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Research Article

Integrating D-dimer Levels in Revised Wells Score to Improve the Clinical Prediction of Pulmonary Embolism

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Abstract

Background

Pulmonary embolism (PE) probability is based on clinical criteria (e.g. Wells score) and D-dimer. However, the answer on a major Wells criterion, whether an alternative diagnosis is more likely than PE, is subjective and often equivocal. Current algorithms use D-dimer dichotomically and ignore the fact that the likelihood of PE increases with increasing levels of D-dimer.

Objectives

We evaluated potential approaches to improve the prediction of PE: How should the question whether alternative diagnosis is more likely than PE be scored when the answer is equivocal; And how can integration of D-dimer levels improve the positive predictive value (PPV) of PE.

Methods

Retrospective study of 200 consecutive patient's data who underwent pulmonary computed tomography angiography (PCTA) and D-dimer test to diagnose or exclude PE in our hospital was analyzed.

Results

PE was diagnosed in 29 (14.5%) of the patients. Alternative diagnosis more likely than PE was equivocal in 41% of the patients. The Wells score was higher in the PE group (4.4±2.0 vs. 1.7±1.5, $p<0.001$) only when no points were added to the Wells score when alternative diagnosis and PE were equivocal. Computation of several approaches indicated that the best PPV for PE was obtained with a composite score: D-dimer (μg/mL) + Wells score. No patient with a composite score <4.2 had PE (i.e., 100% sensitivity).

Conclusions

When the answer to the question if alternative diagnosis is more likely than PE is equivocal, no scoring points should be added to the Wells score. Integration of D-dimer levels into the clinical algorithm may reduce the number of negative PCTA's considerably.

Keywords: Pulmonary Embolism; D-Dimer; Wells Score

Introduction

The clinical signs and symptoms of pulmonary embolism (PE) PE are often non-specific, rendering the decision whether a more detailed diagnostic work-up to exclude PE is needed highly individual and subjective. Several large prospective studies were performed to provide objective scoring to guide and support the clinical decision. Unfortunately, none of the scoring systems was found superior to the decision of an experienced physician [1-3]. Even after adding the D-dimer test into the diagnostic algorithm [4-6], the concern to miss PE with unusual presentation causes physicians to maintain a low threshold for diagnostic testing, exposing a large number of patients to radiation and contrast material with a relatively low prevalence of positive findings [7-9].

The first step in evaluating patients with suspected PE is the determination of the pretest clinical probability of PE. Whenever the clinical probability is not high, the next successive step in the diagnostic work-up is measurement of D-dimer, to bring the probability below a certain threshold such that diagnostic imaging can be withheld: If the D-dimer level is normal – PE can be ruled out, whereas if the D-dimer level is high – imaging test is needed (Figure 1). We hypothesized that integration of the D-dimer test results to the scoring systems could improve the utilization of the available data used for pre-imaging analysis and the poor adherence to scoring systems [10-13].

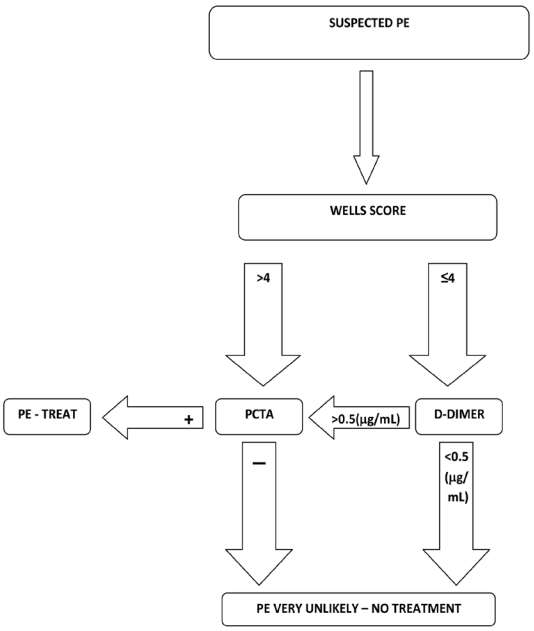

Figure 1. Current algorithm for diagnostic imaging for PE.

The clinical decision rule developed by Wells and colleagues is the most widely known, validated, and implemented tool for the detection of PE (Table 1), although it was not found to be superior to other scoring algorithms [4,5,14]. This scoring system consists of seven items, but the most subjective one with the usually highest impact is the question whether alternative diagnosis is less likely than PE. While this question can be answered sometimes with reasonable confidence, in many patients the answer is equivocal and subjective. The approximate frequency of such uncertain cases and the preferred way to handle this problem is unclear and has not been examined.

Table 1. pretest clinical probability of PE – Wells score. There is a high Clinical Likelihood of PE if Point Score Exceeds 4.

Clinical Variable	Score
Signs and symptoms of DVT	3.0
Alternative diagnosis less likely than PE	3.0
Heart rate >100/min	1.5
Immobilization >3 days; surgery within 4 weeks	1.5
Prior PE or DVT	1.5
Hemoptysis	1.0
Cancer	1.0

Also, the most significant laboratory test used in the PE diagnostic work-up is the D-dimer test. Several studies have demonstrated that the level of the quantitative D-dimer test correlates tightly with the incidence of PE and has, therefore, a high positive predictive value (PPV) [15-17]. However, this information is not utilized, and current guidelines recommend using the D-dimer test non-parametrically (i.e. normal/abnormal), solely as a rule-out tool to allow safe exclusion of PE below specific D-Dimer cutoff levels.

In the present study we addressed these two questions: First, how the question about the likelihood of PE to explain the patient's complaint should be scored when the answer is equivocal. Second, whether the integration of the D-dimer results (rather than a dichotomous approach) can improve the clinical prediction of PE.

Materials and Methods

A review of all records of 200 consecutive patients who underwent pulmonary computed tomography angiography (PCTA), to exclude or approve PE in a single urban teaching hospital. The study was approved by the institutional review board. In our hospital, relevant data including the Wells criteria are recorded and used to estimate the level of clinical suspicion for PE, but no score is calculated, and the decision whether (and which) further diagnostic evaluation is needed is left to the judgment of the more senior physician. Also, D-dimer test is performed in most patients before PCTA, and often also in patients with high clinical suspicion for PE, even though the current algorithm does not recommend routine D-dimer testing in this group of patients.

Wells Score Calculation

The Wells score was calculated retrospectively based on the presence of relevant criteria. The only problematic criterion was the question whether PE was as likely as or more likely than an alternative diagnosis to explain the patient's complaints. This question was assessed by 3 of the authors, based on the pre-imaging clinical and laboratory data (D-dimer excluded). Based on this criterion, all patients could be divided into 3 groups:

1. No better explanation (3 points added to the Wells score).
2. Alternative diagnosis more likely (no points given).
3. Patients in whom the answer to the question was equivocal, and could not be answered unambiguously.

For group 3 patients, 2 different Wells scores were calculated, one with and one without the 3 points given for this criterion, to evaluate the significance for scoring this question.

PE Imaging Evaluation

PCTA was performed on a multi-detector 64 slice scanner (Siemens, Sensation 64, Germany) and analyzed by an expert radiologist. A hypodense intraluminal filling defect causing partial or total obliteration of vascular lumen was taken as positive result for PE on PCTA. The serum D-dimer value was determined using the Vidas immuno-enzyme assay (BioMerieux). A D-dimer value of ≤ 0.5 μg/mL was considered normal.

Statistical Analysis

Data are presented as mean±SD. Parameters of patients with (PE+) and without (PE-) PE were compared using t-test or the chi-square test, as indicated. $p<0.05$ was considered statistically significant.

Integration of D-dimer Test

A specific goal of the present study was to use the quantitative D-dimer test in a non-dichotomous fashion in combination with the Wells score to compute a single combined/composite parameter that would improve the pre-imaging PPV for PE. Aiming for simplicity we avoided complex factors (exponentials etc.), as well as any mode of multiplication by the Wells score (that would result in 0 whenever Wells score = 0), leaving simple addition as the preferred algorithm. To assess the relative weight of D-dimer vs. Wells score, a series of parameters was generated by multiplying the D-dimer levels by weight adjustment factors ranging between 0.5-2, i.e., the computed individual composite parameters were:

Wells score + (weight-adjustment factor (0.5→2.0) x D-dimer).

A composite parameter with a weight adjustment factor<1 (e.g. Wells score + 0.5xD-dimer) presumes the clinical data (i.e., Wells score) to be more important than D-dimer, and vice versa. For each such composite score, the lowest value in the PE+ group was defined as the lower cut-off level (to enforce 100% sensitivity and 100% negative predictive value for the whole cohort). The number of false positive results (i.e. number of patients without PE with composite parameter ≥ this level) enabled calculation of the pre-imaging PPV for each weight-adjustment factor. This approach enabled determination of the most appropriate weight adjustment factor as the one providing the highest PPV, while avoiding false negative results.

Results

PE was diagnosed in 29 patients (14.5%). About half of the PCTA (52%) were ordered in the emergency department. The prevalence of positive PCTA was similar in the emergency and clinical departments (14.3% and 14.9 %, respectively). Comparison of demographic and laboratory data for the PE+ and PE- patients is presented in Table 2.

Table 2. Demographic and laboratory data of patients with and without PE.

	PE (n=29)	no PE (n=171)
Age (years)	21.6 ± 62.9	19.1± 65.4
Gender (% females)	76%	72%
WBC (cells/mL)	± 11,400 4,700	5,100 ± 9,600
WBC>10,000 (%)	52%	30%*
PT (INR)	0.2 ± 1.1	0.4 ± 1.2
INR > 1.5 (%)	0	3%
PCO2 (mmHg)	7.7 ± 44.2	10.0± 44.6
SO2 (%)	4.7 ± 91.2	4.7 ± 93.4

WBC – white cell count; PT (INR) – international normalized ratio of protrombin time; SO2 – oxygen saturation (pulse oxymetry).
PCO2 was measured in venous blood. Mean±SD. * - $p<0.05$.

Wells scores of the PE+ and PE- patients are presented in Table 3. In our patients, only the criteria related to DVT (clinical suspicion now or US-Doppler diagnosis in the past) were significantly different between PE+ and PE- patients, but these criteria were present in only 11% of the patients. The prevalence of tachycardia, immobilization or recent operation, and active cancer was similar in both groups. Considering the question about the likelihood of an alternative diagnosis to explain the patient's complaint, in 37% of all patients PE was considered to be more likely than an alternative diagnosis. An alternative

diagnosis was considered more likely in 22.5% of all patients. Accordingly, the answer on this criterion was unclear in the remaining 40.5%. Almost all of these patients belonged to the PE- (negative) group. Therefore, when these patients were considered to fall under the category of "PE as likely as an alternative diagnosis" (and, as recommended, 3 points added to their Wells score), the calculated Wells (calculation A in Table 3) was similar for the PE+ and PE- patients. On the other hand, if for all patients with equivocal answer an alternative diagnosis was considered to be more likely (i.e., no scoring points added), the difference between the PE+ and PE- patients became highly significant (calculation B, p<0.001). Hence, we considered this later mode of scoring to be more correct and appropriate, and in further analysis only calculation B of the Wells score was used. Calculation B reduced the number of patients with high probability scoring for PE (≥4.5, no D-dimer needed) to ≤4 in 55% of the relevant patients. None of them had PE in PCTA.

Table 3. Wells score in patients with and without PE.
Wells score calculation A – 3 score points **added** to patients with "PE as likely as an alternative diagnosis", as recommended.
Wells score calculation B - **no points added** to patients with "PE as likely as an alternative diagnosis".

	PE (n=29)	**no PE** (n=171)	p
Clinical signs of DVT	(21%) 6	(2%) 3	<0.002
Pulse > 100/min	(24%) 7	(25%) 43	NS
immobilization or surgery	(38%) 11	(37%) 63	NS
Previous DVT/PE	(21%) 6	(7%) 12	<0.05
hemopthysis	0	1	
malignancy	(3%) 1	(4%) 6	NS
PE more likely than an alternative diagnosis	22 (76%)	52 (30%)	<0.001
PE as likely as an alternative diagnosis	3 (10%)	78 (46%)	<0.001
PE less likely than an alternative diagnosis	4 (14%)	41 (24%)	NS
Wells score – calculation A	1.8 ± 4.7	1.6 ± 3.1	NS
Wells score – calculation B	2.0 ± 4.4	1.5 ± 1.7	<0.0001

NS – statistically not significant

D-dimer test was performed in 23 (79%) and 130 (77%) of the PE+ and PE- patients, respectively (Table 4). An almost perfect correlation was found between the prevalence of PE at each D-dimer range and the mean D-dimer of this range (R=0.993). D-dimer >5 had a specificity of 95% for PE+, but its PPV was only 65%.

Table 4. Prevalence of various D-dimer levels in patients with and without PE in patients in whom D-dimer test was performed.

D-dimer range (μg/mL)	**PE** (n=23)	**no PE** (n=130)	P[1]	% PE[2]
<0.5	0	13 (10%)		
0-1	0	50 (38.5%)	<0.0001	0
1-3	5 (22%)	62 (48%)	<0.05	7.5
3-5	5 (22%)	11 (8.5%)	=0.07	31
>5	13 (56%)	7 (5%)	<0.0001	65

[1] – p value for comparison of PE and no-PE at the level of D-dimer range
[2]– % PE (i.e. PPV of D-dimer) at the D-dimer range

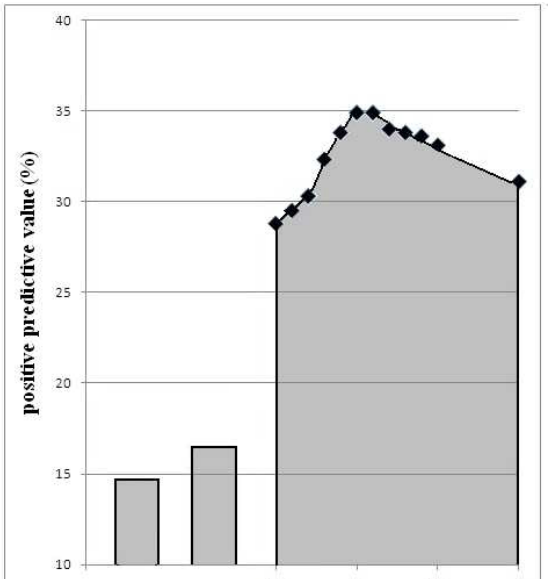

Figure 2. Positive predictive value of various pre-imaging scoring of the probability for PE. The composite score (right side), adding D-dimer (at various ratios, using adjustment factors ranging from half to twice the actual level) to the Wells score, provided better prediction than the other scoring rules. The highest PPV (34.9%) was found when the D-dimer level was multiplied by the adjustment factor 1 (or 1.1), i.e., no adjustment factor was needed, and simply adding up Wells score + D-dimer (μg/mL) provided the best composite parameter. Using adjustment factors <1 or >1.1 resulted in lower PPV. The PPV of the composite parameters was superior not only to the un-

structured decision of our physicians (BL), but also to the calculated PPV based on optimal scoring (OS), i.e. strict adherence to the Wells rule (Wells score ≥4 or Wells score <4.5 and elevated D-dimer), modified to include the PERC (18) and age adjusted D-dimer cut-off level (20-22).

Adjustment factor - a range (0.5-2) of factors multiplied by the D-dimer, to assess the relative proportion between D-dimer and Wells score providing the best prediction (see methods for explanation).

The computation designed to assess the optimal mode of combining the quantitative D-dimer result with the Wells score (see methods) is depicted in figure 2. Surprisingly, the highest PPV (34.9%) was found without any adjustment factor (factor = 1) and simply summing Wells score + D-dimer (μg/mL) provided the best composite score. This composite pre-imaging score reduced the number of patients who needed to undergo PCTA to diagnose one patient with PE from 6.9 patients (unstructured, 200/29, in our hospital) to 2.9 patients. Using this simple approach, no patient in our study with composite score<4.2 had PE, and all patients with a composite score >11.5 had PE (figure 3).

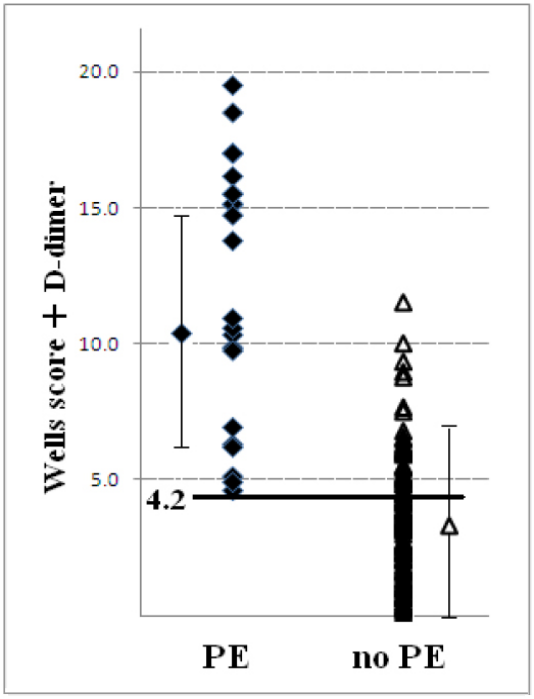

Figure 3. Distribution of the composite (Wells score + D-dimer) score in patients with and without PE. All patients with PE, but only 28.1% of patients without PE, had a score ≥4.2.

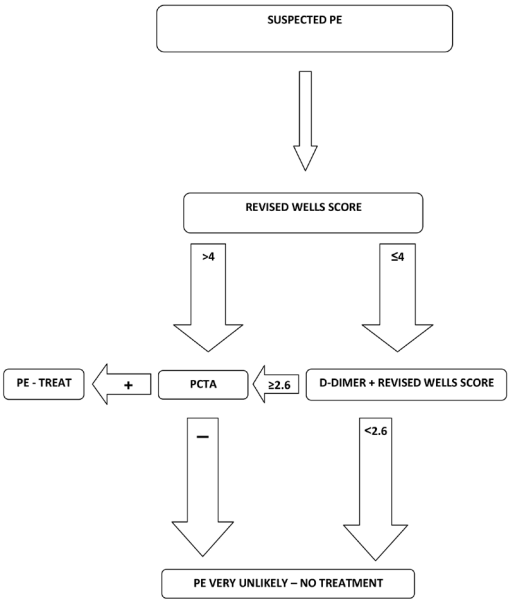

Figure 4. Proposed algorithm for diagnostic imaging for PE. The composite score mean-2SD of our PE+ patients was 2.6, suggesting that below this score PE is most unlikely (5%). This cut off level may help to rule out PE whenever PTCA or lung scan fails to provide a definite diagnosis.

Discussion

The present study was triggered by the need to improve the clinical prediction of PE and reduce the number of negative PCTAs. For this purpose we evaluated two interrelated factors: First, we assessed the adequate approach when the question whether PE was more or less likely than an alternative diagnosis to explain the patient's complaint(s) was equivocal, i.e., the condition that can be defined as "PE is as likely as an alternative diagnosis". We found that this situation is more common than any one of the other two possibilities. The current guidelines indicate that these ambiguous cases should be added to "PE more likely than an alternative diagnosis", thereby adding 3 points to the Wells score. This approach leads often to perform PCTA without the need for D-dimer test (Wells score ≥4.5). Analysis of our results indicated that whenever the decision is equivocal ("PE is as likely as an alternative diagnosis"), no scoring should be added. Practically, this approach results in a lower Wells score, usually leaving the decision whether to proceed to imaging to the result of the D-dimer test.

Secondly, we used our data to evaluate the most appropriate way to integrate the level of D-dimer into the clinical pre-imaging assessment of the probability of PE. As previously shown [15-17], we too found a linear correlation between the level of D-dimer and the incidence of PE (table 3). However, the relative importance (or "weight") of this laboratory parameter as compared to the clinical Wells score cannot be derived in-

tuitively. By constructing a Wells score + (adjustment factor * D-dimer) vs. PPV plot (figure 1), we found that, despite its limited specificity, parametrically used D-dimer has a predictability for PE comparable to the Wells score. Accordingly, simple adding up the clinical and laboratory parameters provided the best PPV, while maintaining 100% sensitivity and 100% negative predictive value: In our cohort, a composite score below 4.2 excluded PE safely.

Due to the often non-specific clinical presentation of PE and the low specificity of D-dimer, current pre-imaging diagnostic algorithms have a low PPV. In our hospital, most physicians based their decision whether specific imaging was needed on the clinical presentation and their experience. Similar to previous studies [10-13], we found that adherence to rules can reduce the need to perform PCTA without affecting sensitivity. However, the magnitude of this reduction is rather modest, and in our cohort, full adherence with the Wells rule could avoid only 4% of the PCTAs. Several attempts have been undertaken to determine age-specific D-Dimer cutoff levels and additional parameters that will allow safe exclusion of PE in a larger majority of patients. However, PE could be excluded by the PERC criteria [18] in only 5 of our patients (2.5%), and including also the age-adjusted D-dimer normal level [19-21] to the algorithm resulted in a reduction of the number of PTCAs by 12.5%. Altogether, even when adapting all recommendations, the false positive pre-imaging prediction (i.e., negative PCTAs) could be lowered only to 85.4% of baseline. While this reduction in negative PCTAs is important, it also suggests that a different approach is needed to achieve a more substantial improvement in the pre-imaging prediction. In our cohort we found that simple adding up the D-dimer level (μg/mL) to the Wells score provided a composite score that reduced the number of negative PCTAs to 28.1% of baseline, without any false negative result (i.e., 100% sensitivity). The composite score supports the recommendation that D-dimer test needs to be performed only in patients with Wells score <4.5: With higher Wells score the composite score will always exceed the cut-off level requiring imaging. Our findings are also in accordance with previous studies that found that higher cut-off levels of D-dimer can be used to exclude deep vein thrombosis (DVT) in patients with low clinical pre-test probability [22,23].

The Wells score (and similar scoring systems) has several well recognized flaws. For example, a high scoring (3 points) is given to clinical suspicion for DVT, although ultrasound-Doppler is readily available in practically every medical facility where PCTA is performed. Using leg- or point-of-care multiorgan ultrasonography [24] can avoid the need to leave the possibility of DVT at the level of suspicion, and add additional information. Also, recent studies found that the scoring for present malignancy and previous DVT may be too low [25-27]. However, as seen in table 2, the most significant item was the scoring for the question whether PE was as likely as or more likely than an alternative diagnosis: other parameters were either equally frequent in PE+ and PE- patients, or relatively uncommon. Therefore, improving the scoring of most parameters is not likely to improve the clinical prediction of PE. On the other hand, although only one out of seven parameters, the question related to alternative diagnosis is usually the most pertinent for nearly all patients. Considering the difficulty to provide a definite answer to the PE probability questions in patients with dyspnea and uncommon presentations like syncope or palpitation [28,29], mild pulmonary changes or exacerbation of COPD [30-32], the finding that the PPV of all scoring systems is similar and none was superior to clinical impression [1-3] is not surprising. The ambiguity of this parameter is reflected by the finding that physicians often change their initial clinical impression after receiving the result of the D-dimer test [33]. On the other hand, physicians often choose to exclude PE even when alternative diagnosis is more likely (like pulmonary congestion, pneumonia, pulmonary neoplasm etc.) either in the presence of high Wells score, or elevated D-dimer. Nevertheless, scoring systems were usually not inferior to clinical gestalt, and the comparisons may not reflect real life conditions, as most retrospective studies found that adherence to rules reduced the number of unnecessary imaging. Also, adequate scoring may be helpful for the less experienced or stressed physician, and the low specificity of present rules only emphasizes the need for continuous efforts to improve the PPV of the pre-imaging evaluation tools and algorithm. Integrating the level of D-dimer parametrically into the decision rule appears to represent a promising approach toward this end.

The relatively small number of patients with PE limits the accuracy of our analysis regarding the composite score cut-off level under which imaging can be safely avoided. Obviously, this level needs to be validated in a much larger cohort, to ascertain acceptable low false negative results. However, the composite score mean-2SD of our PE+ patients was 2.6, suggesting that below this score PE is most unlikely. This cut off level may help to rule out PE whenever PTCA or lung scan fails to provide a definite diagnosis. In addition, the retrospective nature of this study may raise concern regarding the accuracy of the calculated Wells score, and a prospective study might more accurately represent the decision of the physician who sees the patient at presentation regarding the likelihood of an alternative diagnosis. However, as all relevant data was available, the retrospective evaluation, needed for comparison of alternative approaches with current practice in our hospital, did not reduce the validity of our conclusions. Moreover, the evaluation by three experienced clinicians provided a more objective and standardized approach to this rather subjective question. It should be noted that our evaluation was restricted to patients referred for imaging rather than applied to all patients presenting with suspected PE, as prevention of unneeded PCTAs is relevant only in this cohort. The relatively small percentage of patients with PE (14.5%) is similar to the prevalence reported by others [7-12]. In a large recent study that

examined the usage of decision rules in the ED, the diagnostic yield of PCTA was 10% [34], as estimated in the extensive review of Stein and Matta [35].

In conclusion, strict adherence to the Wells rules, even when combined with the PERC recommendations and age-adjusted D-dimer norm values, is not expected to achieve a large improvement in the clinical prediction of PE. Our findings indicate that whenever the question whether an alternative diagnosis is more or less likely than PE cannot be answered with confidence, no points should be added to the Wells score, leaving the decision if imaging is needed to the result of the D-dimer test. Incorporating the level of quantitative D-dimer test into a composite score, with simple adding up the D-dimer level (μg/mL) to the Wells score provides the best outcome, and has the potential to reduce substantially the number of negative PCTAs and the potential hazards of contrast material and radiation.

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