Multicenter Evaluation of the YEARS Criteria in Emergency Department Patients Evaluated for Pulmonary Embolism

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ABSTRACT

Background: It may be possible to safely rule out pulmonary embolism (PE) in patients with low pretest probability (PTP) using a higher than standard D-dimer threshold. The YEARS criteria, which include three questions from the Wells PE score to identify low-PTP patients and a variable D-dimer threshold, was recently shown to decrease the need for imaging to rule out PE by 14% in a multicenter study in the Netherlands. However, the YEARS approach has not been studied in the United States.

Methods: This study was a prospective, observational study of consecutive adult patients evaluated for PE in 17 U.S. emergency departments. Prior to diagnostic testing, we collected the YEARS criteria: "Does the patient have clinical signs or symptoms of DVT?" "Does the patient have hemoptysis?" "Are alternative diagnoses less likely than PE?" with YEARS (+) being any "yes" response. A negative D-dimer was <1000 mg/dL for YEARS (–) patients and <500 mg/dL for YEARS (+) patients. We calculated test characteristics and used Fisher's exact test to compare proportions of patients who would have been referred for imaging and patients who would have had PE "missed."

Results: Of 1,789 patients, 84 (4%) had PE, 1,134 (63%) were female, 1,038 (58%) were white, and mean (±SD) age was 48 (±16) years. Using the standard D-dimer threshold, 940 (53%) would not have had imaging, with two (0.2%, 95% confidence interval [CI] = 0.02%–0.60%) missed PE. Using YEARS adjustment, 1,204 (67%, 95% CI = 65%–69%) would not have been referred for imaging, with six (0.5%, 95% CI = 0.18%–1.1%) missed PE, and using "alternative diagnoses less likely than PE" adjustment, 1,237 (69%, 95% CI = 67%–71%) would not have had imaging with six (0.49%, 95% CI = 0.18%–1.05%) missed PE. Sensitivity was 97.6% (95% CI = 91.7%–99.7%) for the standard threshold and 92.9% (95% CI = 85%–97%) for both adjusted thresholds. Negative predictive value (NPV) was nearly 100% for all approaches.

Conclusions: D-dimer adjustment based on PTP may result in a reduced need for imaging to evaluate possible PE, with some additional missed PE but no decrease in NPV.

Testing for possible pulmonary embolism (PE) in the emergency department (ED) requires a combination of pretest probability (PTP) assessment, biomarkers, and pulmonary or peripheral vascular imaging tests.[1,2] PTP can be determined using clinical gestalt or one of several prospectively validated clinical scores.[1,3–7] Of these, the Wells criteria are the most commonly applied.[3,4] The patient's PTP of PE is

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commonly used to determine whether D-dimer testing is appropriate (i.e., in low or intermediate PTP patients).

Pretest probability can also be used to determine the threshold that defines a positive D-dimer result. Naturally, increasing the positivity threshold decreases the sensitivity of the D-dimer test. However, patients with a low PTP have a very low prevalence of PE (about 3% in the United States),[8] and the sensitivity of most commercially available D-dimer tests is >95% when the standard 500 mg/dL threshold is used.[1,2] Given this, Bayesian analysis suggests that using a higher positivity threshold to rule out PE in low PTP patients should be safe, with no resulting decrease in negative predictive value (NPV).[9,10] Previous research supports this approach and has demonstrated that varying the positivity threshold based on PTP has the potential to reduce the number of imaging studies required by as many as 55 imaging tests per every PE missed.[11,12]

Recently, investigators from across the Netherlands evaluated the YEARS criteria in a multicenter study.[13] The YEARS criteria include three items from the Wells PE score: 1) clinical signs or symptoms of DVT, 2) hemoptysis, and 3) alternative diagnoses are less likely than PE. Patients with no YEARS criteria were defined as having low PTP of PE and selected for D-dimer testing using a positivity threshold of 1,000 mg/dL. Patients with one or more YEARS criteria underwent D-dimer testing using the standard 500 mg/dL threshold. The use of the YEARS criteria and a PTP adjusted D-dimer was associated with a 14% reduction in imaging, but was not associated with an increase in missed clinically significant PE. Whether these results would translate to an independent population is not known.

We therefore undertook an investigation of the YEARS criteria in an independent population. We hypothesized that using a positivity threshold of 1,000 mg/dL in patients with no YEARS criteria would result in a reduction of unnecessary imaging with no increase in missed PE compared to the current standard of care (i.e., low or intermediate PTP [Wells PE score ≤ 6] and D-dimer < 500 mg/dL). We also hypothesized that similar outcomes could be achieved by using a single question from the Wells PE score: "Are alternative diagnoses less likely than PE?" to determine which D-dimer threshold to use.

METHODS

We performed a prospective, follow-up study of consecutive ED patients with suspected PE in 15 EDs in the United States from February 2014 to April 2015. All enrolling centers had access to objective testing for PE in the ED including D-dimer and imaging studies (e.g., computed tomography pulmonary angiography [CTPA], ventilation/perfusion [V/Q] scanning, venous ultrasound). This study was sponsored by Siemens Healthcare Diagnostics, but the sponsor had no role in the analysis or interpretation of the data. The study protocol was approved by each participating institution's institutional review board and the analysis of data was approved by the human research committee of Partners Healthcare.

Research coordinators trained in the study protocol, inclusion and exclusion criteria, the informed consent process, phlebotomy, and sample processing enrolled all patients. We enrolled individuals 18 years of age or older who presented to an ED with a clinical suspicion of PE, were referred for objective testing by the treating clinician, and provided written informed consent. Patients were enrolled if they underwent objective testing for PE sufficient to rule in or rule out PE. For the purposes of this study, a negative D-dimer using the standard threshold was considered sufficient to rule out PE. Because the target population of the study was patients eligible for D-dimer testing, patients who had PE ruled out based on clinical criteria alone (e.g., using the PE rule-out criteria [the PERC rule]) were not eligible for enrollment. Patients who did not complete a diagnostic workup for PE (e.g., positive clinical D-dimer but no further testing, or patients not selected for testing based on contraindications to imaging such as intravenous contrast allergies) were also not enrolled. We enrolled patients eligible for D-dimer testing and therefore excluded patients who had a high clinical PTP for PE (i.e., Wells PE score > 6). As in the YEARS study, we also excluded patients unwilling or unable to participate, patients who had enrolled in the study during a previous visit, women known to be pregnant, and patients using anticoagulants for >24 hours prior to blood sample collection.

We collected baseline demographic data including sex, race, age, and the Wells PE score. The treating clinician provided the answers to the questions required to complete the Wells PE score prior to D-dimer, or imaging tests being performed. The YEARS criteria were calculated based on the responses to the

Wells PE score questions: "Does the patient have clinical signs or symptoms of DVT (yes/no)?" "Does the patient have hemoptysis (yes/no)?" "Are alternative diagnoses less likely than PE (yes/no)?" Patients with a "yes" answer to any of the above questions were considered positive by YEARS criteria.

We collected blood samples from all enrolled patients for D-dimer testing. The D-dimer concentration was measured by INNOVANCE D-dimer (Siemens Healthcare Diagnostics) CS-5100 system. In accordance with the published YEARS study protocol, for our analysis we doubled the standard threshold (i.e., the manufacturer's recommended threshold for the INNOVANCE D-dimer) to 1,000 mg/dL for patients with no YEARS criteria, but used a threshold of 500 mg/dL for those with any positive YEARS criteria.

Patients were required to have a standard diagnostic workup for PE, including either a negative D-dimer using the standard (500 mg/dL) threshold, or imaging in the case of a positive D-dimer test. However, the treating clinician could refer a patient with a negative D-dimer for imaging if they felt it was clinically indicated. Patients were considered to have a PE during the index visit if they had a CTPA showing a filling defect in a pulmonary artery or a V/Q scan read as high probability for PE. Patients with a negative D-dimer plus no imaging ordered, and patients with negative imaging tests were considered to have PE ruled out during the index visit. These patients received a follow-up telephone call and review of their medical records 3 months after the index visit. For rare cases where the results of diagnostic testing for PE were equivocal or unclear, the diagnosis or exclusion of PE was adjudicated by a panel of three study investigators, blinded to D-dimer result. Those reporting a physician diagnosed DVT or PE during the 3-month follow-up period were considered to have PE for the purposes of analysis. Patients who did not respond to five follow-up phone calls were considered lost to follow-up. However, for the purposes of our primary analysis, these subjects were considered not to have clinically significant PE or DVT so long as they had a negative criterion standard evaluation during their index visit.[14]

Our main analysis included all diagnosed PE as our primary outcome. However, because studies suggest high false-positive imaging rates among patients with isolated subsegmental PE on CTPA, we performed a prespecified sensitivity analysis in which we categorized patients whose most proximal PE was isolated to a subsegmental artery as PE-negative.[15,16]

Data Analysis

We report demographic data as means with standard deviations (SDs) or frequency with percentages. We calculated the test characteristics with 95% confidence intervals (CI) of the diagnostic approach using the YEARS criteria and using the single Wells PE score question: "Are alternative diagnoses less likely than PE?" We calculated the proportion of patients who would require imaging using a variable D-dimer threshold based on 1) the YEARS criteria and B) the single Wells PE score question and compared this to the proportion of patients who would require imaging using the standard D-dimer threshold using Fisher's exact test. With a total sample size 1,789, and 95% of subjects expected to test negative for PE, we had >90% power to declare noninferiority of NPV using YEARS, with a noninferiority margin of 1% using a one-sided equivalence test and an alpha of 0.05. Data were analyzed using SAS version 9.4 (SAS Institute).

RESULTS

We enrolled 1,789 patients tested for PE (Figure 1). No site enrolled more than 14% of the total study population (Figure 2). Among the 1,712 patients with negative index visit evaluations for PE, 381 patients (22%) could not be reached for follow-up. One hundred eighty-four (48%) of these patients had negative

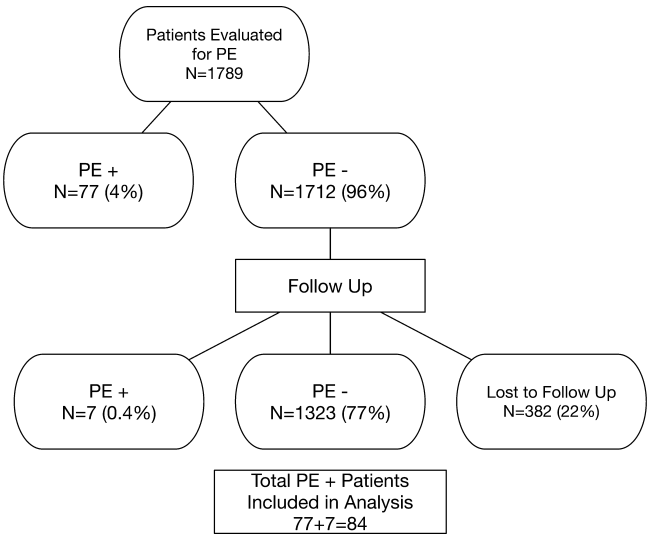

Figure 1. Enrolled patients.

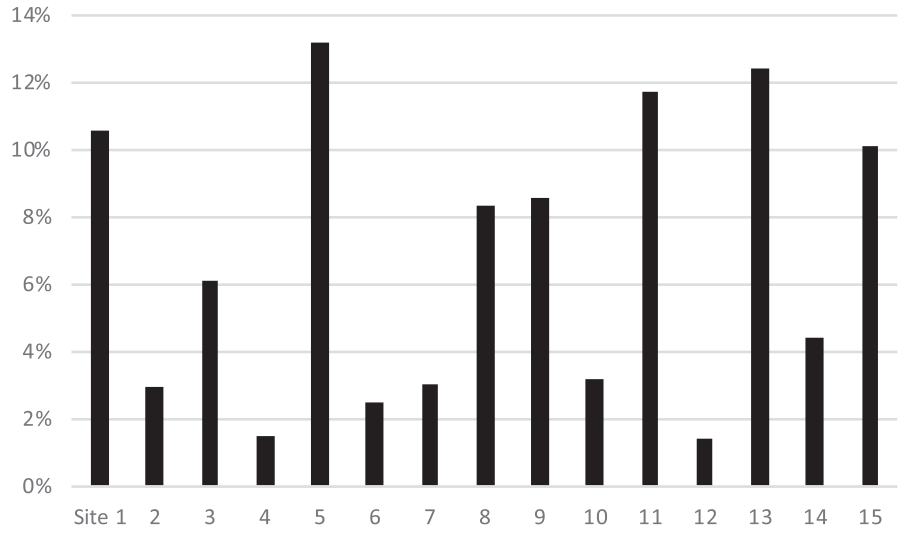

Figure 2. Percentages of patients enrolled by site.

imaging studies during their index visit. Patients who could not be reached for follow-up had similar baseline characteristics to those who completed follow-up including mean (±SD) age 45 (±15) years, female sex (220), 58% white race (191), 50% Wells score (239 [63%] low, 142 [37%] intermediate). Seventy-seven (4%) patients had a PE diagnosis on their index ED visit and seven patients (0.3% of the total, 0.4% of patients with negative index visits, and 0.5% of patients with complete follow-up) were diagnosed with PE during follow-up. The mean (±SD) age of enrolled patients was 48 (±16) years, 1,134 (63%) were female, and 1,038 (58%) were white race. Demographics and data describing PE risk criteria are provided in Table 1.

Using the Wells criteria, 1,152 (64%) had a score < 2 points (low PTP) and 637 (36%) had a score of 2 to 6 points (intermediate PTP). A total of 940 (53%) patients had a low or intermediate PTP (Wells PE score ≤6) and a negative D-dimer using the standard threshold (<500 mg/dL) and would not be referred for imaging (Table 2). Among these patients, two (0.2%, or 2/1789 = 0.1% of total enrolled patients) were diagnosed with PE: one based on CTPA performed during the index visit and one on follow-up. One PE "missed" during initial evaluation was isolated to the subsegmental pulmonary arteries. The test characteristics for the standard approach are presented in Table 3.

The YEARS criteria were negative in 1,235 of 1,789 (69%) and positive in 554 of 1,789 (31%) patients. Of patients with positive YEARS criteria, 142 (26%) had clinical signs or symptoms of DVT, 49 (9%) had hemoptysis, and 403 (73%) had alternative diagnoses less likely than PE.

A total of 982 (55%) would have had a negative initial evaluation for PE based on a negative YEARS criteria and a D-dimer < 1,000 mg/dL and 222 (12%) would have had a negative initial evaluation for PE based on a positive YEARS criteria and a D-dimer < 500 mg/dL. Thus, adjusting the D-dimer based on the YEARS criteria, 1,204 (67%, 95% CI = 65%–69%) would not be referred for imaging (Table 2). Among patients who would not have been referred for imaging, 6 of 1,204 (0.5%, 95% CI = 0.18%–1.1%) were diagnosed with PE: 5 of 1,204 (0.4%, 95% CI = 0.13%–0.96%) based on CTPA performed during the index visit and 1 of 1,204 (0.1%, 95% CI = 0.02%–0.46%) on follow-up. Two of the PE missed during initial evaluation were isolated to the subsegmental arteries. The test characteristics for the YEARS criteria adjusted D-dimer are presented in Table 3.

There were 403 (23%) subjects for whom the clinician stated that alternative diagnoses were less likely than PE. When we adjusted the D-dimer based on the single question: "Are alternative diagnoses less likely than PE?" 1,083 of 1,789 (61%, 95% CI = 58%–63%) would have had a negative initial evaluation for PE based on a negative alternative diagnosis and a D-dimer < 1,000 mg/dL and 154 of 1,789 (9%, 95% CI = 7%–10%) would had a negative initial evaluation for PE based on positive alternative diagnosis and a D-dimer < 500 mg/dL. Thus, adjusting the D-dimer threshold based on the alternative diagnosis question alone, 1,237 of 1,833 (67%, 95% CI = 65%–70%)

Table 1
Characteristics of Enrolled Subjects

	Enrolled Patients (*N* = 1,789)	
Age (years)	48	(±16)
Female sex	1,134	(63)
Race		
White	1,038	(58)
Black	551	(31)
Hispanic	145	(8)
Asian	18	(1)
Other	37	(2)
YEARS criteria		
Clinical signs or symptoms of DVT	142	(8)
Hemoptysis	49	(3)
Alternative diagnoses are less likely than PE	403	(23)
Other Wells PE score factors		
Immobilization	180	(10)
History of previous PE/DVT	166	(9)
Malignancy	129	(7)
HR > 100 beats/min	514	(29)
Imaging performed		
CTPA	813	(45)
V/Q scan	158	(9)
Wells score		
Low risk	1,152	(64)
Intermediate risk	637	(36)

Data are reported as *n* (%) or mean (±SD).
CTPA = computed tomography pulmonary angiography; V/Q = ventilation/perfusion.

would not be referred for imaging (Table 2). Among these patients, six of 1,237 (0.4%, 95% CI = 0.17%–1.05%) were diagnosed with PE: five of 1,237 (0.4%, 95% CI = 0.13%–0.94%) based on CTPA performed during the index visit and one of 1,237 (0.1%, 95% CI = 0.02%–0.45%) on follow-up. Two of the PE missed during initial evaluation were isolated to the subsegmental arteries. The test characteristics for the alternative diagnosis-adjusted D-dimer approach are presented in Table 3 and are similar to those of the YEARS approach.

When we performed our prespecified sensitivity analysis categorizing patients with isolated subsegmental PE as PE-negative, results were essentially unchanged. There were still two patients with diagnosed PE who would not have had imaging recommended by Wells score and six patients who would not have had imaging recommended by either YEARS criteria or "Are alternative diagnoses less likely than PE?" Test characteristics were also essentially unchanged.

DISCUSSION

We performed a large, multicenter observational study of low- to intermediate-risk patients evaluated for possible PE in the United States and found that adjusting the threshold used to define a positive D-dimer based

Table 2
Patients Who Would Require Imaging and in Whom PE Would Be Diagnosed According to Three Diagnostic Strategies (*N* = 1,789)

	Imaging Recommended	Imaging Not Recommended	PE Diagnosed	"Missed" PE*
Wells score ≤ 6 and D-dimer > 500†	849 (47%, 95% CI = 45%–50%)	940 (53%, 95% CI = 50%–55%)	82 (5% [95% CI = 4%–6%] of total) (98% [95% CI = 92%–99%] of PE+)	2 (0.2% [95% CI = 0.02%–0.6%] of subjects with no imaging recommended (2% [95% CI = 0.3%–8%] of PE+)
YEARS criteria and variable D-dimer	585 (33%, 95% CI = 31%–35%)	1204 (67%, 95% CI = 65%–70%)	78 (4% [95% CI = 3%–5%] of total) (93%, 95% CI [85%–97%] of PE+)	6 (0.5% [95% CI = 0.2%–1.1%] of subjects with no imaging recommended (7% [95% CI = 3%–15%] of PE+)
Alternative diagnosis less likely than PE and variable D-dimer	552 (31%, 95% CI = 29%–33%)	1,237 (69%, 95% CI 67%–71%)	78 (4% [95% CI = 3%–5%] of total) (93% [95% CI 85%–97% of PE+)	6 (0.5% [95% CI = 0.2%–1.1%] of subjects with no imaging recommended) (7% [95% CI = 3%–15%] of PE+)

Difference in percentage of patients for whom imaging would be recommended was statistically significant (based on $\alpha = 0.05$) for both YEARS ($p < 0.0001$ for 47% vs. 33%) and "alternative diagnosis less likely than PE" ($p < 0.0001$ for 47% vs. 31%). Difference between YEARS and "alternative diagnosis less likely than PE" was not statistically significant ($p = 0.24$ for 33% vs. 31%). Difference in "missed" PE was not statistically significant ($p = 0.14$ for 2/84 vs. 6/84).
PE = pulmonary embolism; PTP = pretest probability.
*"Missed" PE includes PE diagnosed on imaging during the index visit or diagnosed on follow-up among patients with low/intermediate PTP and negative D-dimer. This includes imaging performed by the clinician during the index visit despite a negative D-dimer based on the standard < 500 mg/dL threshold.
†Limited to enrolled patients who, by study enrollment criteria, had Wells score ≤ 6.

Table 3
Test Characteristics of the D-dimer Using the YEARS Criteria, Standard Threshold, and "Alternative Diagnosis Less Likely than PE" (*N* = 1,789)

	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)	Negative Likelihood Ratio (95% CI)
Wells score ≤ 6 and D-dimer > 500	97.6% (91.7%–99.7%)	55.0% (52.6%–57.4%)	99.8% (99.2%–100%)	9.7% (7.8%–11.8%)	0.04 (0.01–0.17)
YEARS criteria and variable D-dimer	92.9% (85.1%–97.3%)	70.3% (68.0%–72.4%)	99.5% (98.9%–99.8%)	13.3% (10.7%–16.4%)	0.10 (0.05–0.22)
Alternative diagnosis less likely than PE and variable D-dimer	92.9% (85.1%–97.3%)	72.2% (70.0%–74.3%)	99.5% (98.9%–99.8%)	14.1% (11.3%–17.3%)	0.10 (0.05–0.21)

NPV = negative predictive value; PE = pulmonary embolism; PPV = positive predictive value.

on PTP using the YEARS criteria could result in a 14% absolute reduction (from 47% to 33%) in imaging compared to the standard approach. This is the same percentage reduction as demonstrated in the original YEARS validation study. In our study, this reduction in imaging would have been associated with 7% (6/84) of PE being missed, compared to 2% (2/84) of PE being missed using the standard approach (i.e., Wells PE score ≤ 6 and D-dimer < 500 mg/dL). While the sensitivity of the combination of a negative YEARS criteria and a negative D-dimer was somewhat lower (93% vs. 98%), the low prevalence of PE among enrolled patients resulted in near 100% NPV (negative likelihood ratios of 0.04–0.10) for all three strategies. Thus, our results indicate that the YEARS criteria are valid in this independent American population.

Our results also suggest that a simpler model, using only one question of the Wells score, resulted in greater reductions in required imaging and the same rate of missed PE. Thus, it may be possible to reduce the use of imaging for PE by adjusting the D-dimer threshold using a simplified approach based on the presence or absence of an alternative diagnosis more likely than PE. However, previous studies have found poor to fair intra-rater reliability in the assessment of alternative diagnoses for PE, so this approach requires further validation.[17,18]

While clinicians undoubtedly vary in what they consider an acceptable proportion of missed PE, previous analyses suggest that approximately 2% of PE may be missed even when criterion standard diagnostic strategies are employed and that below 2% probability of PE, the risk of testing may outweigh the benefits.[19] The results of our study suggest that D-dimer adjustment using the YEARS criteria or "alternative diagnoses are less likely than PE" would result in six of 1,789 (0.3%) patients evaluated for PE having false-negative evaluations. This is similar to the point estimate reported in the original YEARS validation study, in which 0.6% (95% CI = 0.4%–10%) were found to have PE on follow-up.[13]

Notably, the YEARS study was a management study, so patients with a negative YEARS-adjusted D-dimer did not undergo imaging. False-negative ED evaluations were therefore only detected if a patient underwent diagnostic testing sometime after ED discharge. In contrast, in our study, most of the "false-negative" YEARS-adjusted evaluations were the result of imaging performed in the ED. Only one (0.1%) PE was detected on follow-up after a negative YEARS-adjusted D-dimer, a rate similar to that of the YEARS study.

Reducing imaging for PE has several potential benefits, to both patients and the healthcare system. CTPA exposes patients to ionizing radiation, with an associated increase in the risk of incident cancer, especially among younger patients and women.[20] There are also risks associated with the use of intravenous contrast.[21] A small minority of patients will have a life-threatening allergic reaction, and there may be adverse effects on renal function. From a systems and operational standpoint, reducing imaging can reduce cost and length of stay for patients receiving emergency care. In the United States, approximately 1% of the 1.2 million ED visits involve a CTPA.[22,23] Thus, a 14% reduction in the need for imaging for PE could have a large impact on the public health and the cost of health care.

There are several reasons that D-dimer adjustment based on alternative diagnosis may perform as well as the YEARS criteria. By far, the alternative diagnoses criterion was the most common reason for the YEARS criteria to be positive (403/554, 73%). Relatively few (*n* = 49, 9%) YEARS-positive patients had hemoptysis, and of those, 12 (24.5%) also met YEARS criteria based on alternative diagnosis criterion. Similarly, (*n* = 142, 25%) YEARS-positive patients met criteria

due to clinical signs or symptoms of DVT, and of those, 26 (18%) also met criteria based on the alternative diagnosis criterion. Thus, the YEARS criteria are highly dependent on whether an alternative diagnosis is more likely than PE. Second, when presented with a patient who might have PE, concomitant clinical signs/symptoms of DVT (or, to a lesser extent, hemoptysis) are likely to reinforce a clinician's assessment that PE is the most likely diagnosis. In a previous analysis, we found that the six "objective" questions of the Wells PE score were collinear with the "subjective" question about alternative diagnoses, suggesting that clinicians incorporate the data from the objective questions into their more global assessment of PE likelihood.[24]

One strength of our study was the timing of PTP assessment relative to D-dimer testing. We assessed PTP and the Wells PE score prior to the results of D-dimer testing or imaging for PE. In contrast, the report of the YEARS validation study notes that many patients who present to emergency care in the Netherlands have a D-dimer sent prior to being evaluated by a physician.[13] Therefore, the Wells Score/YEARS criteria may have been influenced by the D-dimer result. In fact, knowing the D-dimer result prior to assessing PTP would essentially allow the physician to determine which diagnostic pathway a patient went down. Unfortunately, it is impossible to determine exactly how much influence D-dimer results had on the YEARS criteria, and in particular, the assessment of whether alternative diagnoses were less likely than PE. Therefore, external validation of the YEARS study approach, with blinded PTP assessment, is essential.

LIMITATIONS

Our study does have some limitations. We used an observational study design, so the diagnostic workup was determined by the clinical team, rather than the study protocol. A management study, in which imaging is solely determined by the YEARS or other criteria may have allowed a more accurate assessment of the effect of PTP-based D-dimer adjustment on the use of imaging. However, in clinical practice, chest imaging with CTPA is often ordered to evaluate more than just PE. Clinicians often use CTPA to make alternative diagnoses, like pneumonia, when PE is also on the differential diagnosis.[22] Thus, it may not be realistic to expect PE imaging to be completely determined by the PTP of PE. In fact, the use of CTPA was performed against protocol in 40 of 3,465 (1%) of patients enrolled in the YEARS validation study, three of whom had PE. We therefore believe our results are in line with clinical practice. In addition, we only enrolled patients with low or intermediate PTP based on the Wells PE score, so we could not assess the performance of the YEARS criteria in high PTP patients. However, guidelines do not recommend D-dimer testing for high PTP patients, and patients with a Wells score > 6 only represent about 5% of all patients evaluated for PE. We feel that exclusion of these patients is both justified clinically and unlikely to have altered our results. We were unable to contact 21% of patients by phone after their index visit. It is therefore possible that we missed some PE diagnosed during the follow-up period. However, the number of PE diagnoses made during follow-up was small (n = 7, 0.5% of those with follow up). We estimate, based on an assumption that loss to follow-up is independent of subsequent PE diagnosis, that complete follow-up would have resulted in the inclusion of only one additional PE, although the 95% CI for this estimate is between 0 and 4 additional PE. This is unlikely to have influenced our results. Finally, we used the same D-dimer adjustment approach employed by the YEARS study authors, doubling the standard D-dimer threshold for patients with low PTP. For the INNOVANCE D-dimer we used, the doubled threshold is 1000 mg/dL, but is important to recognize that different D-dimer assays may have different standard thresholds, and accordingly, doubling of the threshold may not result in an increased threshold equal to 1,000 mg/dL. Additionally, it is likely that a more refined approach, perhaps using a continuous upward adjustment of the D-dimer based on PTP, would further improve testing efficiency. This deserves further exploration.

CONCLUSION

In conclusion, we believe that D-dimer adjustment based on pretest probability may result in a 14% reduction in the need for imaging performed to evaluate possible pulmonary embolism, with an increase in "missed pulmonary embolism" from 0.2% (using standard D-dimer cutoff) to 0.5% (using a variable D-dimer cutoff) of those evaluated for pulmonary embolism and no decrease in NPV or negative likelihood ratio in this low-prevalence population. D-dimer adjustment based on the YEARS criteria appear valid

and safe. However, a simpler model with D-dimer adjustment based on the presence or absence of an alternative diagnosis more likely than pulmonary embolism performs similarly.

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