Age-Adjusted D-dimer Cutoff for Reducing CT Pulmonary Angiography Tests in Elderly Patients With Suspected Pulmonary Embolism

Improvement or Restoration Back to Normal?

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In a famous paper from the late 1970s, Robin¹ postulated his concerns about overdiagnosis and overtreatment of pulmonary embolism (PE), stating that “the emperor of embolism may have no clothes.” He was mainly concerned about overdiagnosing PE in previously healthy young women, arguing that the prior probability of PE is low in these patients, and this subsequently results in a lower positive predictive value of perfusion scans (following Bayes’ theorem). Today, concerns about overdiagnosing PE still remain highly relevant.² However, in addition to concerns about overdiagnosing PE in young adults, current research also focuses on referring (thus, also overdiagnosing) frail elderly patients too often or too soon for suspected PE: The naked emperor of embolism is aging. The main reason behind this problem comes from the fact that D-dimer testing yields more false-positive results in the elderly as compared with a non-aged population. Thus, many patients need to be referred, and typically only 10% to 15% of these patients have confirmed PE. The use of an age-adjusted cutoff for D-dimer testing (age × 10 in those aged > 50 years) has been proposed, aiming to reduce this number of false-positive results and, thus, the number of patients for whom imaging (CT pulmonary angiography [CTPA]) is required to confirm or refute the diagnosis.³

In this issue of CHEST, Woller et al⁴ (see page 1444) further expand the evidence behind this so-called age-adjusted cutoff for D-dimer testing. They used a previously described impressive cohort of 3,500 patients with suspected PE⁵ and identified a subset of 934 patients aged > 50 years combined with a low risk of acute PE (using a Revised Geneva Score). All patients underwent CTPA to confirm or refute a diagnosis of PE. Among these 935 patients, 273 patients (29%) had a D-dimer value below this age-adjusted cutoff. During 90 days of follow-up, only four patients were diagnosed with PE, yielding a failure rate of 1.5% “missed” PE cases (95% CI, 0.4%-3.7%). If the conventional cutoff (< 500 ng/mL) had been used, only 104 patients (11%) had a negative D-dimer, yet in this group no PE cases were missed. Thus, they demonstrated an almost 20% reduction of required CTPA tests for this age-adjusted cutoff, as compared with the conventional cutoff. These findings—a sharp reduction in CTPA tests at the cost of a slightly higher failure rate—are largely in concurrence with previous studies, including a recent meta-analysis (not yet including the current article from Woller et al⁴) on this age-adjusted D-dimer cutoff.⁶

Now, the question arises: Would this higher failure rate (still) be acceptable in the context of fewer CTPA tests in these elderly patients? Basically, this comes back to answering the following two questions. First, how many additional PE cases are missed, and how many of them are fatal? Second, how many CTPA tests are avoided? This is important as at least in some patients CTPA will be performed without PE being present, and these patients are at risk for unnecessary iatrogenic damage from CTPA (including radiation and contrast nephropathy). Ideally, these questions should be addressed in a formal randomized controlled trial (RCT) comparing both diagnostic strategies. However, RCTs comparing diagnostic strategies are in general difficult to perform (as well as to finance) and for now are lacking. Indirect

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To summarize, the use of an age-adjusted cutoff for a subgroup of patients that benefit most from using this test would provide us valuable information on the safety and efficiency of this age-adjusted D-dimer. This leaves us startled. Comparisons within cohorts demonstrate a sharp reduction of required CTPA tests, notably in the eldest elderly. Yet, an indirect comparison over different cohorts does not demonstrate this reduction of CTPA tests. Obviously, inherent problems related to this indirect (nonrandomized) comparison play a role here. Combining individual patient data (IPD) of these studies and using state-of-the-art IPD meta-analysis could allow us to explain these different findings between within and over cohort comparisons. For instance, the number of comorbidities, the applied clinical decision rule, the prevalence of PE in different studies, increasing age, D-dimer assay used, as well as the applied reference standard (as over time CTPA has become increasingly more sensitive in finding smaller emboli) could all be evaluated as potential modifiers of the safety and efficiency of this age-adjusted D-dimer. This would provide us valuable information on the subgroup of patients that benefit most from using this age-adjusted cutoff.

To summarize, the use of an age-adjusted cutoff for D-dimer testing seems to be a promising and safe tool in patients with suspected PE, and the current study by Woller et al reaffirms this finding also in older patients. One of the most promising aspects includes the possibility of reducing the number of CTPA tests required in frail elderly and, thus, also iatrogenic damages (and costs) caused by CTPA. This comes at the cost of a small (negligible) increase of missed PE cases. A formal randomized comparison between the age-adjusted and the conventional cutoff for D-dimer testing is preferable to confirm these findings. Yet—before we embark on such a costly and difficult RCT—first more indirect comparisons can be done using IPD meta-analysis, allowing us to better appreciate the potentially huge merits of this age-adjusted cutoff in various subgroups of elderly patients with suspected PE.

### References


### Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>CTPA Required, No. (%)</th>
<th>Low-Risk, No. (%)</th>
<th>Missed PE, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christopher Studya</td>
<td>3,306</td>
<td>2,249 (68)</td>
<td>1,057 (32)</td>
<td>5 (0.5)</td>
</tr>
<tr>
<td>ADJUST-PEb</td>
<td>3,324</td>
<td>2,170 (65)</td>
<td>1,154 (35)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Study by Woller et ala</td>
<td>934</td>
<td>661 (71)</td>
<td>273 (29)</td>
<td>4 (1.5)</td>
</tr>
</tbody>
</table>

None of the missed PE cases were fatal PE. Both the ADJUST-PE and the study by Woller et al evaluated the age-adjusted cutoff for D-dimer testing; the Christopher Study evaluated the use of a conventional cutoff. The ADJUST-PE study is the only currently available prospective evaluation. Moreover, in the evaluation by Woller et al, only patients ≥50 y are included, whereas in both the Christopher and the ADJUST-PE studies patients <50 y are also included. CTPA = CT pulmonary angiography; PE = pulmonary embolism.