The Burden of Unnecessary Testing From a Regularly Ordered Laboratory Assay: Age-Adjusted D-Dimer Quality Improvement Study

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Abstract
Diagnosing acute pulmonary embolism (PE) involves clinical suspicion in combination with sequential diagnostic tests including D-dimer laboratory assays. Although the sensitivity of this assay is well validated and thoroughly tested, a false-positive result can lead to unnecessary and costly testing. The age-adjusted D-dimer (AADD) has been suggested in the literature to improve the usefulness of D-dimer cutoffs and safely decrease iodine and radiation exposure associated with definitively ruling out PE with computed tomographic angiography (CTA).1 We present an internal retrospective review utilizing the novel AADD cutoff to rule out PE and evaluate the potential extent of unnecessary testing with CTA. Using the AADD cutoff would have led to a 21.2% reduction in computerized tomography pulmonary embolus protocol. This internal quality improvement study suggests that changing our institutional conventional D-dimer to the novel AADD would provide a superior quality and cost–benefit.

Keywords
pulmonary embolism, biomarkers, diagnosis, risk assessment

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Introduction
The diagnosis of pulmonary embolism (PE) can be difficult due to variable clinical presentation with symptoms that are often shared with several other disease entities, namely shortness of breath, chest pain, and tachycardia. Laboratory assays are used to help clinicians decide when imaging is required. The D-dimer assay is a commonly used and highly sensitive screening test to assist in the diagnosis of venous thromboembolism (VTE) including deep vein thrombosis and PE. Despite the frequent clinical utility of this assay, there is lack of standardization with cutoff values varying from 200 ng/mL to 500 ng/mL depending of the institution and type of assay.2 Another pitfall to the D-dimer assay is the decrease in specificity for diagnosing VTE with increasing age, falling from 67% in patients <40 years of age to only 10% in patients >80.3 Compared to conventional D-dimer (CDD) cutoffs, a novel approach using age adjusted D-dimer (AADD) has been proposed and externally validated by Douma et al.1,3,4

The AADD cutoff value calculated as ([age (years) × 10] ng/mL) was proposed by Douma et al after their analysis of 1721 consecutive outpatients with clinical suspicion for PE. This was then validated using 3 large cohorts of patients with an unlikely Wells score or a non-high probability Geneva score inpatients ≥50 years of age. The researchers concluded that PE could be ruled out in an additional 25% to 30% of patients whom would have had a positive conventional D-dimer Assay (> 500 ng/mL [fibrinogen equivalent units] or >230 ng/mL [D-Dimer unit]).1

Multiple previous studies have demonstrated that the novel AADD cutoff has a greater clinical utility compared to the

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traditional cutoff value without sacrificing sensitivity. In light of this evidence, we decided to revisit our institutions d-dimer protocol with a laboratory cutoff of 230 ng/mL. We present an internal quality improvement study using the proposed and validated AADD cutoff value to potentially decrease costly and unnecessary imaging.

Methods

We retrospectively searched for patients 50 years of age and older at our institution who presented with a chief complaint of either “shortness of breath” or “chest pain” in a 1-year time period that were evaluated with CDD. We accumulated 4000 encounters and then reviewed d-dimer levels and included patients with a positive laboratory test, which was defined as d-dimer greater than our standard institutional laboratory cutoff (230 ng/mL). Along with a positive d-dimer assay, the patients included had to have underwent a computerized tomography pulmonary embolus protocol (CT-PE) scan. In our institution, the d-dimer assay can be ordered at the discretion of the managing physician and is present on emergency room “shortness of breath” and “chest pain” order sets. The clinical history along with d-dimer value promotes the decision for further imaging. The Wells criteria clinical prediction assessment is also required, but can be bypassed, amid ordering a CT-PE protocol. Patients with a high or likely clinical probability of PE, determined as greater than a Wells score of 6, were excluded from the study group. Of the 4000 encounters 132 patients met the inclusion criteria. The average age of the study population was 64 (95% CI: 62.1-65.5) with an average Wells score of 3.3 (95% CI: 3.08-3.58), a high percentage of female sex (73.5%), and majority with a history of hypertension (87.8%). The baseline demographics can be seen in Table 1.

In our institution, d-dimer quantification testing is performed internally from the Instrumentation Laboratory Company. The turbidimetric immunoassay performed is a d-dimer unit (d-DU) with a recommended high normal cutoff of 230 ng/mL. As our institution uses the d-DU assay, the appropriate AADD cutoff was calculated by (age [years] × 5) ng/mL. Using this adjusted value, we determined the number of CT-PE scans that would no longer be necessary if our institution endorsed the AADD cutoff. The CDD and AADD data were compared to ascertain whether a change to our protocol would support an improvement of our patient care and cost savings efforts.

Results

Of all, 132 of 4000 patients met criteria for inclusion. With the CDD cutoff value, 124 (94.0%) patients had false positives and 8 (6.1%, Table 2) patients had true positives. In the AADD cutoff cohort 104 patients would have a positive laboratory value to warrant a CT-PE scan for diagnosis. The remaining 28 patients would have initially screened negative and would not have warranted diagnostic imaging resulting in a 21.2% (28 of 132) reduction in CT-PE scans (Table 2). Positive predictive value for the CDD group was 6.1% versus 6.7% for the AADD group. Across all age groupings, there was a relative increase in negative AADD testing. This was appreciated most in the 70 to 79 age-group (27.3%) and least in the 50 to 59 age-group (13.7%) as shown in Figure 1.

Discussion

In patients with an intermediate or low clinical risk for PE, a highly sensitive screening laboratory test such as d-dimer can be quite valuable. However, it has been well-documented that this assay can be elevated in a multitude of disease pathology, especially in aging populations. We have revisited our institutional protocol in an effort to improve the diagnostic accuracy and quality of care of our institution.

Table 1. Demographics of Study Population.

| Total population | N = 132 (100%) |
|------------------|----------------|
| Female           | 97 (73.5%)     |
| Male             | 35 (26.5%)     |
| Age (average)    | 64 (95% CI: 62.1-65.5) |
| 50-59            | 51 (38.6%)     |
| 60-69            | 45 (34.1%)     |
| 70-79            | 22 (16.7%)     |
| ≥80              | 14 (10.6%)     |
| BMI (average)    | 32.6 (95% CI: 31.2-32.7) |
| Hypertension     | 116 (87.8%)    |
| Current tobacco abuse | 23 (17.4%)   |
| History of PE or DVT | 16 (12.1%)  |
| History of cancer/malignancy | 22 (16.7%) |
| History of stroke | 9 (6.8%)      |
| Wells score (average) | 3.3 (95% CI: 3.08-3.58) |
| Low risk Wells score (<2) | 13 (9.8%) |
| No Wells score recorded | 30 (22.7%) |

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

Table 2. Findings Based on Laboratory Assay Cutoff of Conventional d-Dimer (CDD; 230 ng/mL) and Age Adjusted d-Dimer (AADD; [Age (Years) × 5] ng/mL).a

| Assay cutoff | Total positive (%) | FP (%) | TP (%) | FN (%) | TN (%) | CT-PE required by assay cutoff (%) |
|--------------|--------------------|--------|--------|--------|--------|-----------------------------------|
| CDD          | 132 (100)          | 124 (93.9) | 8 (6.1) |        |        | 132 (100)                         |
| AADD         | 104 (78.8)         | 97 (93.2) | 7 (6.7) | 1 (0.01) | 27 (20.5) | 104 (78.8)                        |

Abbreviations: AADD, age-adjusted d-dimer; CT-PE, computerized tomography pulmonary embolus protocol; FN, false negative; FP, false positive; PE, pulmonary embolism; TN, true negative; TP, true positive.

aValues are numbers (percentages) of patients unless otherwise specified.
The AADD cutoff has a significant increase in accuracy and specificity compared to our institution’s CDD cutoff. When we initially used the CDD, there were 132 patients that qualified for a CT-PE scan based on their clinical presentation and laboratory assay. Using the AADD cutoff, 104 (78.8%) patients out of those 132 would have continued to have a positive D-dimer level warranting a CT-PE scan. Therefore, a 21.2% relative increase in negative D-dimer assay could be achieved with the AADD cutoff in our entire population. The validation studies for AADD have demonstrated the most benefit in the elderly population, particularly in patients over 70 years of age.4 The discrepancy among different age groups was not as dramatic as previously reported; however, our data did show the highest relative increase of negative D-dimer in the 70 to 79 age grouping (Figure 1.)

The ADJUST-PE study was a prospective management validation study of the AADD cutoff.7 They showed an additional reduction in CT imaging of 23.3% without a significant change in false-negative results when compared to a standard D-dimer cutoff level of 500 ng/mL.7 Our study shows a comparable simulated reduction of 21.2% of CT-PE scans using the AADD cutoff. The AADD can serve as a tool to prevent clinicians from ordering unnecessary CT-PE in our institution. Importantly, we found a false-negative rate of 0.76% (1 patient) which is well within the 95% CI that was used in prior validation studies (<3%). This false negative rate is similar to what has been reported in the literature for AADD and CDD cutoff (0.5% false-negative rate).8

Health care costs in the United States continue to grow at an exponential level and cause grave concern. With almost daily negative reports about the state and cost of health care in this country, it is important to understand the value of quality care. In a 220 patient study out of South Chicago, an estimated US$200 000 of billed testing was performed due to elevated D-dimer.9 With the average cost of a CT-PE being US$1000 to US$2500 nationally, decreasing unnecessary testing using the AADD cutoff will also lead to health cost savings.

In addition to the financial benefit, reducing CT-PE will decrease adverse outcomes related to contrast administration. The elderly individuals (>65 years of age) have lower baseline kidney function due to an increased prevalence of diabetic nephropathy, dehydration, congestive heart failure, and concurrent use of nephrotoxic drugs.10 These preexisting risk factors lead to an increase in acute kidney injury by way of contrast induced nephropathy (CIN). The prevalence of CIN has been reported as high as 5% for inpatients and up to 14% for patients needing intensive care unit care.10 This makes the AADD cutoff especially useful in the elderly population where complications of CIN can be more severe.

The increase in radiation exposure is also a concern, even in the elderly individual. A Retrospective analysis of 5203 patients older than the age of 50 receiving a 10-year cumulative cancer screening radiation dose of 9 to 13 mSv had a 0.05% increased risk of major cancer.11 Patients with symptoms of “chest pain” or “shortness of breath” often have disease processes that lead to multiple recurrent emergency room presentations and hospital admissions. This produces clinical situations for recurrent need of CT-PE and hence higher doses of radiation. We should strive for As Low As Reasonably Achievable radiation doses for our patients which is better achieved utilizing the AADD cutoff for reduction in CT-PE scans.

Standardization on D-dimer testing has been proposed in the literature similar to the International. This has been described as a burden on the medical industry and could be quite costly as each manufacturer of the laboratory assay would have to perform standard curve testing followed by an external validation standard.² Clinically, using the modern AADD is simple and

Figure 1. Relative increase in patients with negative AADD results by age-group. AADD indicates age-adjusted D-dimer.
can be quickly calculated by the physician to improve their accuracy of diagnosis and necessity of testing. The argument for using AADD over CDD in patients older than 50 years of age has been well described and is currently the recommended approach by clinical guidelines committee of the American College of Physicians.12

There are several limitations to our study including the absence of Wells score in 30 of our patients along with a low risk Wells score (<2) in 13 of our patients. In both these circumstances, there is an override option that allows the ordering physician to bypass the Wells score entirely or proceed with the order despite a low risk Wells score. We also found that in our study population, the CDD carries a true-positive rate of 6.1%. This is quite low and believed to be both from unnecessary CT-PE scans and an over utilization of the D-dimer assay. Some of these orders, especially those without Wells scores, were placed while the patient was being triaged without a provider having seen the patient. This was thought to be during times of high volume when patients were triaged by advance nursing staff with ordering of imaging after verbal consulting with the managing provider. However, applying current literature and guidelines in our retrospective quality improvement study, we believe that we can significantly improve our care of this patient cohort.

Conclusion
In conclusion, using the CDD to determine the necessity of CT-PE imaging for patients with symptoms such as shortness of breath, chest pain, and tachycardia has a low utility in the absence of useful clinical criteria such as the Wells criteria. The improved accuracy of implementing the AADD cut-off for diagnosing PE in our institution would lead to a decrease in unnecessary testing; however, this is no substitute for astute clinical judgment. In performing this analysis, we have also identified areas of improvement in our process for care of patients with suspected PE. We hope that this study encourages other institutions to revisit utilizing the AADD cutoff and current procedure for diagnosis of PE which ultimately will produce cost savings and higher quality patient care.

Authors’ Note
Ethical approval to report this case was obtained from Ascension Providence Hospital Southfield Campus institutional review board (Project Title: [1240969-1] The Role of Age Adjusted D-Dimer Levels in Diagnosing Pulmonary Embolism by CT Imaging). Informed consent for patient information to be published in this article was not obtained because it was required due to retrospective chart review nature of our study. This was approved by the research chair.

Declaration of Conflicting Interests
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