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Article type : Original Article

External validation of the YEARS diagnostic algorithm for suspected pulmonary embolism

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Word count : 2364

Abstract word count : 250

Tables: 3

Figures: 2

Essentials

- The YEARS diagnostic algorithm was developed to reduce the proportion of patients with suspected PE who need CTPA.
- We performed an external validation of this algorithm in three previous prospective studies of outpatients with suspected PE.
- Overall the YEARS algorithm allowed safely ruling out PE, with a low 3-month thromboembolic risk.
- Caution may be needed in patients with no YEARS items and D-dimer levels < 1000 ng/mL but above the age-adjusted cutoff.

Abstract

Background: Validated diagnostic algorithms are used to manage patients with suspected pulmonary embolism (PE). The recently published YEARS study proposed a simplified diagnostic strategy to reduce the use of computed tomography pulmonary angiography.

Objectives: To externally validate this strategy in an independent cohort.

Methods: We analyzed data from three previous prospective cohort studies of outpatients with suspected PE. We retrospectively applied the YEARS algorithm. The three YEARS clinical criteria are: clinical signs of deep vein thrombosis, hemoptysis, and PE as the most likely diagnosis. If zero YEARS criteria are met, a D-dimer < 1000 ng/mL will rule out PE. If ≥1 YEARS criteria are met, a D-dimer < 500 ng/mL will rule out PE.

Results: Of the 3314 patients, 731 (22.1%) had PE. Applying the YEARS diagnostic algorithm, 1423 (42.9%) patients could have had PE ruled out without imaging. Of these patients, 17 (1.2%; 95% CI 0.8 – 1.9) were diagnosed with PE at initial testing. All 17 had no YEARS item and a D-dimer < 1000 ng/mL. All 17 had a D-dimer level above their age-adjusted cutoff. Among the 272 patients with no YEARS criteria and a D-dimer < 1000 ng/mL but above their age-adjusted D-dimer cutoff, PE was diagnosed in 6.3% (17/272; CI 3.9 - 9.8%).

Conclusion: We provide external validation of the YEARS diagnostic algorithm in an independent cohort. The rule appears to safely exclude PE. However, caution is required in patients with no YEARS item and a D-dimer < 1000 ng/mL but above their age-adjusted D-dimer cutoff.

Keywords: pulmonary embolism, D-dimer, diagnosis, venous thromboembolism, computed tomography.

Introduction/Background

Patients with clinically suspected pulmonary embolism (PE) should be managed according to a validated diagnostic algorithm. These algorithms include a clinical decision rule to determine pretest probability, D-dimer testing with subsequent computed tomography pulmonary angiography (CTPA) if indicated.[1] However, adherence to diagnostic algorithms varies. Challenges include cumbersome prediction rules and inconvenience of sequential testing. Additionally, increasing availability and use of CTPA has resulted in over-testing with a decreasing prevalence of PE in patients referred for imaging as well as overdiagnosis of subsegmental PE.[2,3]

The combination of a non-high pretest probability and negative D-dimer test excludes a PE without the need for additional imaging.[4] Use of this algorithm was shown to avoid imaging in 32% of patients with clinically suspected PE.[5,6] Use of an age-adjusted D-dimer cut-off in patients with a non-high clinical probability was prospectively studied and resulted in a further 11.2% absolute decrease in the need for CTPA, i.e. PE could be excluded in 40% of patients without imaging.[7]

In the YEARS study, a simplified diagnostic strategy was proposed in which three clinical elements of the Wells score were used along with differential D-dimer cutoff values.[8] This was prospectively evaluated in 12 hospitals in the Netherlands and resulted in a 14% absolute reduction in the use of CTPA imaging as compared with a conventional strategy, without altering the safety outcome, i.e. the rate of venous thromboembolic events (VTE) at three months, so-called “failure rate”. However, before recommending the use of this simplified management strategy in a clinical setting, further external validation with use of an independent cohort was lacking. We aimed to fill this knowledge gap by conducting a post-hoc analysis of previous PE diagnostic studies.

Design and Methods

Patients and setting

We analyzed combined data from three prospective management outcome studies that included a total of 3414 outpatients with suspected PE.[6,9,10] These outcome studies were all designed to evaluate diagnostic strategies for PE, comprising of a sequential assessment of clinical probability, plasma D-dimer measurement, lower limb venous compression ultrasonography (CUS), and CTPA with some variations described below. All consecutive outpatients admitted to the participating emergency departments were included if they had a clinical suspicion of PE defined as acute onset of new or worsening shortness of breath or chest pain without any other obvious etiology. Written informed consent was obtained from all patients. All three studies were multicenter studies conducted in Belgium, France, and Switzerland. [6,9,10]

Clinical probability assessment was performed using the Geneva score in the first two studies, and the revised Geneva score in the third study. D-dimer was performed in patients with a non-high clinical probability. Only patients with a positive D-dimer (> 500ng/mL) or a high clinical probability underwent further testing. The first study was conducted between October 2000 and June 2002 and therefore single-detector CTPA was performed in the majority of patients.[9] The second study conducted between August 2002 and November 2003 used multi-detector CTPA.[10] Finally, the third study performed between January 2005 and August 2006 had a randomized non-inferiority design comparing a strategy with multi-detector CTPA with or without CUS.[6] Therapeutic anticoagulation was initiated in patients with confirmed PE, while the rate of VTE was assessed at 3 months in patients left untreated following a negative diagnostic work-up.

The YEARS algorithm

The YEARS diagnostic algorithm has been outlined in the original study paper[8], and is depicted in Figure 1. In summary, patients with clinically suspected PE are evaluated based on three clinical criteria: clinical signs of deep vein thrombosis (DVT), hemoptysis, and PE as the most likely diagnosis. If zero criteria are met, a D-dimer < 1000 ng/mL will rule out a PE, while a D-dimer ≥ 1000 ng/mL results in the need for imaging. If 1 or more of the clinical criteria are met, a D-dimer < 500 ng/mL will rule out PE, while a D-dimer ≥ 500 ng/mL results in the need for imaging.

Data Analysis

Of the 3414 patients included in our evaluation, 100 (2.9%) were excluded due to missing data, leaving 3314 patients for analysis. All three YEARS criteria and D-dimers were part of the prospectively collected data in the three studies, including the item "PE as the most likely diagnosis" which had been assessed and collected prospectively. We determined the proportion of patients with no YEARS criteria. For these patients, we then recorded the number of patients with a D-dimer < 1000 ng/mL who would have a PE ruled out without imaging. As an extra step, for patients > 50 years with a D-dimer < 1000 ng/mL, we stratified patients based on the age-adjusted D-dimer cutoff (D-dimer < age x 10). For patients with one or more YEARS criteria, we determined the number of patients with a D-dimer < 500 ng/mL who would have PE ruled out without imaging. We also stratified the patients based on the number of positive YEARS items and calculated the proportion of patients diagnosed with a PE in each group.

For all patients who would have had PE ruled out by the YEARS algorithm, we recorded the number of patients who were diagnosed with PE at initial testing or within a 3 month follow-up period.

Results

General characteristics of the patients are shown in Table 1. The hypothetical diagnostic management according to the YEARS algorithm is described in Figure 2.

Overall population

Overall, 1783 (53.8%) patients had no YEARS items and 1531 (46.2%) had ≥ 1 YEARS items. PE was diagnosed in 731 (22.1%) of the total cohort of 3314 patients: in 151 (8.5%) of 1783 patients with no YEARS item and 580 (37.8%) of 1531 patients with ≥ 1 YEARS items. Table 2 outlines the rates of PE diagnosis based on individual YEARS items, as well as on cumulative number of YEARS criteria met. We found that compared to the 8.5% PE prevalence in patients with 0 YEARS criteria, the prevalence was of 33%, 57%, and 75% for patients with 1, 2, or 3 positive YEARS criteria, respectively.

Of the 1423 (42.9%) patients in whom PE would have been excluded without use of CTPA on the basis of a negative YEARS strategy, 17 patients (1.2%, 95% CI 0.8 – 1.9) were diagnosed with PE at initial testing. No additional PEs were diagnosed during the follow-up (Figure 2). The overall failure rate (VTE rate at three months) of the YEARS model in our cohort was therefore of 17/1423 (1.19%, 95% CI 0.8-1.9%). All of these 17 patients were in the group of 1142 patients with 0 YEARS criteria and a D-dimer < 1000 ng/mL.

Patients with no YEARS items

We further stratified the 1142 patients with no YEARS item and D-dimer < 1000 ng/mL based on the age-adjusted D-dimer cutoff. Of the 870 patients with 0 YEARS criteria and a negative age-adjusted D-dimer, 0 patients were diagnosed with PE (0.0%; CI 0.0-0.4%). All 17 PE patients were among the 272 patients with 0 YEARS criteria and D-dimer ≥ the age-adjusted D-dimer cutoff and < 1000 ng/mL (6.3%; 95% CI 3.9 - 9.8%). The median age of the 1142 patients with no YEARS items and D-dimer < 1000 ng/mL was of 53 years [IQR 39-67] , and 609/1142 (53%) were > 50 years old. The median age of the 870 patients with no YEARS items, and D-dimer below the age-adjusted cutoff was of 51 years [IQR 39-66] , and 452/870 (52%) were > 50 years old. The median age of the 272 patients with no YEARS items, and D-dimer below 1000 ng/mL but above the age-adjusted cutoff was of 56 years [IQR 41-69] , and 157/272 (58%) were > 50 years old. The most proximal location of PE was lobar in 2, segmental in 11, multiple subsegmental in 2; the remaining 2 patients were diagnosed with PE based on the presence of proximal DVT on lower limb CUS.

Discussion

Our study provides external validation of the YEARS algorithm. Using this diagnostic strategy, 42.9% of patients would have PE excluded without the need for imaging, with an overall failure rate of 1.2% (95% CI 0.8–1.9%). This is below the proposed updated diagnostic safety threshold of 2.0%.[2]

The YEARS algorithm has the potential to significantly reduce CTPA use. In the YEARS study, the YEARS algorithm resulted in an absolute decrease of 14% in the rate of patients requiring CTPA compared to a standard algorithm using the Wells' score and a fixed D-dimer threshold <500 ng/mL. The failure rate in our study was overall in line with the one reported in the YEARS study of 0.6% (95% CI 0.4-1.0%).[8] In patients with no YEARS items and D-dimer < 1000 ng/mL, the overall three-month VTE rate in our cohort was low at 17/1142 (1.6%; 95% CI: 0.9-2.4%). However, we observed a higher failure rate of the YEARS algorithm for patients with no YEARS items but a D-dimer between their age-adjusted cut-off and 1000 ng/mL (17/272; 6.3%, 95%CI: 3.9-9.8%). Of note, the prevalence of PE in this specific subgroup of patients was not reported in the YEARS study. The efficiency gain of the 1000 ng/mL cutoff compared to the age-adjusted D-dimer cutoff was a hypothetical absolute 15% reduction (913/1783 to 641/1783) in the proportion of patients who need CTPA, which was nevertheless achieved at the expense of a higher failure rate (17/1142 compared to 0/1142). This means that among the 272 patients with D-dimer levels above the age-adjusted cutoff in whom imaging could have been avoided by the YEARS model, one in sixteen would have a missed PE diagnosis. Admittedly, our results are obtained in a retrospective analysis. It is impossible to comment on what would have been the outcome should these patients not have undergone CTPA and been left untreated based on the YEARS algorithm alone. The favorable 3-month outcome rate observed in the YEARS study could indicate that the algorithm is able to detect most clinically relevant PE. Noteworthy, the most proximal location of the 17 PE which would have been missed by the YEARS algorithm in our study was lobar in 2, segmental in 11, multiple subsegmental in 2, and PE diagnosis based on proximal DVT in the remaining 2 patients. An isolated subsegmental PE on CTPA was not sufficient to establish diagnosis. Another important point to highlight is that the prevalence of PE was lower in the YEARS study (13%) compared to our cohort (22%). In our study, 8.5% of patients with no YEARS item had PE diagnosed as compared to 3.4% in the YEARS study. The higher prevalence in our cohort could have contributed to a higher failure rate in patients with zero YEARS item and D-dimer <1000 ng/mL.

In a post-hoc analysis of the YEARS study by van der Pol et al., various associations of the YEARS model and the ADJUST model were analysed. The authors presented four different scenarios: patients managed according to the YEARS algorithm, then patients aged ≥ 50 years managed according to three hypothetical scenarios: 1/ using the age-adjusted D-dimer cutoff in patients with ≥1 YEARS items, 2/ using the age-adjusted D-dimer cutoff in all patients and 3/ using the age-adjusted cutoff as validated in the ADJUST-PE study, i.e. in patients with a non-high pretest probability (Wells score ≤4). Their conclusion was that the additional yield of imbedding the age-adjusted cutoff in the YEARS algorithm in any scenario was marginal. They also concluded that this was obtained at the expense of a higher failure rate. Nevertheless, it is not a surprise that using the age-adjusted cutoff in patients with higher pretest probability (first scenario) or without any pretest probability assessment (second scenario) increases the failure rate. In the third scenario where the actual ADJUST algorithm was used, i.e. age-adjusted D-dimer in patients with a unlikely pretest probability according to the Wells rule, the failure rate was low. Altogether, because of the difference in PE prevalence between the two cohorts (13% versus 22%), and the difference in the hypothetical combinations of algorithms used, the data presented by van der Pol et al. cannot be directly compared to our data.

Strengths of our study include the use of a large database of patients in centers independent from that of the YEARS study. A standardized diagnostic algorithm and follow-up was used to gather information for this database. There was independent adjudication of events. One potential concern raised for the YEARS study was the prior knowledge of the D-dimer result at the time of pretest probability assessment. However, our study is reassuring in that regards, given that data needed to assess the YEARS items were prospectively collected without knowledge of D-dimer result and without knowledge of the YEARS rule. The three YEARS items were chosen as they were found to be the most predictive items of the Wells score for PE. Our study provides further data on the yield of these individual items; hemoptysis was the least predictive, whereas 47% of patients with signs of DVT and 42% of patients with PE as the most likely diagnosis were found to have PE. We also document an increasing rate of PE diagnosis with increasing number of positive YEARS items, providing external accuracy validation data.

Limitations of our study include missing values, of which the majority was documentation of an alternative diagnosis and PE as the most likely diagnosis. However, the number of patients excluded for this was small, at only 2.9% of the whole cohort. In this database, the Geneva score was used for pretest probability

assessment and thus not every patient was required to have a D-dimer test if they had a high pretest probability, explaining our 17 missing results for D-dimer values. Moreover, although it was prospectively collected, the likelihood of an alternative diagnosis to PE had no role in the diagnostic management, which could have impacted assessment of this variable by the attending physicians.

In summary, we were able to externally validate the YEARS algorithm. Overall, the rule appears to safely exclude PE. However, caution is required in patients with no YEARS items and a D-dimer greater than their age-adjusted D-dimer cutoff, especially in centres with a higher prevalence of PE. A large international individual patient level data meta-analysis of available diagnostic studies for PE is currently being undertaken and will shed further light on tailoring diagnostic strategies (Prospero trial registration: ID 89366).[11]

Acknowledgements

The CT-EP2 and the CT-EP4 studies were supported by the following grants from the Swiss national Research Foundation: 32-61773.00 and 32-00BO-105988. The CT-EP3 study was supported by a grant from the Hirsch Foundation.

Dr. Le Gal Chair on Diagnosis of Venous Thromboembolism from the Department of Medicine at the University of Ottawa.

Author contributions

M. Eddy, H. Robert-Ebadi, M. Righini and G. Le Gal contributed to the design of the study, the acquisition, and the interpretation of the data. L. Richardson, T. Moumneh, F. Verschuren, M. Bellesini, and G. Meyer contributed to the interpretation of the data. M. Eddy drafted the work. All authors revised the work critically for important intellectual content and approved the final version to be published. H. Robert-Ebadi, M. Righini and G. Le Gal had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis

Conflicts of interest

The authors report no conflicts of interest relevant to this work.

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Table 1. Baseline characteristics of the study population.

Characteristics	**Patients (n = 3314)**
Mean age (years)	60 (+/- 19)
Women	56.9%
Chest pain	2257 (68.1%)
Dyspnea	2316 (69.9%)
Hemoptysis	159 (4.8%)
History of VTE	581 (17.5%)
Cancer	282 (8.5%)
Signs/symptoms of DVT	376 (11.3%)
Immobilization or surgery	179 (5.4%)
PE as most likely diagnosis	1300 (39.2%)
Estrogen use (OCP)	198 (6.0%)

VTE: venous thromboembolic disease, DVT: deep vein thrombosis, OCP: oral contraceptive pill.

Table 2. Rates of pulmonary embolism diagnosis based on YEARS criteria.

	Patients, n (%)	**PE confirmed, n (%)**
YEARS criteria		
Signs of deep vein thrombosis	376 (11.3%)	178/376 (47%)
Hemoptysis	159 (4.8%)	38/159 (24%)
PE as most likely diagnosis	1300 (39.2%)	540/1300 (42%)
Total Number of YEARS criteria		
0	1783 (53.8%)	151/1783 (8.5%)
1	1235 (37.3%)	410/1235 (33.2%)
2	288 (8.7%)	164/288 (56.9%)
3	8 (0.2%)	6/8 (75%)

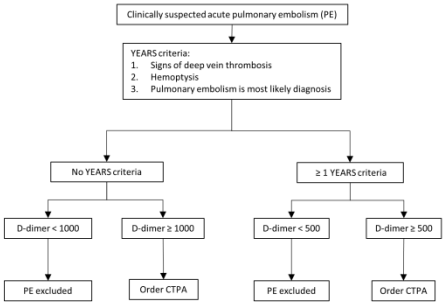
Table 3. Characteristics of the 17 patients with no YEARS items and D-dimer levels < 1000 ng/mL but > AADD cutoff

Patients	Age (years)	Previous VTE	Cancer	Immobilization or surgery	Chest pain	Shortness of breath	Heart rate (bpm)	Clinical probability (Simplified Geneva score)	D-dimer levels (ng/mL)	Objectively confirmed VTE event
1	49	Yes	No	No	No	No	88	Low	520	Proximal DVT
2	25	No	No	No	Yes	No	78	Low	523	Segmental PE
3	58	No	No	No	Yes	Yes	80	Low	668	Lobar PE
4	32	No	No	No	Yes	Yes	77	Low	674	Segmental PE
5	68	Yes	No	No	Yes	Yes	98	Low	697	Segmental PE
6	28	Yes	No	No	Yes	Yes	79	Intermediate	714	Segmental PE
7	58	No	No	No	Yes	No	110	Low	733	Segmental PE
8	53	No	No	No	Yes	Yes	76	Low	800	Segmental PE
9	80	No	No	No	Yes	No	70	Low	813	Segmental PE
10	42	No	No	No	Yes	No	89	Low	866	Segmental PE
11	66	No	No	No	Yes	Yes	100	Low	884	Segmental PE

12	37	No	No	No	Yes	Yes	70	Low	890	Multiple subsegmental PE
13	51	No	No	No	Yes	No	80	Low	909	Segmental PE
14	49	No	No	No	Yes	Yes	81	Low	927	Multiple subsegmental PE
15	88	Yes	No	No	No	Yes	147	Intermediate	946	Lobar PE
16	42	No	No	No	Yes	No	88	Low	976	Proximal DVT
17	56	No	No	No	Yes	Yes	97	Intermediate	983	Segmental PE

VTE: venous thromboembolism; bpm: beats per minute; DVT: deep vein thrombosis; PE: pulmonary embolism

Figure 1



External validation YEARS in CTEP234

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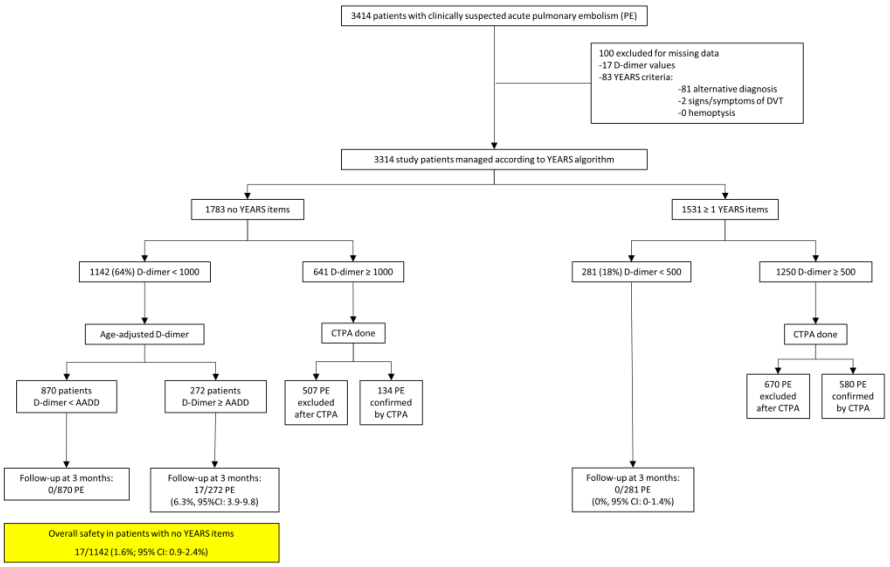

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