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Original Contribution

Investigation of age-adjusted D-dimer using an uncommon assay

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ABSTRACT

Background: Use of an age-adjusted D-dimer for the evaluation of acute pulmonary embolus (PE) has been prospectively validated in the literature and has become a practice recommendation from major medical societies. Most research on this subject involves the most common D-dimer assays reporting in Fibrinogen Equivalent Units (FEU) with a non-age-adjusted manufacturer-recommended cutoff of 500 ng/ml FEU. Limited research to date has evaluated age-adjustment in assays that report in D-Dimer Units (D-DU), which use a manufacturer-recommended cutoff of 230 ng/ml D-DU. Despite scant evidence, an age-adjusted formula using D-DU has been recently endorsed by the American College of Emergency Physicians (ACEP). This formula seems arbitrary in its derivation and unnecessarily deviates from existing thresholds, thus prompting the creation of our novel-age adjustment formula. The goal of this study was to retrospectively evaluate the test characteristics of our novel age-adjusted D-dimer formula using the D-DU assay in comparison to existing traditional and age-adjusted D-dimer thresholds for the evaluation of acute PE in the ED.

Methods: This was a retrospective chart review at an academic quaternary health system with three EDs and 195,000 combined annual ED visits. Only patients with D-dimer testing and CT PE protocol (CTPE) imaging were included. Admission and discharge diagnosis codes were used to identify acute PE. Outcome measures were sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of an unadjusted traditional threshold (230) compared with both novel and ACEP-endorsed age adjusted thresholds, (Age × 5) − 20 and Age × 5 if >50, respectively. Estimates with their exact 95% threshold were performed.

Results: 4846 adult patients were evaluated from January 2012 to July 2017. Group characteristics include a mean age of 52 and a frequency of acute PE diagnosis by CTPE of 8.25%. Traditional D-dimer cutoff demonstrated a sensitivity of 99.8% (95% CI 98.6–100), specificity of 16.7% (95% CI 15.6–17.8) and NPV of 99.9% (95% CI 99.3–100). Our novel age-adjusted D-dimer thresholds had a sensitivity of 97.0% (95% CI 94.8–98.4), specificity of 27.9% (95% CI 26.6–29.2) and NPV of 99.0% (95% CI 98.3–99.5) with the ACEP-endorsed formula demonstrating similar test characteristics.

Conclusion: Use of an age-adjusted D-dimer on appropriately selected patients being evaluated for acute PE in the ED with a D-DU assay increases specificity while maintaining a high sensitivity and NPV. Both our novel formula and the ACEP-endorsed age-adjusted formula performed well, with our novel formula showing a trend towards improved testing characteristics.

1. Introduction

Pulmonary embolism (PE) is a disease entity with a variety of clinical presentations and a potential for high morbidity and mortality. The combination of low or moderate clinical pre-test probability and a D-dimer below a standard cutoff value has been prospectively validated to safely obviate the need for further testing [1-4]. While D-dimer testing is highly sensitive at its traditional cutoff value, the low specificity has led to excessive radiographic imaging. The specificity further diminishes in an inverse relationship to patient age [5,6]. Recent studies have retrospectively and prospectively validated the use of an age adjusted D-dimer value that improves specificity while maintaining high sensitivity [7-9]. In February 2018, the American College of Emergency Physicians (ACEP) recommended the use of age-adjusted D-dimer values in appropriate patients over 50 years old [10]. This new age-adjusted D-dimer level has demonstrated the ability to decrease imaging studies in patients over 50 with low to moderate pre-test probability for PE.

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D-dimer assays identify protein degradation products that are elevated in venous thromboembolic (VTE) states. There are multiple variations of assays for detecting these particular proteins, including turbidimetric and enzyme-linked immunosorbent assays. Since multiple companies provide D-dimer assays, there is no International Reference Standard. Some manufacturers report their results in FEU (Fibrinogen Equivalent Units) and others in D-DU (D-dimer Units) with 500 and 230 manufacturer threshold values, respectively. Since both of these assays are measuring levels of the same type of protein, there is an equivalence between these 2 units of approximately 2 ng/ml FEU–1 ng/ml D-DU [11].

The overwhelming majority of studies demonstrating the safety of age-adjusted D-dimer levels have used the more prevalent FEU assays with thresholds of 500, applying an age-adjustment of (age × 10 ng/ml) for patients over 50. This strategy has been endorsed by ACEP's 2018 clinical policy on the emergency department (ED) evaluation of VTE [10]. To date, scant evaluations of an age-adjusted approach with the less common D-DU assay have been conducted. Despite limited clinical evidence, the 2018 ACEP clinical policy has nonetheless recommended using this approach with a formula of (age × 5 ng/ml) for patients over 50 using the D-DU assay. Given the lack of rigorous data with this approach, we have identified a novel age-adjusted formula using the D-DU assay that provides a trend towards greater precision and safety in appropriately selected ED patients. The goal of this study was to perform a retrospective analysis of the test characteristics of our novel age-adjusted formula in comparison to both a traditional threshold and the ACEP-endorsed age-adjusted formula on patients suspected of PE presenting to our EDs.

2. Methods

2.1. Study design and setting

This retrospective study was performed at Christiana Care Health System in northern Delaware. Christiana is an academic quaternary care center with 3 EDs and over 195,000 combined ED visits per year. Our laboratory uses the Hemosil D-Dimer HS automated latex enhanced immunoassay which reports values in D-DU ng/ml, with a negative result reported as under 230 ng/ml. The historical prevalence rate of acute PE at our institution prior to our study is unknown. The requirement to obtain informed consent was waived by the institutional review board as this retrospective analysis was in compliance with the Health Insurance Portability and Accountability Act.

2.2. Selection of participants

From January 1, 2012 to July 31, 2017, consecutive adult (18 or older) ED patients undergoing diagnostic evaluation for PE were identified in our electronic health record (EHR). The start date was chosen based on data availability and efficiency of data extraction with the implementation of a new EHR in our health system. Patients over 18 years of age undergoing both a D-dimer test and a CT PE protocol (CTPE) while in the ED were included. Patients evaluated by ventilation/perfusion scanning were excluded as the interpretation of intermediate probability results is difficult and the frequency of testing with this method is low at our institution. PE positive patients were identified by an admission or discharge diagnosis (ICD-9 & ICD-10 codes) in the EHR that correlated with an acute PE (see Tables 1 & 2).

Table 1
PE prevalence in traditional 230 ng/ml D-dimer threshold.

	PE −	PE +	Total
D-dimer −	741	1	742
D-dimer +	3705	399	4104
Total	4446	400	4846

Table 2
PE prevalence with age-adjusted ((Age × 5) − 20) ng/ml D-dimer threshold in patients over 50 years old.

	PE −	PE +	Total
D-dimer −	1240	12	1252
D-dimer +	3206	388	3594
Total	4446	400	4846

Appropriate ICD codes were identified by a committee of researchers on the team. Any diagnoses involving chronic PE were excluded.

2.3. Methods and measurements

Data variables including age, sex, D-dimer value, and admission/discharge diagnosis were extracted from the EHR by one trained abstractor (TL) into a customized database. For the subgroup of patients identified with PE and negative age-adjusted D-dimer values, one clinical researcher (CP) extracted more detailed data from our health system's EHR, including clot burden on CTPE report, 3-month mortality, and disposition. Manufacturer-recommended (230 ng/ml) and age-adjusted D-dimer thresholds, both (Age × 5) and ((Age × 5) − 20) for patients greater than age 50, were evaluated on all patients included in the study (Tables 1, 2, and 3 include all patients >18).

2.4. Outcome

The primary outcomes were diagnostic parameters between the manufacturer-recommended and age-adjusted thresholds including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

2.5. Analysis

Diagnostic parameters were calculated for all thresholds. Estimates with their exact Clopper-Pearson 95% confidence intervals are reported. SAS v9.4 was used for calculations.

3. Results

3.1. Characteristics of study subjects

Our investigation included 4846 adult patients during the 5-year study period. Mean patient age was 52.2 years and 66.3% of patients were female. Acute PE was diagnosed by CTPE in 8.25% of the patients.

3.2. Main results

Use of our age-adjusted D-dimer threshold maintained a high sensitivity and NPV while increasing specificity in comparison to a traditional threshold (see Table 4). If our age-adjusted strategy had been used instead of the traditional 230 ng/ml threshold over this period, 510 CTPE studies might have been avoided with 11 PE cases potentially being missed (see Tables 1 & 2). In comparison to the ACEP-recommended formula, our novel formula demonstrated a trend towards slightly improved sensitivity and NPV and also had the potential to miss 5 less PE cases.

Table 3
PE prevalence with age-adjusted Age × 5 ng/ml D-dimer threshold in patients over 50 years old

	PE −	PE +	Total
D-dimer −	1515	17	1532
D-dimer +	2931	383	3314
Total	4446	400	4846

Table 4
Comparison of diagnostic parameters of standard (230 ng/ml) and both age-adjusted D-dimer thresholds for patients >50 [(Age × 5 ng/ml) and ((Age × 5) − 20 ng/ml)].

Diagnostic parameters	230 threshold	Age × 5 if age > 50 threshold	(Age × 5) – 20 if age > 50 threshold
Sensitivity (%) (95% CI)	99.8 (98.6–100)	95.8 (93.3–97.5)	97.0 (94.8–98.4)
Specificity (%) (95% CI)	16.7 (15.6–17.8)	34.1 (32.7–35.5)	27.9 (26.6–29.2)
PPV (%) (95% CI)	9.7 (8.8–10.7)	11.6 (10.5–12.7)	10.8 (9.8–11.9)
NPV (%) (95% CI)	99.9 (99.3–100)	98.9 (98.2–99.4)	99.0 (98.3–99.5)

CI; Confidence interval.

Detailed chart review of the 12 patients identified to have an acute PE despite a negative age-adjusted D-dimer was evaluated (Table 5). One patient, patient 12, was provided an incorrect discharge diagnosis of acute PE. Another patient, patient 6, was found to have a subsegmental embolus versus possible motion/filling artifact. It has been noted that subsegmental PE is of questionable clinical significance [13]. Patient 9 was found to have evidence of chronic pulmonary emboli. Of the remaining patients in Table 4, all demonstrated acute segmental clot burden and had uncomplicated hospital courses as noted.

4. Limitations

Research staff was not blinded to the study hypothesis. We cannot evaluate whether D-dimer testing was utilized in an appropriate Bayesian decision-making process in our patient cohort. Within our health system's EDs, a D-dimer is only ordered by a clinician who has evaluated the patient and found them to have a non-high clinical pretest probability of acute PE. While our clinicians routinely use a combination of clinical gestalt and Well's criteria, we were unable to collect and analyze pre-test risk stratification scores in patients for whom a D-dimer was ordered. It is also possible that some patients may not have had D-dimer testing prior to CTPE imaging and, therefore, were not included in this study. Data capture was conducted entirely in our health system's EHR, limiting the reliability of several variables in Table 5. Lastly, determination of PE positive patients relied upon admission and discharge diagnoses in the EHR, and a manual review of all patient charts was not conducted.

5. Discussion

We found that an age-adjusted D-dimer threshold strategy in the evaluation of acute PE in the ED is associated with increased specificity while maintaining high sensitivity and NPV. This has the potential to decrease costly and time-intensive radiographic testing in appropriately selected patients. Our study is one of the first to evaluate D-dimer assays that report in D-DU, and we have used a novel age-adjusted formula that has a trend towards improved test characteristics in comparison to existing age-adjusted formulas that have had limited clinical research evaluation.

Surprisingly, the 2018 ACEP guidelines on evaluation of acute VTE in the ED gave a Level B recommendation for an age-adjusted approach using a D-DU assay and formula of (Age × 5 if age > 50) based on one class III study published in 2017 [10]. This study was a retrospective analysis of patients being evaluated for both acute PE and DVT in an ED in the United Kingdom [12]. Analysis of 1649 patients revealed that the proportion of patients that could be ruled out for DVT or PE was increased from 64.9% to 74.7% using an age-adjusted (Age × 5 if age > 50) threshold. A major limitation of this study was that only 54.5% of the patients being evaluated for acute PE with a positive D-dimer underwent confirmatory diagnostic imaging. Our study provides a more rigorous evaluation of this D-DU assay as all patients with a positive standard D-dimer (over 230 ng/ml) underwent definitive testing with a CTPE. Our formula, with the correction of minus 20, provides a more precise application of age-adjustment, as resulting values correlate more appropriately with manufacturer recommended thresholds. For example, a 51-year-old in our formula would have an age-adjusted value of 235 versus 255 for the ACEP-endorsed formula. This is a much larger variation from an accepted 230 value for a 50 year old that is just 1 year younger. We directly compared our novel formula ((Age × 5) − 20) to their recommended formula (Age × 5), and our formula's the test characteristics showed a trend towards greater sensitivity and negative predictive value while demonstrating the potential to miss fewer PE's.

The rate of missed PE's in our study represented 0.25% of all patients evaluated. The PERC rule, a widely accepted and validated risk stratification tool for patients presenting to the ED for possible acute PE has an estimated miss rate of 1.8% [14]. Another analysis created a model to determine the "testing threshold," the point at which benefits of testing and treatment equal the risk of not testing, and recommended 1.4% for use in the evaluation of acute PE [15]. The test characteristics of our age-adjusted formula fall well below this recommended testing threshold, as well as the PERC rule miss rate. We are hopeful that future studies using this assay might externally validate this age-adjustment formula for assays that report in D-DU.

Our data shows that an age-adjusted approach using D-DU assays safely obviates the need for CT imaging in appropriately selected patients over the age of 50. Evaluation of both our novel formula and ACEP's endorsed formula maintained very high sensitivity and NPV while increasing specificity. These findings should reassure clinicians at the bedside who aim to safely rule out PE without further testing. The ACEP-endorsed formula may appear simpler without subtracting 20 from the Age × 5 value. Our formula, by comparison, demonstrates a trend towards better sensitivity and NPV while respecting the manufacturer-recommended threshold as a starting point for the age-adjustment.

Table 5
Evaluation of patients with negative Age-adjusted D-dimer values and positive acute PE as primary diagnosis.

Patient	Age	D-dimer (ng/ml)	CTA result	Disposition	3 Month mortality
1	82	271	Acute, segmental	Discharged	None
2	77	285	Acute, segmental	Discharged	None
3	80	313	Acute, segmental	Discharged	None
4	92	411	Acute, segmental	Discharged	None
5	79	264	Acute, segmental	Discharged	None
6	72	251	Subsegmental PE vs motion/flow artifact	Discharged	None
7	77	275	Acute, segmental	Discharged	None
8	64	253	Acute, segmental	Discharged	None
9	66	280	Chronic, segmental	Discharged	None
10	51	230	Acute, segmental	Discharged	None
11	81	247	Acute and chronic, segmental	Discharged	None
12	58	214	Negative for acute PE	Discharged	None

CTA Results were extracted by manual review from radiology report.
Disposition refers to patient's disposition from index admission as studied in this analysis.
3 Month Mortality was performed by chart review within our health system.

Declarations of interest

None.

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Presentation

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