 67 years, \( P \leq .001 \)) and, not unexpectedly, included fewer patients with recent surgery, fracture, or trauma, no other difference between groups was observed, suggesting, though not conclusively, that adoption an age-adjusted D-dimer threshold may be safe when CTPA is withheld. This supports our initial impression that selection bias did not meaningfully influence the primary observations. No formalized protocol existed for the assessment of

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, y</th>
<th>Sex</th>
<th>D-dimer Level, ng/mL</th>
<th>Age-Adjusted D-dimer Threshold</th>
<th>Conventional D-dimer Threshold (&gt;500 ng/mL)</th>
<th>PE Present on CTPA at Presentation</th>
<th>Unprovoked PE Within 90 d (d)</th>
<th>RGS\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75</td>
<td>M</td>
<td>715</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>...</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>92</td>
<td>F</td>
<td>872</td>
<td>–</td>
<td>+</td>
<td>+</td>
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<tr>
<td>3</td>
<td>80</td>
<td>F</td>
<td>553</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+ (32)</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>F</td>
<td>573</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+ (63)</td>
<td>3</td>
</tr>
</tbody>
</table>

\( F = \text{female}; M = \text{male}; – = \text{not exceeded}; + = \text{exceeded}. \) See Table 1 and 2 legends for expansion of abbreviations.

\( \text{a Time interval between index presentation to the ED and the diagnosis of PE.} \)

\( \text{b Calculated at the time of index presentation.} \)
suspected PE in the participating EDs at the time of this study, and the assessment for suspected PE occurred as part of routine clinical care. The study included two institutions in the same metropolitan area staffed by the same ED physicians and radiologists, perhaps limiting the generalizability of the observations. We used retrospective electronic capture to identify VTE within 90 days followed by manual chart review to calculate the false-negative rate, and we acknowledge that our capture is limited to patients obtaining care within our health-care system. However, Intermountain Healthcare serves approximately 50% of the population of Utah through 24 hospitals and ≥ 200 clinics, making it likely that patients would follow up within this system. Additionally, the observed safety and efficacy rates did not differ significantly from those reported by others.\textsuperscript{7,23}

We observed that the use of an age-adjusted D-dimer threshold improved the efficiency of evaluating suspected PE among patients with an RGS ≤ 10 compared with the use of a conventional D-dimer threshold. This observation was especially compelling among patients aged > 75 years for whom adoption of an age-adjusted threshold reduced the rate of a positive D-dimer test from 95% to 70%. Adoption of an age-adjusted threshold represents a novel use of D-dimer level that will disproportionately influence a subset of patients (elderly) who are comparatively at a higher risk for thrombosis yet for whom the conventional D-dimer threshold is more likely to be positive in the absence of disease. We believe that a burden of proof for safety exists before this approach can be adopted. Our observation of improved efficiency supports initial reports by others\textsuperscript{7,23} and reinforces the value associated with prospective randomized management studies investigating the safety of adopting an age-adjusted D-dimer threshold.

Conclusions

We report that the use of an age-adjusted D-dimer threshold among patients considered unlikely to have PE was associated with a low 90-day rate of failure to diagnose PE, although using an age-adjusted D-dimer threshold did result in missing more cases of PE. Using an age-adjusted D-dimer threshold could enhance the efficiency for the work-up of suspected PE by decreasing the number of patients exposed to the risk and expense of CTPA. Upon considering the 90-day false-negative rate for PE calculated among patients with negative age-adjusted D-dimer tests but with PE identified upon presentation, the present observations are encouraging that an age-adjusted D-dimer threshold is probably safe. However, we caution that a prospective study designed with adequate power for prespecified subgroup analyses to ensure the safety of adopting an age-adjusted D-dimer threshold among older patients is essential before this practice is implemented in clinical care.
Acknowledgments

Author contributions: S. C. W. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. S. C. W., S. M. S., D. M. A., B. S. Voller, Stevens, Adams, Evans, Snow, Bledsoe, Gay, and Patten; Mr Lloyd; and Ms Aston have reported to

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Additional information: The e-Tables can be found in the Supplemental Materials section of the online article.

References


