Diagnosis of pulmonary embolism in patients with haemoptysis: the POPEIHE study

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Shareable abstract (@ERSpublications)
Pulmonary embolism is an uncommon cause of haemoptysis. The majority of patients with haemoptysis and pulmonary embolism have segmental or subsegmental embolus distribution and are stratified as intermediate–low or low risk. https://bit.ly/4dVblM9

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Abstract

Aim To determine the prevalence and characteristics of pulmonary embolism (PE) in patients presenting with haemoptysis. Additionally, we assessed the efficiency and failure rates of different clinical diagnostic algorithms for PE in this patient population.

Methods We enrolled consecutive adult patients who presented to nine Italian emergency departments with haemoptysis as the primary complaint. PE diagnosis was ruled out in patients with a low pre-test probability in combination with a negative age-adjusted D-dimer (referred to as the "age-adjusted" D-dimer strategy), a negative computed tomography pulmonary angiography or when a clear alternative source of bleeding was identified, along with negative findings for venous thromboembolism during a 30-day follow-up.

Results A total of 546 patients were included in the study. The prevalence of PE, including the 30-day follow-up, was 4.2% (95% CI 2.7–6.3%). The majority of these cases (78%) exhibited distal (segmental or subsegmental) emboli and there were no PE-related fatalities. The "age-adjusted" D-dimer strategy initially excluded PE in 24% of patients (95% CI 21–28%), with a failure rate of 0.8% (95% CI 0.0–4.1%). Retrospectively applied, the "clinical probability-adjusted" D-dimer strategies, specifically the YEARS and Pulmonary Embolism Graduated d-Dimer (PEGeD) algorithms, excluded PE in a significantly higher proportion (30% and 32%, respectively) compared with the "age-adjusted" D-dimer strategy ($p<0.05$ for both), with similar failure rates.

Conclusions PE is infrequent among patients presenting with haemoptysis, showing segmental or subsegmental emboli distribution. The "clinical probability-adjusted" D-dimer strategies seem to have significantly higher efficiency compared with the "age-adjusted" strategy.

Introduction

Haemoptysis refers to the expectoration of blood originating from below the glottis, typically from the lungs or the bronchial tree [1]. It can result from various causes, including infectious, neoplastic, vascular diseases and trauma [2–4]. The severity of haemoptysis can vary widely and its course is often challenging

to predict, occasionally leading to fatal outcomes [5, 6]. Most patients with haemoptysis present directly to the emergency department (ED), and emergency physicians are often the first to evaluate and manage these patients.

Haemoptysis can also result from acute ischaemic damage in a peripheral lung region due to pulmonary embolism (PE), which is among the potentially lethal causes of haemoptysis [1, 7–12]. However, the prevalence and clinical characteristics of PE in consecutive patients presenting to the ED with haemoptysis remain unknown. While established diagnostic scores for PE, such as Wells [13], Geneva [14], PE rule-out criteria (PERC) [15] and YEARS [16], include haemoptysis among their criteria, the efficiency and failure rates of the standard diagnostic workup for PE in this specific patient group are not well defined.

The POPEIHE (Prevalence of Pulmonary Embolism in patients with Haemoptysis) study is the first prospective, multicentre investigation employing a systematic diagnostic approach to determine the prevalence and clinical characteristics of PE in consecutive patients presenting to the ED with haemoptysis as their primary complaint. The study also aims to assess the efficiency and failure rates of various diagnostic algorithms to rule out PE.

Material and methods

Study design and setting

This was a prospective, multicentre, observational study conducted to determine the prevalence of PE among patients older than 18 years who presented to the ED with haemoptysis and voluntarily participated in the study protocol. The study protocol received approval from the ethical committee at each of the participating hospitals (approval no. 15954_oss). The study considered all consecutive patients with haemoptysis (cough with bloody sputum) as the main symptom of presentation who presented to the ED of nine participating hospitals from January 2020 to April 2023. These hospitals included three academic and six nonacademic institutions, each serving populations of over 200 000 inhabitants.

Outcome measures

The primary outcome was to determine the prevalence and clinical characteristics of PE. The secondary outcomes were to assess the efficiency and failure rates of various diagnostic algorithms to rule out PE.

Study patients

Patients were considered for inclusion in the study prior to completing the diagnostic workup, often before definitively establishing whether the origin of blood was from the upper or lower airways. Specifically, patients were included in the study if their clinical history suggested that the source of the blood was from the lungs or bronchial tree, *i.e.* when patients reported or showed the emission of bright red blood or blood-streaked sputum from the mouth with cough.

Patients who met any of the following criteria were excluded from the study: those under 18 years of age, pregnant patients, those with terminal illnesses expected to have a prognosis of less than 3 months or those unable to participate in the 30-day follow-up or provide informed consent. Written informed consent was obtained from all recruited patients. A 30-day follow-up assessment was conducted through ambulatory visits. In cases where the 30-day follow-up could not be completed (during the COVID pandemic waves from 2020 to 2022), we attempted to contact the patients by telephone using a standardised interview. When a telephone interview was not feasible, hospitalisation records, scheduled outpatient visits and any re-admissions to EDs within the region were reviewed. If no re-admissions or follow-up information were found, the patient was considered lost to follow-up.

Study assessments

The patient evaluation process adhered to the study protocol (trial registration number on clinicaltrials.gov: NCT06067997).

At triage, vital signs, including oxygen saturation, respiratory rate, heart rate and systolic blood pressure, were recorded. At triage, a priority code ranging from 1 (emergency) to 5 (nonurgent) was assigned based on local protocols [17]. The study physician collected patient medical histories, including age, sex, history of conditions such as hypertension, diabetes, smoking, COPD, known diseases predisposing to haemoptysis (*e.g.* upper or lower respiratory tract infections, bronchiectasis, lung cancer, atelectasis, coagulation disorders and vasculitis of pulmonary vessels) and heart diseases (*e.g.* ischaemic heart disease, atrial fibrillation and valvulopathies), renal failure and risk factors for venous thromboembolism (VTE) (*e.g.* previous VTE, recent surgery or trauma, prolonged immobilisation of 1 week or longer and active cancer). Patients were also questioned about specific signs and symptoms related to both haemoptysis (type of haemoptysis (pure

bright red blood or blood-tinged sputum), number of episodes in the last 24 h and other previous episodes) and VTE (limb pain or oedema, dyspnoea, chest pain or syncope). Information about ongoing antithrombotic therapy with antiplatelet agents, heparin or oral anticoagulants was documented.

Regarding haemoptysis, patients typically underwent arterial blood gas and routine blood testing, ear–nose–throat evaluation, including upper respiratory tract endoscopy to exclude bleeding from the upper airway (pseudo-haemoptysis) and chest radiography. Subsequently, chest computed tomography (CT) was performed based on the attending physician's clinical judgment. CT pulmonary angiography (CTPA) was reserved for patients suspected of having PE (see below) or those presenting with profuse haemoptysis as determined by the attending physician. Additionally, invasive procedures, such as diagnostic or operative bronchoscopy, bronchial artery angiography, embolisation or surgery, were performed as deemed necessary by the attending physician and consultants. To ensure the privacy and confidentiality of patient data, information was anonymised and securely stored, protected by encryption and accessible only through password-protected access.

Ascertainment of pulmonary embolism and follow-up

The diagnosis of PE adhered to the 2019 European guidelines diagnostic algorithm [18]. In patients categorised as nonhigh-risk (those with systolic blood pressure above 90 mmHg and no clinical signs of cardiovascular shock), the pre-test clinical probability of PE was determined either by the Wells score or the revised Geneva score, depending on local policy. It was dichotomously classified as "unlikely" or "likely" [14, 19]. In patients classified as "unlikely", D-dimer levels were measured during the initial evaluation, before second-level diagnostic tests, using the routinely employed quantitative assay at each participating centre, when indicated. The cut-off for a positive result was adjusted for age [20], with a negative result defined as below 500 $\mu g \cdot mL^{-1}$ in patients younger than 50 years. For each subsequent decade of age, the cut-off level increased by 100 $\mu g \cdot mL^{-1}$.

Patients with a low pre-test clinical probability ("unlikely") and a negative age-adjusted D-dimer had PE excluded and no further tests for PE were performed unless necessitated by the diagnostic process for haemoptysis or the emergence of new signs or symptoms of VTE during follow-up.

In patients with a high pre-test clinical probability ("likely") or positive D-dimer results or both, CTPA was the preferred diagnostic method. PE diagnosis was confirmed by identifying at least one intra-luminal filling defect within the pulmonary arterial tree, visible on CTPA in at least two consecutive axial slices.

In patients with a clear alternative source of bleeding (CaSB) identified during the initial diagnostic workup, such as pseudo-haemoptysis, open tuberculosis, actively bleeding endobronchial lesions or a severe pro-haemorrhagic conditions (*e.g.* acute leukaemia or severe thrombocytopenia below 20 000 $\cdot \mu L^{-1}$) or ongoing anticoagulant treatment, PE could be excluded without the need for CTPA or other second-level diagnostic tests.

At the conclusion of the initial visit, data recorded for each patient included the final diagnosis made by the attending physicians (PE *versus* other diagnosis), disposition (home discharge or hospital admission) and death in the ED. Participants were instructed to return to the ED if their initial symptoms did not improve or if new symptoms arose. According to the study protocol, no treatment strategies were predetermined; treatments were administered based on the clinical judgment of the attending physician.

Patients were followed for 30 days post-index visit through ambulatory visits. When patients were unable to attend the ambulatory visit, a phone contact and interview was performed to assess clinical outcomes. This included queries regarding hospital admissions, ED revisits and deaths. Hospital and ED charts, data from subsequent CTPA or other second-level diagnostic tests were obtained. For each patient, the final diagnosis was dichotomously adjudicated as either PE present or absent, based on 30-day follow-up data. The diagnosis was established at each participating centre by the local investigator. In patients without PE, the adjudication process assigned one of the following predefined alternative diagnoses: pseudo-haemoptysis (bleeding from the upper respiratory tract or gastro-oesophageal tract), pneumonia, malignancy, acute bronchitis, bronchiectasis, COPD, bleeding from endobronchial lesions or arteriovenous malformation of the bronchial tree, open tuberculosis, heart disease, bleeding disorders or trauma. Subsequently, the input data underwent a thorough review and discussion by a central committee comprising three expert physicians (S.V., P.N. and S.G.) to confirm the final diagnoses. For deaths occurring in patients without conclusive imaging or autopsy, diagnosis was clinical and cases of uncertainty were considered potential cases of PE.

Statistical analysis

Assuming an expected prevalence of PE of 10% [21, 22], we determined that to achieve a two-sided 95% confidence interval (CI) with a margin of error of 2.5%, a sample size of 500 patients was necessary. All participating hospitals were requested to enrol patients until this estimated sample size was reached. The prevalence of PE and the associated 95% CI were computed for the entire patient cohort, including those with a final diagnosis of pseudo-haemoptysis, as well as for other relevant subgroups. We also planned to calculate a "worst-scenario condition" considering patients lost to follow-up as affected by PE.

To compare baseline characteristics between patients with and without PE, Pearson's chi-squared or Fisher exact test (when cells had an expected value of 5 or less) were used for categorical variables, and t-test was employed for continuous variables. The nonparametric Mann–Whitney test was used for continuous variables without normal distribution.

Furthermore, the efficiency (proportion of patients in whom PE could reasonably be excluded) and the failure rate (false-negative rate) of the age-adjusted D-dimer strategy [20] were retrospectively assessed and compared with the YEARS [16] and PEGeD [23] diagnostic strategies, both employing a "D-dimer adjusted for clinical probability" approach. We used a modified YEARS algorithm, in which the item haemoptysis was not considered a high-risk feature; thus, patients with haemoptysis and without clinical signs of deep vein thrombosis (DVT) or PE as the most likely diagnosis were considered at low risk. Within them, a D-dimer value lower than 1000 $ng \cdot mL^{-1}$ excluded PE. The different diagnostic strategies were compared using the McNemar test. The diagnostic performance of D-dimer was evaluated through receiver operating characteristic (ROC) curve analysis.

Continuous variables were reported as mean±SD, while dichotomous variables were expressed as percentages±95% CI. Missing values were excluded from the analysis pairwise. The calculation of 95% CI and p-values followed the normal approximation of the binomial distribution. No adjustments were made for multiple testing. All p-values were two-sided, with statistical significance set at $p<0.05$. Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS), version 22.0 (SPSS, Chicago, IL, USA).

Results

Patients and follow-up

From January 2020 to April 2023, a total of 631 patients were considered for the study, 85 (13.5%) were excluded for various reasons (figure 1), leaving a final inclusion of 546 patients. The main demographic and clinical characteristics of the patients are summarised in table 1. The median age of the cohort was 62 years. Male patients comprised approximately two-thirds of the entire population. The most commonly associated conditions were arterial hypertension, COPD and active neoplasia. The mean value of Wells score, used in more than 90% of the cohort, was 2±1.5.

Among the entire cohort, 63 (11.4%) patients were classified as "PE likely" (see figure 1). Of these, 22 (34.9%) exhibited a clear source of bleeding at the index visit (10 with pseudo-haemoptysis, 7 with actively bleeding endobronchial lesions detected during bronchoscopy, 3 with bleeding disorders and 2 with open tuberculosis; see table 2). The remaining 41 "PE likely" patients underwent CTPA as part of their initial diagnostic workup. Among the 483 (88.6%) patients classified as "PE unlikely," 64 (13.3%) had a clear source of bleeding at the index visit (20 with pseudo-haemoptysis, 19 with bleeding endobronchial lesions, 13 with bleeding disorders, 4 with open tuberculosis and 8 with other diagnoses). In addition, 133 (27.5%) patients had PE initially excluded due to a negative age-adjusted D-dimer, while 286 (59.2%) underwent CTPA as part of their initial diagnostic evaluation. Among the 546 patients included in the study, 541 completed the 30-day follow-up and 5 were lost to follow-up. Four out of five patients lost at follow-up were at low risk with a negative D-dimer and three did not undergo CTPA. One patient was at high risk of PE and underwent CTPA, which did not show PE. Disposition from the ED included 259 patients (47.4%) being discharged, 34 (6.4%) managed in the short-term observation unit and 253 (46.3%) admitted to the hospital, including 24 (4.4%) in the intensive care units. Over the study period, 12 patients (2.2%) died: 5 during the index ED visit (2 with lung cancer, 1 with oesophageal cancer and 2 with COPD), 5 during their in-hospital stay (1 with pneumonia, 1 with congestive heart failure, 1 with COPD and 2 with lung cancer) and 2 during the follow-up period (1 with lung cancer and 1 with pneumonia).

Prevalence and characteristics of pulmonary embolism

PE was diagnosed in 23 of 546 patients (4.2%, 95% CI 2.7–6.3%), with 11 cases (2.3%, 95% CI 1.1–4%) in the "PE unlikely" group and 12 cases (19.1%, 95% CI 10.3–30.9%) in the "PE likely" group. In a

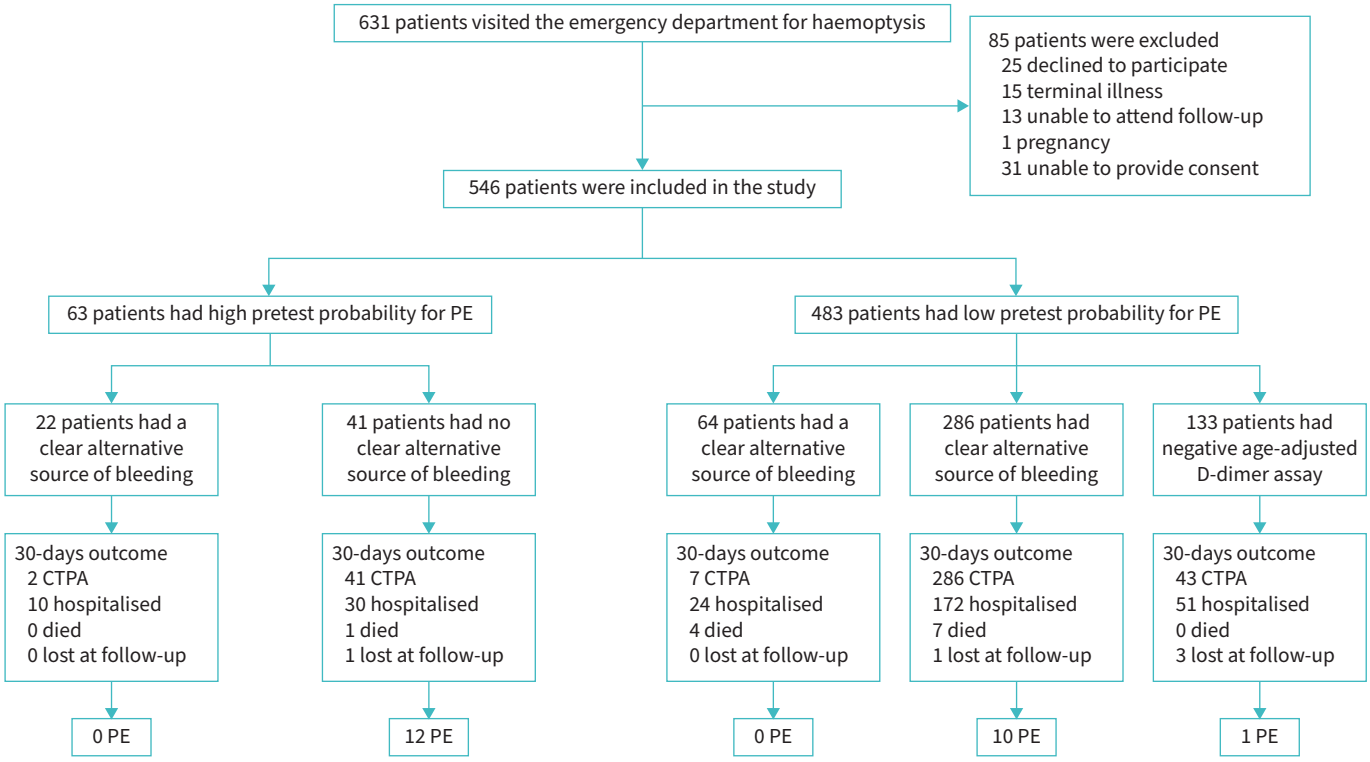

FIGURE 1 Workup for pulmonary embolism among patients admitted to the hospital for haemoptysis. PE: pulmonary embolism; CTPA: computed tomography pulmonary angiography.

"worst-case scenario", where the five patients lost to follow-up were assumed to have developed PE, the calculated prevalence would have been 5.1% (28 out of 546 patients; 95% CI 3.4–7.3%). No patient who was considered to have a CaSB (15.7%) at the index visit, in either the "PE likely" or "PE unlikely" group, developed PE or DVT during follow-up.

Among the patients with PE, the embolus was located in a lobar artery in 5 patients (21.7%), in a segmental artery in 12 patients (52.2%) and in a subsegmental artery in 6 patients (26.1%). Seven (30.4%) patients had bilateral PE and seven presented with pulmonary infarction (table 2). In patients with subsegmental unilateral PE, the CT scan was checked by a second radiologist and PE was confirmed.

The average PE Severity Index score was 88±37.8. According to the prognostic model outlined in the latest European Society of Cardiology guidelines for PE, 2 patients (8.7%) were categorised as intermediate–high risk, 13 patients (56.5%) as intermediate–low risk and 8 patients (34.8%) as low risk. No patients were classified as high risk. All patients with PE began anticoagulant therapy except for one out of six patients with subsegmental PE.

The prevalence of alternative diagnoses to PE are reported in table 3. In 94 patients (17%), the cause of haemoptysis remained undetermined.

The all-cause 30-day mortality rate was 4.3% in patients with PE and 2.1% in patients without PE (p=0.41). There was no death directly attributable to PE. The only death observed in the PE group resulted from massive haemoptysis secondary to advanced lung cancer and concomitant subsegmental PE.

Comparison of diagnostic algorithms for pulmonary embolism

Risk factors for PE were more frequent in patients with PE compared with those without (table 1). However, among the clinical findings, only signs or symptoms of DVT were more common in patients with PE. Notably, among the 23 patients diagnosed with PE, 15 (65%) did not exhibit typical clinical manifestations of PE, such as tachypnoea, tachycardia, hypotension or clinical signs or symptoms of DVT, apart from haemoptysis.

TABLE 1 Descriptive characteristics of the population enrolled in the POPEIHE study: anamnestic, therapeutic and laboratory features of the enrolled patients

Variable	Population (n=546)	Pulmonary embolism (n=23)	Nonpulmonary embolism (n=523)	p-value
Age, years (n=546)	62±18	60±20	62±18	0.23
Females (n=546)	37.7%	30.4%	37.9%	0.31
Triage code 1–2 (n=545)	15.8%	21.7%	15.5%	0.29
Comorbidities				
COPD (n=546)	21.3%	21.7%	21.3%	0.56
CAD (n=546)	13.5%	8.7%	13.7%	0.38
TDM2 (n=546)	8.7%	8%	8.7%	0.67
AH (n=546)	40.7%	43%	40.5%	0.47
CKD (n=546)	3.7%	0%	3.8%	0.41
AF (n=546)	12.1%	4.3%	12.4%	0.20
Clinical risk factors for PE				
Active cancer (n=546)	16.2%	34.8%	15.4%	0.02
Previous PE or DVT (n=546)	3.7%	21.7%	2.5%	<0.001
Active tobacco use (n=546)	37.5%	26.1%	37.9%	0.18
Surgery/fractures (within 30 days) (n=546)	1.1%	8.7%	0.7%	0.02
Immobilisation (at least 1 week) (n=546)	2.7%	17.4%	2%	<0.001
Signs of DVT (n=546)	0.9%	8.7%	0.5%	0.01
Referred pain to lower limbs (n=546)	0.4%	4.3%	0.1%	0.05
Pre-test probability				
Wells score (n=500)	2±1.5	4±2.5	2±1	<0.001
Revised Geneva score (n=46)	5.5±2.5	7±3.5	5.5±2	<0.001
Vital parameters and laboratory results				
SBP, mmHg (n=537)	139±22	132±13	139±22	0.02
Hypotension (<100 mmHg) (n=537)	1.6%	0%	1.7%	0.53
HR, beats per min (n=538)	84±16	91±19	83±15	0.24
Tachycardia (>100 beats per min) (n=538)	12.7%	21.7%	12.3%	0.18
Respiratory rate, breaths per min (n=409)	17±7	17±2	17±7	0.66
Tachypnoea (>20 breaths per min) (n=409)	12.7%	11.8%	12.7%	0.91
S_{pO_2}, % (n=538)	96±3	97±2	96±3	0.08
F_{IO_2}, % (n=538)	22±6	24±7	22±6	0.05
GCS (n=540)	15	15	15	0.57
P_{aO_2}, mmHg (n=303)	76.9±22.5	77.2±16.1	76.9±22.8	0.68
WBC, $\times 10^3 \cdot \mu L^{-1}$ (n=543)	8.86±3.67	11.3±4.5	8.8±3.5	0.47
Hb, $g \cdot dL^{-1}$ (n=526)	13.1±2.1	12.9±2.4	13.2±2.1	0.12
PLT, $\times 10^3 \cdot \mu L^{-1}$ (n=543)	244±96	269±98	243±96	0.99
INR (n=512)	1.2±0.4	1.2±0.1	1.2±0.4	0.07
D-dimer, $ng \cdot dL^{-1}$ (n=359)	1880±6566	4827±7448	1712 ±6490	0.08
Creatinine, $mg \cdot dL^{-1}$ (n=524)	0.93±0.53	0.86±0.16	0.95±0.54	0.13
Antithrombotic treatment				
Warfarin (n=546)	6.6%	0%	6.8%	0.20
Antiplatelet (n=546)	19.2%	21.7%	19.1%	0.46
LMWH (n=546)	2.8%	4.3%	2.7%	0.49
DOAC (n=546)	8.7%	8.6%	8.7%	0.68

Data are presented as percentage or mean±SD, unless otherwise stated. CAD: coronary artery disease; TDM2: type 2 diabetes mellitus; AH: arterial hypertension; CKD: chronic kidney disease; AF: atrial fibrillation; PE: pulmonary embolism; DVT: deep vein thrombosis; SBP: systolic blood pressure; HR: heart rate; S_{pO_2}: peripheral oxygen saturation; F_{IO_2}: inspiratory oxygen fraction; GCS: Glasgow coma scale; P_{aO_2}: arterial oxygen tension; WBC: white blood cell; Hb: haemoglobin; PLT: platelet; INR: international normalised ratio; LMWH: low-molecular-weight heparin; DOAC: direct-acting oral anticoagulant.

The area under the ROC curve of D-dimer was 0.79 (p<0.01 *versus* chance). Although the mean D-dimer value was 2.7-times higher in patients with PE, this difference did not reach statistical significance (p=0.08). In our cohort, the age-adjusted D-dimer strategy for PE demonstrated an efficiency of 24% and a failure rate of 0.8% (table 4, figure 2). For comparison, when we retrospectively applied the YEARS algorithm, considering "PE likely" as those with signs of DVT or with PE as the most likely diagnosis, and using different D-dimer cut-off values for "PE likely" (<500 $ng \cdot mL^{-1}$) and "PE unlikely" (<1000 $ng \cdot mL^{-1}$) patients, we observed higher efficiency (30.0%, p<0.001 *versus* age-adjusted D-dimer) with the same failure rate (0.6% *versus* 0.8%). Furthermore, retrospective application of the strategy

TABLE 2 Characteristics of patients with pulmonary embolism (PE)

Population (n=23)	Age, years	Sex	Triage code	Episodes of haemoptysis (24 h), n	Associated conditions	Clinical probability of PE	Localisation and distribution of PE	PESI	ESC risk stratification	Pulmonary infarction
Patient 1	68	F	1	4	Lung cancer	PE likely	Subsegmental - unilateral	178	Intermediate–low	No
Patient 2	85	M	3	1		PE likely	Lobar - bilateral	135	Intermediate–high	No
Patient 3	82	M	3	1	Lung cancer	PE likely	Lobar - unilateral	132	Intermediate–low	No
Patient 4	81	M	2	4	Lung cancer	PE likely	Segmental - unilateral	122	Intermediate–low	No
Patient 5	82	M	3	1	Lung cancer	PE unlikely	Segmental - unilateral	122	Intermediate–low	No
Patient 6	65	M	3	1	Lung cancer	PE likely	Subsegmental - unilateral	115	Intermediate–low	No
Patient 7	70	F	3	3		PE likely	Subsegmental - unilateral	112	Intermediate–low	No
Patient 8	83	F	3	2	Lung cancer	PE unlikely	Segmental - unilateral	110	Intermediate–low	No
Patient 9	68	M	2	3	Bronchiectasis	PE unlikely	Segmental -unilateral	108	Intermediate–low	No
Patient 10	87	F	2	1		PE unlikely	Segmental - unilateral	97	Intermediate–low	No
Patient 11	48	M	3	2	Lung cancer	PE likely	Lobar - bilateral	88	Intermediate–high	No
Patient 12	40	M	3	1	Surgery/Fracture	PE likely	Segmental - unilateral	80	Low	Yes
Patient 13	73	M	3	1		PE likely	Segmental - unilateral	79	Low	Yes
Patient 14	67	M	3	2	Surgery/Fracture	PE likely	Segmental - unilateral	77	Low	No
Patient 15	62	M	3	4	Pneumonia	PE unlikely	Segmental - bilateral	72	Intermediate–low	Yes
Patient 16	70	F	3	1	Immobilisation	PE likely	Lobar - bilateral	70	Low	No
Patient 17	38	M	2	1	Immobilisation	PE likely	Lobar - unilateral	68	Low	Yes
Patient 18	55	F	3	2		PE unlikely	Segmental - bilateral	55	Low	No
Patient 19	43	M	3	2	Pneumonia	PE unlikely	Segmental - bilateral	53	Intermediate–low	No
Patient 20	42	M	3	4		PE unlikely	Subsegmental - unilateral	51	Low	No
Patient 21	28	M	3	1		PE unlikely	Subsegmental - unilateral	38	Intermediate–low	Yes
Patient 22	22	M	3	2		PE unlikely	Segmental - unilateral	32	Intermediate–low	Yes
Patient 23	23	F	3	1		PE unlikely	Subsegmental - unilateral	24	Low	Yes

PESI: Pulmonary Embolism Severity Index; ESC: European Society of Cardiology; F: female; M: male.

outlined in the Pulmonary Embolism Graduated d-Dimer (PEGeD) study resulted in an efficiency of 32% ($p<0.05$ *versus* age-adjusted D-dimer) with the same failure rate (0.7% *versus* 0.8%).

Discussion

We found that PE affects approximately 4% of patients presenting with haemoptysis, with the majority of cases being distally located and associated with a low risk of all-cause mortality, while no patients died due to PE. Furthermore, the classic diagnostic algorithm's efficiency in excluding PE within this specific patient subset is lower compared to what has been reported in the general population of individuals suspected of having PE (24% *versus* ~30–50%) [13, 20, 21]. Finally, none of the patients initially diagnosed with a CaSB during the initial diagnostic workup experienced a PE event within the 30-day follow-up period.

TABLE 3 Causes of haemoptysis identified in the study population

Causes of haemoptysis	
Pneumonia	97 (17.8%)
Lung cancer	65 (11.9%)
Upper respiratory tract bleeding[#]	45 (8.2%)
Bronchial lesion[#]	40 (7.3%)
Bronchiectasis	37 (6.8%)
Acute bronchitis	28 (5.1%)
Bleeding disorders[#]	28 (5.1%)
Tuberculosis[#]	26 (4.8%)
Pulmonary embolism	23 (4.2%)
COPD	13 (2.4%)
Angiodysplasia/AVM[#]	11 (2.0%)
Others[¶]	39 (7.1%)
Undetermined	94 (17.2%)
Total	546

Data are presented as n (%) of the study population. AVM: arteriovenous malformations. [#]: Clear alternative source of bleeding at index visit. These patients were excluded from the standard diagnostic workup for PE at the index visit and were followed for 30 days. [¶]: Other causes include cardiac conditions (2.0%), SARS-CoV-2 infection (2.0%), cystic fibrosis (1.1%), gastro-oesophageal bleeding (1.1%), trauma (0.5%) and vasculitis (0.4%).

TABLE 4 Diagnostic accuracy measures of three diagnostic prediction models, combined with D-dimer testing, to rule out pulmonary embolism, with (95% CI)

Measure	Age-adjusted Wells	PEGeD	Modified YEARS
Sensitivity	92% (67–100%)	81% (55–95%)	92% (63–100%)
Specificity	58% (56–58%)	70% (68–71%)*	72% (70–72.%)*
Positive predictive value	11% (8–12%)	15% (10–18%)	16% (11–17%)
Negative predictive value	99% (95.0–100%)	98% (96–100%)	99% (96–100%)
Efficiency	24% (21–28%)	32% (28–36%)*	30% (26–34%)*
Failure rate	0.8% (0.0–4.1%)	1.7% (0.4–5.0%)	0.6% (0.0–3.4%)

PEGeD: Pulmonary Embolism Graduated d-Dimer. *: p<0.05 *versus* age-adjusted Wells.

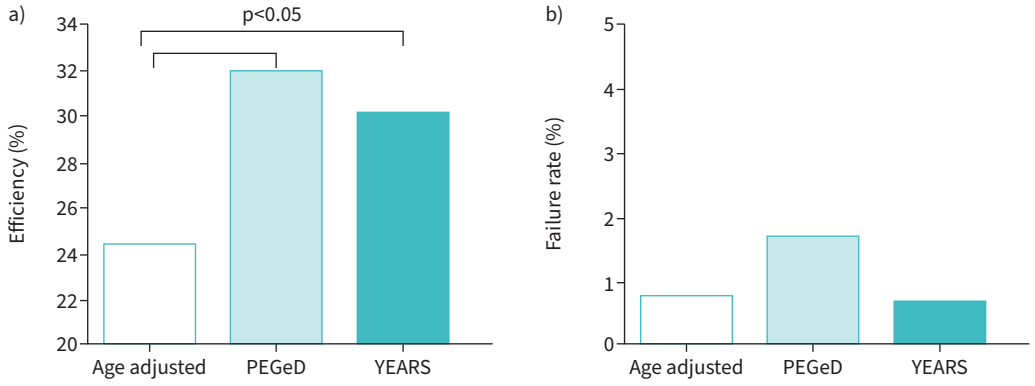

FIGURE 2 Efficiency and failure rate of the different diagnostic protocols. a) The efficiency was 24%, 32% and 30% for age-adjusted, Pulmonary Embolism Graduated d-Dimer (PEGeD) and modified YEARS, respectively. b) The failure rate was 0.8%, 0.7% and 0.6% for age-adjusted, PEGeD and YEARS, respectively.

Existing data on the prevalence of PE in haemoptysis patients is limited and primarily derived from single-centre retrospective studies [3, 4, 7, 24]. These studies have reported prevalence rates ranging from 1% to 3%, likely underestimating the true prevalence encountered in clinical practice. Our study for the

first time, employed a systematic diagnostic workup for PE in a series of 546 patients who were prospectively evaluated for haemoptysis in the ED of nine different hospitals. Our findings indicated a PE prevalence of 4.2% or, in the worst-case scenario, 5.1%. This prevalence, even if it could be considered the highest possible estimate, remains significantly lower than expected, based on the pre-test probability estimate according to the mean Wells score of our cohort (8–12%) [21, 22]. We acknowledge that the observed discrepancy may, in part, be attributed to differences in demographic characteristics and the clinical context compared with previous studies. Notably, our study cohort exhibited a younger age profile and a higher prevalence of outpatients. Furthermore, the lower-than-expected prevalence of PE in our study is likely attributed to the pragmatic nature of our research, which was conducted on an unselected population of patients presenting to the emergency room with haemoptysis. Additionally, our study encompassed patients who exhibited a distinct alternative source of bleeding. However, it is crucial to underscore that our data stem from a robust, large-scale, prospective, multicentre cohort study conducted within the ED, the primary setting where patients with haemoptysis typically present and receive their initial evaluation. The strength and precision (95% CI <2.5%) of our estimate challenges the rising and undemonstrated belief that all patients presenting with haemoptysis should be screened for PE just because haemoptysis is included in all diagnostic clinical scores for PE. First, within our cohort, approximately 16% of patients who exhibited a clearly identifiable alternative source of bleeding during their initial assessment were not subjected to PE screening. Remarkably, this subset of patients did not experience any venous thromboembolic events during the 30-day follow-up period, even without receiving anticoagulant treatment. Furthermore, within the “PE unlikely” group, the prevalence of PE approached 2%, a level consistent with the generally accepted pre-test probability threshold at which PE can be safely ruled out without further diagnostic testing [25]. This aligns with a recent study by Bannellier *et al*., which conducted a *post hoc* analysis of two extensive European prospective cohorts comprising 2968 patients presenting to the ED with a low likelihood of PE with the aim of evaluating the impact of removing the “haemoptysis” item from the PERC, YEARS and PEGeD clinical diagnostic rules (CDRs). Based on their findings, the authors suggested that haemoptysis could feasibly be omitted from CDRs for PE [26]. The results of the present study, in our opinion, do not actually criticise the clinical usefulness of haemoptysis as an item of CDRs for pre-test probability stratification but underline the concept that the CDRs should be applied selectively. Specifically, they should be used in patients with haemoptysis and suspected PE, in particular, those without a clear alternative diagnosis, rather than universally in all patients with haemoptysis. Similar limitations in the efficiency of CDRs have been found in recent individual-patient data meta-analyses in different subsets of patients with suspected PE [27]. For example, such limitations were observed in patients aged 80 years or older and those with underlying cancer [27]. These observations may shed light on the inherent limitations of employing a single cut-off or age-adjusted D-dimer as a universal screening tool within these particular patient populations.

In our study cohort, a substantial majority (78%) of patients diagnosed with PE exhibited segmental or subsegmental emboli. Notably, none of these individuals was classified as high risk, admitted to an intensive care unit or experienced mortality attributed to PE. Moreover 6 out of 23 PE cases were subsegmental (26%) a well-known clinical condition at risk of over or under treatment if not accurately evaluated. This novel finding, presented here for the first time, lacks comparative data from previous studies. However, these findings, probably related with the systematic diagnostic approach of our study, closely align with the prevailing epidemiological trends concerning PE over recent decades. These trends have shown an increase in the number of PE diagnoses without corresponding changes in mortality rates [28]. Consequently, the efficiency of the classic diagnostic algorithm, even with the age-adjusted D-dimer, is lower than previously reported [13, 20–22]. New strategies using a “clinical probability-adjusted” D-dimer, such as the YEARS [16] and PEGeD [23] algorithms, excluded PE in a higher proportion of this low-risk population. Similar advantages were found also in the recent meta-analysis by Stals *et al.* across different clinically relevant patient subgroups [27].

One of the main limitations of our study is that, given the pragmatic nature of the protocol, patients at low risk for PE with low D-dimer levels also underwent CTPA for other reasons than PE and patients with a CaSB were not always tested with D-dimer, thus precluding us to directly calculate the impact of using one diagnostic strategy in comparison with others in terms of CTPA sparing. These data could have been of clinical value considering that in the “PE unlikely” population a high number of tests (about 60% of patients) were performed in the initial diagnostic workup. Another important limitation is that the majority of patients were stratified using Wells score, which limits our ability to extrapolate our findings to other commonly used clinical scoring systems, such as the Geneva score or to make direct comparisons with clinical gestalt. Furthermore, no treatment strategy was predetermined, resulting in a discrete proportion (15.3%) of patients who were already receiving anticoagulant therapy. This may have influenced the incidence of PE compared with other studies. Additionally, in an attempt to estimate the prevalence of PE

in the widest possible group of patients with haemoptysis, we also included patients who showed a CaSB and did not undergo CTPA. To mitigate the possibility of diagnostic bias, we followed them up within 30 days after discharge to rule out new symptomatic episodes of VTE requiring anticoagulant treatment. Last, the YEARS and PEGeD algorithms were retrospectively ascertained and the conclusion and interpretation of the results should therefore be judged as conservative and only hypothesis forming.

Conclusion

In conclusion, PE is infrequent among patients with haemoptysis, showing an intermediate–low-risk profile in most cases. "Clinical probability-adjusted" D-dimer strategies seem to have a higher efficiency with a similar low failure rate in comparison to the "age-adjusted" strategy. This last finding warrants further validation through prospective management studies.

Provenance: Submitted article, peer reviewed.

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This study is registered at www.ClinicalTrials.gov with identifier number NCT06067997.

Ethics statement: The study protocol received approval from the ethics committee at each of the participating hospitals (no. 15954_oss). The study considered all consecutive patients with haemoptysis (cough with bloody sputum) as the main symptom of presentation who presented to the EDs of the nine participating hospitals.

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Conflict of interest: The authors have nothing to disclose.

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