CHAPTER 7

Effectiveness of a simple diagnostic algorithm in patients with clinically suspected acute recurrent pulmonary embolism

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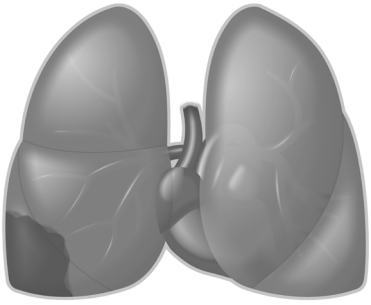

ABSTRACT

Background

The value of diagnostic strategies in patients with clinically suspected acute recurrent pulmonary embolism (PE) has not been established. The objective was to determine the safety of a simple diagnostic strategy using the Wells clinical decision rule (CDR), quantitative D-dimer testing and computed tomography pulmonary angiography (CTPA) in patients with clinically suspected acute recurrent PE.

Methods and Results

This multicenter clinical outcome study included 516 consecutive patients with clinically suspected acute recurrent PE. An unlikely clinical probability (Wells rule 4 points or less) was found in 182 of 516 patients (35%), and the combination of an unlikely CDR-score and normal D-dimer result excluded PE in 88 of 516 patients (17%), without recurrent venous thromboembolism (VTE) during 3-month follow-up (0%; 95% CI 0.0-3.4%). CTPA was performed in all other patients and confirmed recurrent PE in 175 patients (overall prevalence of PE 33%) and excluded PE in the remaining 253 patients (49%). During follow-up, seven of these 253 patients returned with recurrent VTE (2.8%; 95% CI 1.2-5.5%), one of which was fatal (0.4%; 95% CI 0.02-1.9%). The diagnostic algorithm was feasible in 98% of patients.

Conclusions

An algorithm consisting of a clinical decision rule, D-dimer test and CTPA is effective in the diagnostic management of patients with clinically suspected acute recurrent PE and provides reasonable safety with a low risk for recurrent non-fatal and fatal VTE at follow-up.

INTRODUCTION

Pulmonary embolism (PE) is a frequent disease, occurring in 0.5-1.2 per 1000 persons per year.[1,2] The risk of recurrent PE is 10-20% in the first two years after discontinuation of anticoagulant therapy.[3,4] Little evidence is available regarding the best diagnostic strategy for patients presenting with suspected recurrent PE. The consequences of a false positive or false negative diagnosis of recurrent PE are substantial. An incorrect diagnosis of recurrent PE exposes the patient to prolonged and often life-long anticoagulation, with its costs, inconvenience, and bleeding risks, and on the other hand, a falsely negative diagnosis places the patient at high risk of – potential fatal – recurrent PE.

The safety of withholding anticoagulant therapy in patients with a first episode of clinically suspected PE in the presence of an unlikely score using a clinical decision rule (CDR) in combination with a normal D-dimer result, or a normal CTPA has been demonstrated in several prospective studies.[5,6,7] In case of suspected recurrent PE, there are several diagnostic challenges. Since all patients score at least 1.5 points due to the item "history of VTE", patients are more likely to be classified as 'PE likely' according to the Wells rule. And in case of a likely clinical probability it is not possible to exclude PE with D-dimer testing alone. Furthermore, the specificity of a D-dimer test has been shown to be less in case of a recurrent thrombotic disease.[8,9] Finally, interpreting the CTPA in patients with a previous PE is challenging because of the presence of residual thrombi, complicating the differentiation between old or a new PE.[10]

In two studies, a diagnostic algorithm was evaluated in patients presenting with clinically suspected recurrent PE.[9,11] In both studies no recurrent VTE (0% failure rate) was observed during 3-month follow-up in patients with a CDR indicating PE to be unlikely and a normal D-dimer test result. However, due to the modest sample sizes, the upper limits of the 95% confidence intervals (CI) were high (7.9 and 6.9%, respectively) in both studies. In the latter study, the VTE failure rate following a negative CTPA was 0.8% (95%CI 0.02-4.3)[11] The goal of the present study was to evaluate the safety of withholding anticoagulant treatment in patients in whom recurrent acute PE was excluded on the basis of a predefined diagnostic algorithm using the Wells clinical decision rule, quantitative D-dimer test and CTPA.

METHODS

This study was a prospective multicenter clinical outcome study in 7 hospitals in the Netherlands in patients with clinically suspected recurrent acute PE. The primary study goal was to establish the safety of withholding anticoagulant treatment in patients with

normal diagnostic tests using the predefined algorithm. The study was approved by the institutional review boards of all participating hospitals.

Patient population

Consecutive in- and outpatients with clinically suspected recurrent acute PE were eligible. Clinical suspicion for recurrent PE was defined as acute onset of shortness of breath, deterioration of existing shortness of breath or acute onset of pleuritic chest pain without another explicit explanation for these complaints. A previous PE had to be objectively diagnosed according to the following criteria: intraluminal filling defects on pulmonary angiography or CTPA, likely probability ventilation perfusion scintigraphy (VQ-scan) or intermediate probability VQ-scan in combination with objectively diagnosed deep venous thrombosis (DVT).

It was not known how many previous events the patients had in history, at least one event and more events are not likely because of the indication for life-long anticoagulation treatment.

The presence of one or more of the following criteria excluded potentially eligible patients from the study: age < 18 years, treatment with full-dose therapeutic low molecular weight or unfractionated heparin (LMWH) initiated 24 hours or more prior to eligibility assessment, treatment with vitamin K antagonists, contraindication to CTPA (i.e. allergy to intravenous iodinated contrast or renal dysfunction (creatinine clearance < 30 ml/min)), life expectancy less than 3-month, current pregnancy, or impossibility to return for follow-up.

Study Flow

The diagnostic workup scheme is illustrated in Figure 1. Information regarding risk factors for recurrent PE was gathered along with patients' presenting signs and symptoms. The

Table 1. Clinical Decision Rule according to Wells.

Items	Points
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3.0
Alternative diagnosis less likely than PE	3.0
Heart rate > 100/min	1.5
Immobilization (>3 days) or surgery in the previous four weeks	1.5
PE or DVT in history	1.5
Hemoptysis	1.0
Malignancy (receiving treatment, treated in the last 6 months or palliative)	1.0
PE unlikely ≤ 4 points; PE likely > 4 points	

DVT: deep vein thrombosis; PE: pulmonary embolism.

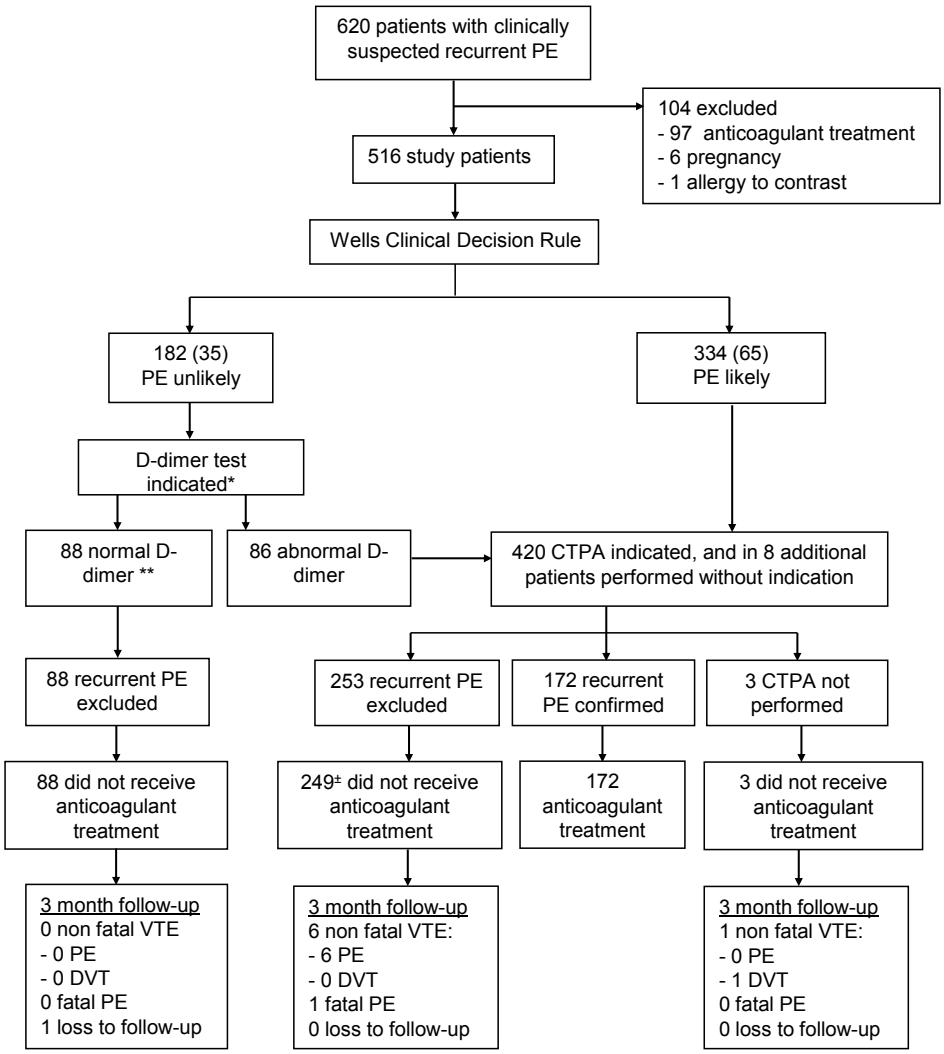

Figure 1. Flowchart and results of the diagnostic strategy. *8 patients did not undergo D-dimer testing, despite clinical decision rule indicating pulmonary embolism (PE) unlikely, protocol violation; **6 of these 88 patients underwent computed tomography pulmonary angiography (CTPA) (protocol violation), and did not show PE in any of these patients; ±3 patients received anticoagulant therapy for other reasons than PE, one patient was regarded as having PE despite negative CTPA test results. The numbers in parentheses represents percentages.

Wells clinical decision rule was calculated in all patients (Table 1).[8] In patients with a CDR score indicating an unlikely clinical probability defined by four points or less, a high sensitive D-dimer test was performed (Tinaquant, Roche Diagnostica, Mannheim, Germany; VIDAS, Biomerieux, Marcy Letiole, France; STA Lia, Diagnostica Stago, Asnieres, France or Innovance, Siemens, Marburg, Germany). In patients with an unlikely CDR score and a

normal D-dimer result (< 500 ng /mL) recurrent PE was considered to be excluded and anticoagulant treatment was withheld, without further diagnostic testing. In patients with a CDR score of more than four points (likely clinical probability), or an abnormal D-dimer test result, CTPA was performed within 24 hours of presentation. Anticoagulant treatment was withheld in patients with a CTPA negative for recurrent PE. Patients with a CTPA demonstrating recurrent PE were treated with standard anticoagulant therapy. All patients in whom recurrent PE was excluded were followed for a period of three months.

Imaging protocols

Standard contrast enhanced CTPA was performed using a 4-row, 16-row, or 64-row scanner with acquisition of 0.5-1mm sections of the entire chest. Acquisitions were done during single breath hold lasting 10-12 seconds. The rotation time was 0.4 sec. The tube current was 250-300 mA and the tube voltage was 100kV. 80-100 mL contrast material was injected in the antecubital vein at an injection rate of 4 mL/sec. The diagnosis of PE was confirmed by the presence of an intraluminal filling defect in the pulmonary artery tree in at least two projections. In those with a prior CTPA available for comparison, PE was diagnosed by the presence of a new intraluminal filling defect present on CTPA. Recurrent PE was considered to be excluded in the presence of an unchanged or normal CTPA. If no prior CTPA was available for comparison, the CTPA result was analyzed by comparing with the anatomical localization of the prior PE with the anatomical area of the prior PE on the pulmonary angiogram or ventilation perfusion scintigraphy or by comparing with the description of the prior PE on the radiology report. Trained radiologists judged the CTPAs to directly determine whether PE was present or excluded and the radiologist knew that a patient referred to CTPA either had a D-dimer level above 500 and/or a CDR score that was higher than 4 points, but had no knowledge of which of these items was the reason for performing a CTPA.

Follow-up

The primary outcome measure for this study was the 3-month VTE recurrence rate in patients with normal initial test results. Patients in whom PE was excluded by an 'unlikely' probability for PE and a normal D-dimer test result or by negative CTPA were followed for three months in order to ensure the correctness of the diagnosis. All patients were instructed to return to the hospital when they developed complaints, suggestive of VTE. If there was a suspicion of VTE during follow-up, objective tests were performed: CTPA, ventilation perfusion scintigraphy and/or compression ultrasonography. In case of death, information was obtained by reviewing hospital charts, results from autopsy or by contacting the general practitioner. Death was classified as due to PE in case of objective confirmation of PE prior to death or if PE could not be confidently excluded as the cause of death.

Sample size calculation and statistical analysis

For the primary study objective, we needed a sample size sufficiently large to provide reliable estimates of the negative predictive value (NPV) of both a CDR score of 4 points or less in combination with a normal D-dimer result, and the NPV of a negative CT for PE. Based on previous studies we expected that around 20% of the included patients would have a CDR of 4 points or less in combination with a normal D-dimer.[5] Of these, we assumed that at most 1% would return with symptomatic VTE during follow-up. We expected that approximately 80% of the total sample size would have an indication for CTPA, and of these, 66% would have a normal CTPA result. We assumed that 1.5% of the patients with a normal CTPA would have a symptomatic VTE during follow-up. Based on these estimates we expected an observed NPV in the group with unlikely clinical probability and normal D-dimer test results of at least 99% with a 95% CI of 95% to 100% and an observed NPV of the group with PE excluded by CT of at least 98.5% with a 95% CI of 96% to 100%. For this, a sample size of 500 patients was needed.

Exact 95% confidence intervals (CI) were calculated for the observed incidences.

RESULTS

Patients

During the study period from November 2002 to November 2009, a total of 620 patients were screened for eligibility, of whom 104 (18%) were excluded because of predefined exclusion criteria. The majority (93% of these 104 patients) was excluded due to treatment with anticoagulants prior to inclusion. The final study population consisted of 516 patients (Figure 1). Characteristics of these patients are shown in Table 2. The mean age was 55 years, 305 of the 516 (59%) were females, most patients (89%) were outpatients and 13% had active malignancy. A total of 172 patients (33%) were diagnosed with acute recurrent PE and the median time since first PE diagnosis was 3 years (25^{th} and 75^{th} percentiles 1-6 years). The mean age was approximately 10 years older in patients with recurrent PE present compared to patients in whom recurrent PE was excluded.

Diagnostic algorithm

CDR and D-dimer

Of the 516 patients with suspected recurrent PE, 182 (35%) had a CDR indicating recurrent PE unlikely, of whom 88 (17%) had a normal D-dimer test result. In six patients, CTPA was performed despite a normal CDR and D-dimer result (protocol violation). These CTPAs were negative for PE in all patients. During follow-up, one patient was lost to follow-up.

Table 2. Clinical characteristics of the included patients.

	All patients N = 516	Recurrent PE excluded N = 333	Recurrent PE present N = 183
Age, mean (SD), y	54.7 (17)	51.3 (17)	61.0 (16.4)
Female,%	59.2	64.6	50.0
Outpatient, %	88.8	90.0	85.1
Duration of complaints, median (25^{th}-7^{th} ‰), d	3 (1-9)	3 (1-9)	3 (1-9)
Time since prior PE, median (25^{th}-75^{th} ‰), y	3 (1-6)	3 (1-6)	2 (1-6)
Body mass index, mean (SD), kg/m2	27.3 (5.4)	27.2 (5.6)	27.4 (5.2)
Risk factors			
Immobilization or recent surgery, %	12.5	4.8	18.5
COPD with treatment, %	15.6	18.5	10.1
Heart failure with treatment, %	10.1	8.3	13.3
Active malignancy, %	13.3	9.6	20.0
Estrogen use, women, %	6.2	6.0	6.7
Body mass index ≥ 30 kg/m2, %	24.2	25.5	22.4
Symptoms and clinical presentation			
Clinical symptoms of deep vein thrombosis, %	8.3	5.4	13.5
Heart rate, mean (SD), bpm	83.4 (18.3)	81.4 (19.6)	86.5 (16.5)
Hemoptysis, %	5.9	3.8	9.7
Heart rate > 100 bpm,%	16.7	11.9	25.6

Bpm: beats per minute; COPD: chronic obstructive pulmonary disease; SD: standard deviation; VTE: venous thromboembolism. Complete information was not available on all patients, the n represents the number of patients in whom the information was present.

None of the remaining 87 patients received anticoagulant treatment during follow-up, and all of these patients had an uneventful follow-up, resulting in a failure rate of 0% (95% CI 0.0-3.4) and a NPV of 100% (95%CI 96.6-100). In case the patient who was lost to follow-up is counted for as a diagnostic failure, the failure rate increases to 1.1% (95%CI 0.05-5.8).

CTPA

CTPA was indicated in 420 patients (81%); 334 had a CDR indicating recurrent PE likely and 86 patients had a CDR indicating recurrent PE unlikely but an abnormal D-dimer test result. Protocol violations occurred in 11 patients. In eight patients CTPA was performed, despite an unlikely CDR result without D-dimer testing - and no PE was detected - and in three patients CTPA was indicated but not performed. In one of these latter patients, DVT was detected during follow-up (Table 3, patient 1). In total 425 patients underwent CTPA and recurrent PE was confirmed in 172 of these patients (prevalence of recurrent

Table 3. Characteristics of patients in whom venous thrombo-embolism was detected during 3-month follow-up, despite initial exclusion of the diagnosis.

Patient				Outcome of diagnostic tests at inclusion					Follow-up
Pt.	**Sex**	**Age**	**Duration of OAC discontinuation**	**Wells (points)**	**DD**	**CTPA at presentation**	**VTE**	**Day (d)**	**Brief description**
1	Male	60	unknown	9	-*	-*	DVT	54	Deep-vein thrombosis.
2	Male	80	15 years	6	600	Alternative diagnosis: pneumonia	PE	11	CTPA: extensive bilateral thrombi.
3	Female	38	2 months	6	200	Normal	PE	61	CTPA: extensive bilateral PE.
4	Female	43	2 weeks	5.5	-*	Alternative diagnosis: infection with bronchiectasis	PE	60	CTPA: PE in the artery of the left upper lobe.
5	Female	87	3 weeks	7	1744	Alternative diagnosis: pleural effusion	PE	24	CTPA: new bilateral filling defects.
6	Female	40	2 years	4 **	-*	Normal	PE	30	V/Q during follow-up showing mismatch, same localisation as previous PE. Considered as new recurrent PE and anticoagulant treatment given
7	Male	49	3 months	7	-*	Normal	PE	28	CTPA: extensive bilateral central PE.
8	Female	65	1month	5.5	-*	Normal	PE	44	CTPA: extensive PE, patient died 11 days later attributable to PE.

Pt.: patient; OAC: oral anticoagulant treatment; DD: D-dimer; CTPA: computed tomography pulmonary angiography; PE: pulmonary embolism; DVT: deep vein thrombosis; V/Q: ventilation perfusion scintigraphy; *Test not performed. ** Patient 6. CTPA performed despite unlikely clinical probability; D-dimer test was not performed (protocol violation). During follow-up V/Q scintigraphy was performed showing a mismatch compatible with recurrent PE.

PE in patients with a PE likely probability was 43%; 143/334, 95% CI 38-48). PE was excluded by CTPA in 253 patients, of whom 207 had a normal CTPA. In 46 patients, an alternative diagnosis (e.g. pneumonia, pleural effusion or malignancy) was established. There were no non-diagnostic CTPA's in this cohort. None of the 253 patients with CTPA negative for recurrent PE were lost to follow-up. Three patients received vitamin K antagonists for other reasons than VTE and one patient was judged to have recurrent PE despite a negative baseline CTPA and received anticoagulant treatment. During 3-month follow-up, seven of the remaining 249 patients were diagnosed with recurrent VTE, according to the predefined criteria (Table 3, patient 2-8). The 3-month VTE failure

rate after negative CTPA was therefore 2.8% (7/249 patients; 95% CI 1.2-5.5), resulting in a NPV of 97% (95%CI 95-99). The majority of these failures occurred 1-2 months after initial investigations. In 6 patients recurrent PE was obvious with a new location or new extensive filling defects and in an additional patient PE was classified as recurrent PE (Table 3, patient 6). Five of the eight patients with recurrent VTE had active malignancy. Overall 22 patients died during follow-up of whom one patient of fatal PE (Table 3), 1/513, 0.2% (95% CI 0.01-1.0%). And 1/249 (0.4%; 95% CI 0.02-1.9%) of patients with negative CTPA died. Overall, the 3-month failure rate of the designated strategy including CDR, D-dimer and CTPA was 7/513 (1.4%; 95% CI 0.6-2.7), and 8/516 (1.6%; 95%CI 0.7-2.9) when considering all included patients, including three patients treated with anticoagulants during follow-up for other reasons than PE. The complete diagnostic algorithm could be completed in 505 patients (98%).

DISCUSSION

The present diagnostic strategy in patients with clinically suspected recurrent PE was effective. It was feasible in 98% of patients and excluded recurrent PE in 17% patients by an unlikely clinical probability combined with a normal D-dimer test, without recurrent VTE at follow-up. After a normal CTPA, patients with high risk of recurrent PE (patients had either likely probability by the CDR or an abnormal D-dimer test) had an absolute 2.8% recurrent VTE risk during 3-month follow-up. Of note, only one patient (0.4%) in whom recurrent PE developed had a fatal recurrent event. This figure is low and compares well with the 0.5% fatal PE, observed in an earlier study by our group involving a majority of patients presenting with a first episode of suspected acute PE.[5] Admittedly, the observed overall VTE recurrence rate is higher than the 1.2% (95% CI 0.6-2.0) after normal CTPA, described in a recent meta-analysis in patients with suspected PE. In that meta-analysis, the majority of patients had presented with a first episode of suspected PE.[12] There are likely several explanations for this difference. First, all patients who went for CTPA had a substantial risk of recurrent PE despite normal initial testing, since they already proved to be relatively thrombogenic by their first PE and had a likely clinical probability for a recurrent PE (high CDR or elevated D-dimer level). Second, six of eight recurrent events occurred at least 1-2 months after initial presentation and five of eight patients had active malignancy. Taken together, the observed VTE incidence is most likely the real risk in these patients, rather than a failure of the diagnostic strategy. It remains to be demonstrated whether the safety of excluding recurrent PE by alternative diagnostic algorithms, e.g. with performance of compression ultrasonography after normal CT, can be increased. Although ultrasonography will detect new DVT, the question remains if additional testing will avoid recurrent PE events and mortality. It should be

noted that ultrasonography had no additional value after a negative CTPA in an overall population suspected of PE including recurrent PE.[12]

This study confirms previous observations indicating that recurrent PE can be safely ruled out in case of an unlikely clinical probability assessed with the Wells rule and a normal D-dimer test result. Recurrent PE could be excluded in approximately one-fifth of our study population without the need for radiological imaging. This is slightly lower compared to patients with a first episode of PE, but still leads to the exclusion of PE without the need of additional imaging.[13]

The incidence of PE in patients with an unlikely or likely clinical probability for recurrent PE was 22% and 43% respectively, indicating that a CDR is of diagnostic value in the setting of suspected recurrent PE. The ability to distinguish patients with an unlikely and likely clinical probability was comparable to that in patients with a suspected first PE in which an incidence of 15% was seen in patients with an unlikely probability and 43% in patients with likely probability.[13]

Strengths of this study include the large cohort of patients suspected of recurrent PE. Also, the number of protocol violations was low (3%). We included patients from academic and non-academic hospitals and the baseline characteristics were comparable to other PE-outcome studies.[9,11,13] The diagnostic algorithm could be completed in 98%, which was similar in comparison with previous diagnostic outcome studies.[5] Some additional aspects require comment. First, the possibility of false-positive CTPAs, resulting in over diagnosis of recurrent PE, was not assessed. CTPA at time of stopping anticoagulant treatment after the first PE was not available as baseline-imaging test, and therefore old thrombi could have been judged to represent acute PE. It has been estimated that about 20-50% of patients have residual thrombus on CTPA, 6 months after diagnosis of PE.[10,14,15] However, the mean time since the prior PE in the present study was three years and importantly, the observed prevalence of objectively confirmed recurrent PE (33%) is in line with previous studies, this is in our view supportive of a true incidence of recurrent PE (27-40%).[9,11] Second, in spite of efforts, we have no recording of how many patients had a previous CTPA for comparison. Third, since the clinical decision rule includes the item "history of VTE", all patients scored at least 1.5 points. As a result, fewer patients could be classified as PE unlikely then is the case in patients suspected of a first PE (35 vs. 72%).[13] Despite this, the combination of CDR and a normal D-dimer test result was present in 17% compared to 23% in patients with suspicion of first PE.[13] Fourth, a large proportion of patients with suspected recurrent PE on anticoagulant treatment were excluded from this analysis. CDRs are not validated in these patients and sensitivity of D-dimer tests is decreased during anticoagulant treatment.[16,17] Therefore, direct imaging tests (CTPA) are recommended in these patients. The study mostly involved outpatients, therefore extrapolating the results to inpatients is difficult. And finally, despite the relatively large patient cohort, the upper limits of the CIs are still wide.

In conclusion, this study demonstrates that a diagnostic strategy, with a simple algorithm is effective in patients with clinically suspected recurrent acute PE. The diagnostic algorithm safely excluded recurrent PE based on a very low risk of fatal recurrent PE during follow-up and given the high a priori risk in these patients.

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