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ORIGINAL ARTICLE

External validation of the YEARS diagnostic algorithm for suspected pulmonary embolism

Maggie Eddy[1] | Helia Robert-Ebadi[2] | Lydia Richardson[3] | Marta Bellesini[2] | Frank Verschuren[4] | Thomas Moumneh[5] | Guy Meyer[6] | Marc Righini[2] | Grégoire Le Gal[7,8]

[1]Internal Medicine, Comox, BC, Canada

[2]Division of Angiology and Hemostasis, Faculty of Medicine, Geneva University Hospitals, Geneva, Switzerland

[3]Department of Family Medicine, Montfort Hospital, Ottawa, ON, Canada

[4]Emergency Department, Saint-Luc University Hospital, Brussels, Belgium

[5]Department of Emergency Medicine, University Hospital of Angers, Angers, France

[6]Department of Respiratory Disease, Hôpital Européen Georges Pompidou, APHP, Université Paris Descartes, Paris, France

[7]Department of Medicine, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada

[8]EA3878 University of Brest, Brest, France

Correspondence
Grégoire Le Gal, Division of Hematology, The Ottawa Hospital, General Campus, 501 Smyth Rd, Box 201A, K1H 8L6, Ottawa, ON, Canada.
Email: glegal@ohri.ca

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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% confidence interval 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; 95% confidence interval 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

computed tomography, D-dimer, diagnosis, pulmonary embolism, venous thromboembolism

Maggie Eddy and Helia Robert-Ebadi contributed equally.

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1 | 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 overtesting, 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 cutoff 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 (ie, 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 compared with a conventional strategy, without altering the safety outcome (ie, the rate of venous thromboembolic events [VTE] at 3 months), the 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.

Essentials

- The YEARS algorithm was developed to reduce CTPA in patients with suspected PE.
- This work provides external validation in three previous prospective cohorts.
- Overall the YEARS algorithm allowed safely ruling out PE, with a low 3-month thromboembolic risk.
- Caution is needed when no YEARS item and D-dimer <1000 ng/mL but above the age-adjusted cutoff.

2 | DESIGN AND METHODS

2.1 | 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 a sequential assessment of clinical probability, plasma D-dimer measurement, lower limb venous compression ultrasonography (CUS), and CTPA with some variations described in the following section. 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 (> 500 ng/mL) or a high clinical probability underwent further testing. The first study was conducted between October 2000 and June 2002; therefore, single-detector CTPA was performed in the majority of patients.[9] The second study, conducted between August 2002 and November 2003, used multidetector CTPA.[10] Finally, the third study, performed between January 2005 and August 2006, had a randomized non-inferiority design comparing a strategy with multidetector CTPA with or without CUS.[6] Therapeutic anticoagulation was initiated in patients with confirmed PE, whereas the rate of VTE was assessed at 3 months in patients left untreated following a negative diagnostic workup.

2.2 | 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 most likely diagnosis. If zero criteria are met, a D-dimer < 1000 ng/mL will rule out a PE, whereas a D-dimer ≥ 1000 ng/mL results in the need for imaging. If one or more of the clinical criteria are met, a D-dimer < 500 ng/mL will rule out PE, whereas a D-dimer ≥ 500 ng/mL results in the need for imaging.

2.3 | Data analysis

Of the 3414 patients included in our evaluation, 100 (2.9%) were excluded because of 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 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

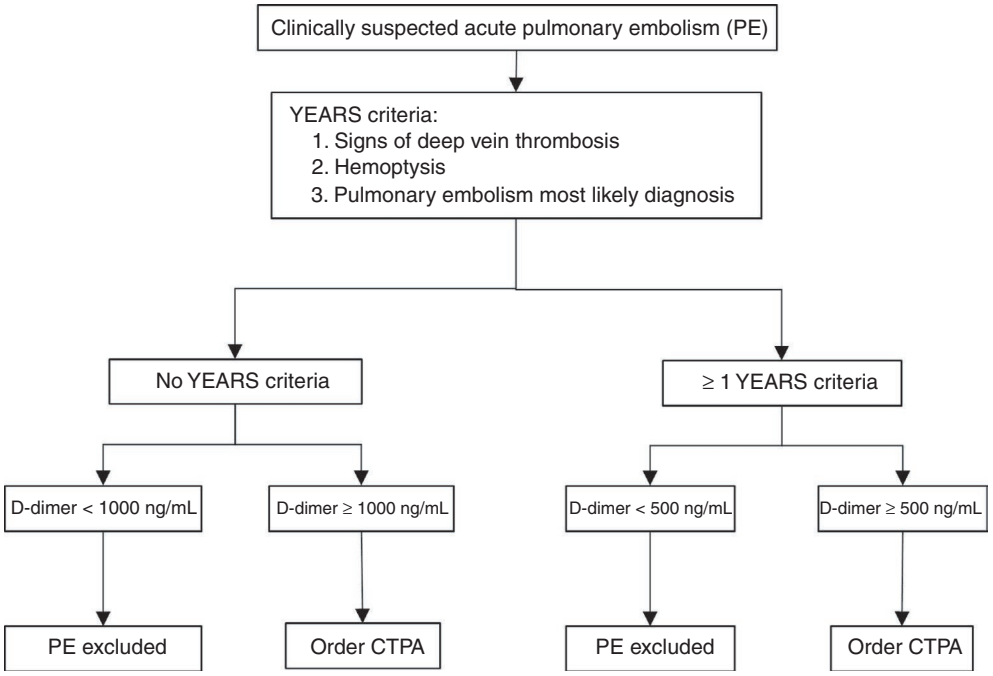

FIGURE 1 The YEARS diagnostic algorithm

of patients with a D-dimer < 1000 ng/mL who would have 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 × 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.

3 | 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.

3.1 | 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 one, two, or three positive YEARS criteria, respectively (Table 2).

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%)

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

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% confidence interval [CI] 0.8-1.9) were diagnosed with PE at initial testing (Table 3). No additional PEs were diagnosed during the follow-up (Figure 2). The overall failure rate (VTE rate at 3 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.

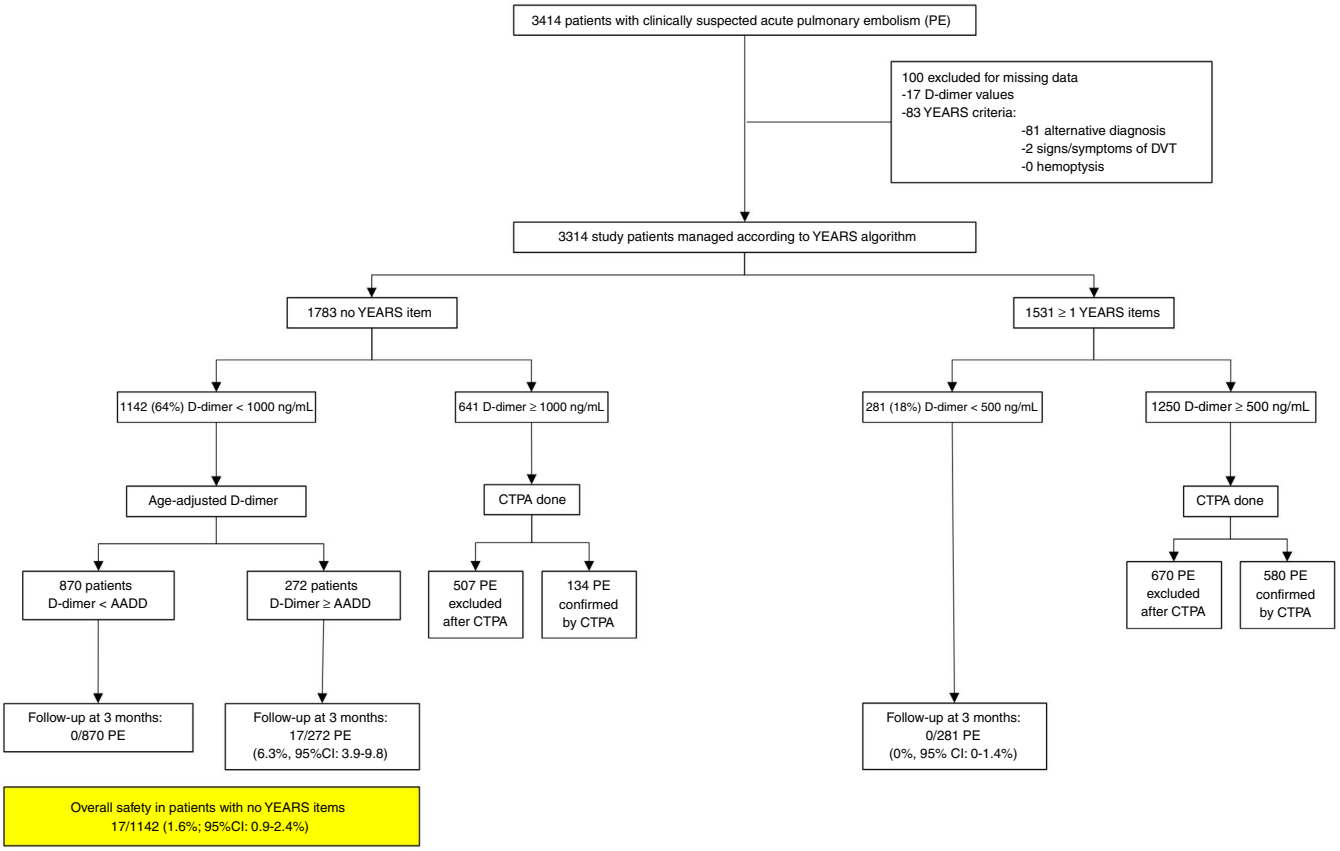

FIGURE 2 Study flowchart according to the YEARS algorithm and to the age-adjusted D-dimer cutoff in patients with no YEARS item.

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 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%)

3.2 | 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%; 95% 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 [interquartile range 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 [interquartile range 39-66], and 452/870 (52%) were > 50 years old. The median age of the 272 patients with no YEARS items, and D-dimer < 1000 ng/mL but above the age-adjusted cutoff, was of 56 years [interquartile range 41-69], and 157/272 (58%) were >50 years old. The most proximal location of PE was lobar in two, segmental in 11, multiple subsegmental in two; the remaining two patients were diagnosed with PE based on the presence of proximal DVT on lower limb CUS (Table 3).

4 | 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 with a standard algorithm using the Wells score

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

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

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 3-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 cutoff 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 with 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 with 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 16 would have a missed PE diagnosis.

Admittedly, our results are obtained in a retrospective analysis of prospectively collected data. 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 two, segmental in 11, multiple subsegmental in two, and PE diagnosis based on proximal DVT in the remaining two 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 with our cohort (22%). In our study, 8.5% of patients with no YEARS item had PE diagnosed compared with 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 analyzed. The authors presented four different scenarios: patients managed according to the YEARS algorithm, then patients aged ≥ 50 years managed according to three hypothetical scenarios: (a) using the age-adjusted D-dimer cutoff in patients with ≥ 1 YEARS items, (b) using the age-adjusted D-dimer cutoff in all patients, and (c) using the age-adjusted cutoff as validated in the ADJUST-PE study (ie, 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 (ie, age-adjusted D-dimer in patients with an 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% vs 22%), and the difference in the hypothetical combinations of algorithms used, the data presented by van der Pol et al cannot be directly compared with 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 regard, 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 because 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 centers 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]

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CONFLICT OF INTEREST

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

AUTHOR CONTRIBUTIONS

Maggie Eddy, Helia Robert-Ebadi, Marc Righini, and Grégoire Le Gal contributed to the design of the study, the acquisition, and the interpretation of the data. Lydia Richardson, Thomas Moumneh, Frank Verschuren, Marta Bellesini, and Guy Meyer contributed to the interpretation of the data. Maggie Eddy drafted the work. All authors revised the work critically for important intellectual content and approved the final version to be published. Helia Robert-Ebadi, Marc Righini, and Grégoire 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.

ORCID

Grégoire Le Gal https://orcid.org/0000-0002-9253-248X

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