PULMONARY EMBOLISM IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATION

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Preface

For this thesis, I started by a thorough literature search on the topic that helped me target knowledge gaps that needed to be filled to improve pulmonary embolism diagnostic management in patients with acute exacerbation of chronic obstructive pulmonary disease. Afterwards, I developed 6 research projects that complemented each other, in order to meet the general objective of my research program. I led every phase of each project, which included study conception, analysis, interpretation of the data and manuscript drafting. A description of my contribution and the contribution of co-authors can be found in the preface of each manuscript.

Abstract

Pulmonary embolism (PE) and acute exacerbation of chronic obstructive pulmonary disease (AECOPD) are two diseases that share similar symptoms which makes the diagnosis of PE challenging. AECOPD is a risk factor for PE, and PE diagnosed in the context of an exacerbation is associated with an increased risk of mortality. Current available PE diagnostic strategies have not been specifically derived and validated in this population. The overall objective of my research program, which include 6 projects, was to determine the optimal management of patients with a suspicion of PE among patients with AECOPD. Project 1 clarified the epidemiology and the burden of PE in patients with AECOPD in North America. It showed that the prevalence of PE in a Canadian center was 1.1% and that in patients with AECOPD, mortality was higher among those diagnosed with PE compared to those without PE. Project 2 and Project 3 presented the performance of available PE diagnostic strategies in patients with chronic lung disease and AECOPD, respectively. These two studies showed that standard diagnostic algorithms were safe, but a high proportion of patients would need imaging to rule out PE. Project 4 evaluated the association between PE and the type of AECOPD and showed that the risk of PE was clinically lower in patients with purulent AECOPD compared to patients with non-purulent/unknown etiology AECOPD. Project 5 presented the derivation of a new diagnostic strategy specifically for patients with AECOPD. The diagnostic strategy consists of a COPD-specific score (type of AECOPD, alternative diagnosis less likely than PE, and clinical signs of deep venous thrombosis) combined with D-dimer testing. Project 6 focused on the feasibility and challenges of a pilot study evaluating prospectively the prevalence of PE in these patients. The study demonstrated its feasibility and targeted challenges such as recruitment of patients, adequate pre-test probability assessment and consistent PE diagnostic strategy use. All 6 projects helped improve PE diagnostic management in patients with AECOPD and thus, clinical care of patients with chronic obstructive pulmonary disease will certainly be improved with this work.

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I would like to give a special thanks to Dr. Steeve Provencher, a mentor for many years, who was my co-director for my master's in clinical epidemiology at Université Laval and who saw my potential in research as I was just starting to work on my first research project. Thank you very much for your continuous support even when I was far away. All your help and all the opportunities you offered me are invaluable and I am very grateful for it.

Finally, I would like to thank my parents, Chanh Ngoc Luong and Eddie Mai, for their unwavering support in my studies. You taught me the value of education, the importance of working hard and the importance in being passionate in everything I do. To my husband, Dr. Frédéric Larose, thank you very much for being supportive and understanding, especially for the time that was needed to complete this work.

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CHAPTER 1: INTRODUCTION

1.1 Venous thromboembolism

1.1.1 Venous thromboembolism and its epidemiology

Venous thromboembolism (VTE) is characterized by a blood clot in a vessel and includes pulmonary embolism (PE) and deep venous thrombosis (DVT). PE is a blood clot in a pulmonary artery and DVT is a blood clot in a deep vein, most frequently in the leg. PE and DVT of the lower extremity are a continuum of the same disease since the vascularization is connected. Most PE originates from a thrombus that developed in the lower extremity and travelled to the lungs(1). VTE is a major health burden with an annual incidence of 1 to 2 per 1000 persons(2, 3) and is the third leading cause of cardiovascular death after myocardial infarction and stroke(4).

1.1.2 Risk factors of VTE

The Virchow triad comprises three elements: venous stasis, vessel injury and hypercoagulable state(5). Many factors can predispose a patient to develop a venous thromboembolic event. These risk factors are categorized in 3 groups: strong risk factors (odds ratio (OR) >10), moderate risk factors (OR 2-9) and weak risk factors (OR <2). Strong risk factors include fracture of a lower extremity, major orthopedic surgery (hip or knee replacement) or trauma and previous VTE. Moderate risk factors include central venous catheter, congestive heart or respiratory failure, estrogen-containing therapy, post-partum, thrombophilia and cancer. Although these moderate risk factors are categorized in the same group, their risk of VTE may be quite variable. Weak risk factors include long car or air travel, increasing age, bed rest > 3 days and obesity(6).

1.1.3 Clinical presentation of PE

The clinical presentation of PE is broad. Patients can present with various symptoms such as sudden onset shortness of breath, pleuritic chest pain, hemoptysis and in more severe cases, syncope can be the main clinical presentation. Signs of PE include tachycardia, tachypnea, hypoxemia and more rarely, hypotension(7). Electrocardiogram can show elements suggestive of PE such as sinus tachycardia, right axis deviation, right bundle branch block, right ventricular strain and S1Q3T3(8). On a chest x-ray, Hampton's hump, a subpleural wedge-shaped pulmonary opacity, the Westermark sign, oligemia distal to a large vessel, can be suggestive of a PE(9-11). With such a wide clinical presentation, diagnosing PE may be challenging. However, it is

important to adequately diagnose PE since PE can be fatal, especially when not treated, and treatments are available(12).

1.1.4 Clinical pre-test probability assessment of PE

In general, when PE is suspected, clinical pre-test probability (c-PTP) is assessed using a clinical decision rule (CDR). Most commonly used CDRs are the Wells PE(13) and the revised Geneva(14) scores. Criteria of the Wells PE score are clinical signs and symptoms of DVT, heart rate > 100 beats per minute, immobilization (≥ 3 consecutive days) or surgery in the previous 4 weeks, previous objectively diagnosed DVT or PE, hemoptysis, malignancy and PE as likely as or more likely than an alternative diagnosis (3 points)(13) (**Table 1**). For the 3-level Wells PE score, patients are categorized as follows: low c-PTP (< 2 points), moderate c-PTP (2-6 points) and high c-PTP (> 6 points)(13). For the 2-level Wells PE score, patients are categorized as follow: unlikely (≤ 4 points) and likely (> 4 points)(15).

Table 1. Criteria of the Wells PE score

Criteria	Number of points
Clinical signs and symptoms of DVT	3.0
Heart rate > 100 beats per minute	1.5
Immobilization (≥ 3 consecutive days) or surgery in the previous 4 weeks	1.5
Previous objectively diagnosed DVT or PE	1.5
Hemoptysis	1.0
Malignancy	1.0
PE as likely as or more likely than an alternative diagnosis	3.0

Criteria of the revised Geneva score are age > 65 years, previous DVT or PE, surgery (under general anesthesia) or fracture of the lower limbs within 1 month, active malignant condition, unilateral lower limb pain, hemoptysis, heart rate, pain on lower limb deep venous palpation and unilateral edema(14). For the revised Geneva score, patients are categorized as follows: low c-PTP (0-3 points), intermediate c-PTP (4-10 points) and high c-PTP (≥ 11 points)(14) (**Table 2**).

Table 2. Criteria of the revised Geneva score

Criteria	Number of points
Age > 65 years	1
Previous DVT or PE	3

Surgery (under general anesthesia) or fracture of the lower limbs within 1 month	2
Active malignant condition	2
Unilateral lower limb pain	3
Hemoptysis	2
Heart rate 75-94 beats per minute ≥ 95 beats per minute	 3 5
Pain on lower limb deep venous palpation and unilateral edema	4

1.1.5 D-dimer testing

D-dimer is a fibrin degradation product. When a thrombus degrades, D-dimer is released to the systemic circulation which explains the elevated D-dimer level in the context of VTE(16). In the general population, D-dimer has a very good, yet not perfect, sensitivity in ruling out VTE(16) and thus, CDRs are combined with D-dimer testing to help decide if radiological imaging is required to rule out PE(17, 18). D-dimer testing is used in patients with non-high c-PTP. A fixed D-dimer cut-off at 500 mcg/L was originally evaluated and used(15, 19) (**Figure 1**). If the D-dimer concentration is higher than the cut-off, then imaging should be performed to rule out PE.

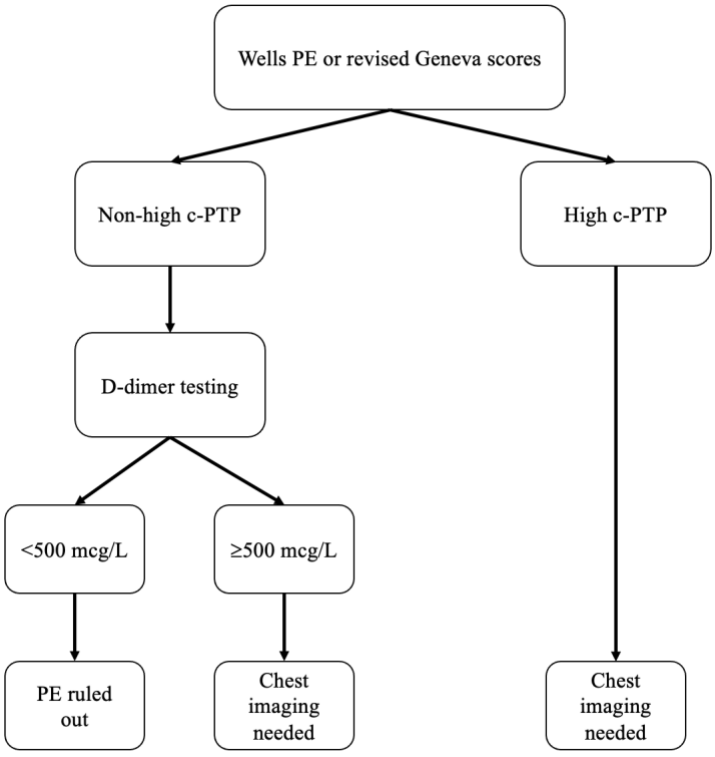

Figure 1. Standard PE diagnostic algorithm

1.1.6 New PE diagnostic strategies

To further reduce the need for imaging, new PE diagnostic strategies have been derived and validated in the general population, such as the ADJUST-PE, the YEARS, the PEGeD and the 4PEPS algorithms. ADJUST-PE consists of c-PTP assessment using the Wells PE score or the revised Geneva score, combined with D-dimer testing using an age-adjusted cut-off. The age-adjusted cut-off is interpreted as follows: 1) in patients ≥ 50 years old, PE is considered ruled out if the D-dimer value is lower than patient's age multiplied by 10 (e.g. 570 mcg/L for a patient aged 57 years, or 720 mcg/L for a patient aged 72 years); 2) in patients < 50 years old, PE is considered ruled out if D-dimer is < 500 mcg/L(20) (**Figure 2**).

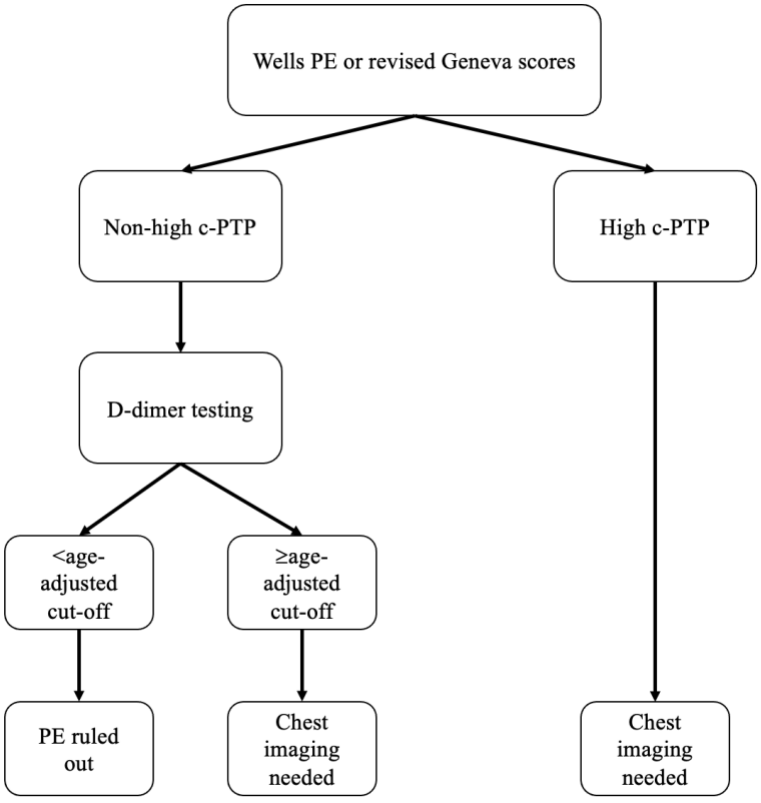

Figure 2. ADJUST-PE algorithm

The YEARS algorithm consists of a clinical assessment with 3-items (clinical signs of DVT, hemoptysis and PE is the most likely diagnosis) combined with D-dimer testing. If patients have 0 YEARS item, the D-dimer cut-off is 1000 mcg/L and if patients have ≥ 1 YEARS items, the D-dimer cut-off is 500 mcg/L(21) (**Figure 3**).

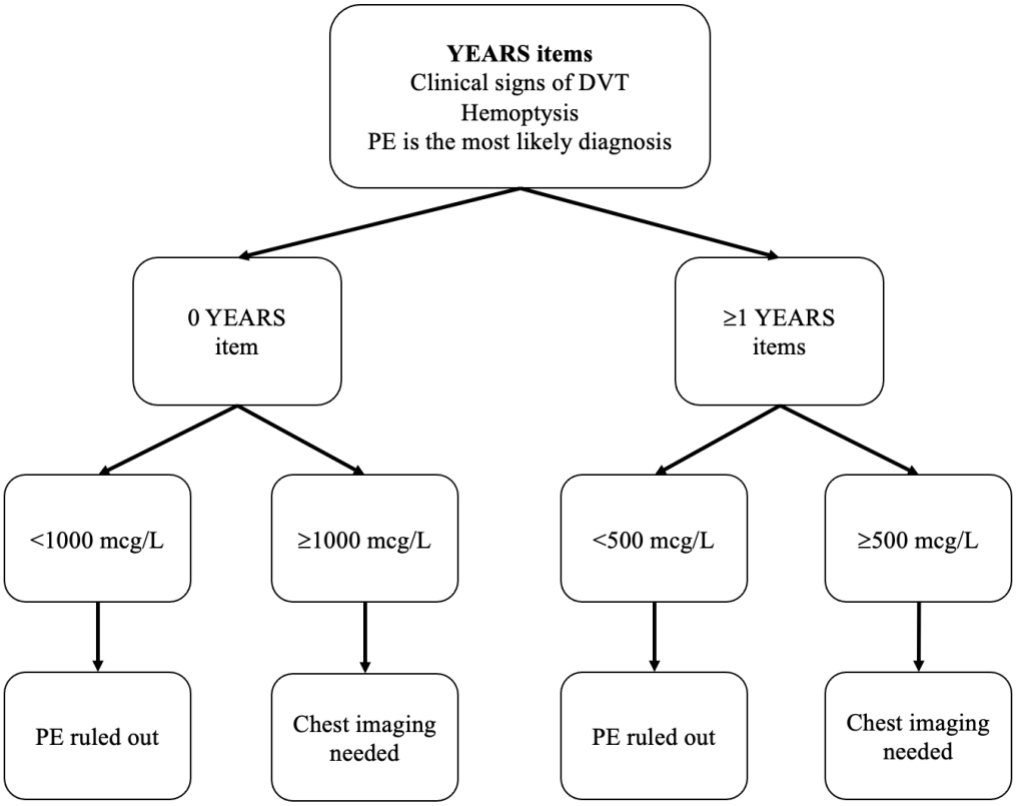

Figure 3. YEARS algorithm

The PEGeD algorithm consists of c-PTP assessment using the Wells PE score (with different number of points attributed per c-PTP compared to the princeps study(13)) combined with D-dimer testing. In the low c-PTP group (0-4.0 points), the D-dimer cut-off is 1000 mcg/L. In the moderate c-PTP group (4.5-6.0 points), the D-dimer cut-off is 500 mcg/L and in the high c-PTP group (≥ 6.5 points), D-dimer is not required since chest imaging to rule out PE should be performed(22) (**Figure 4**).

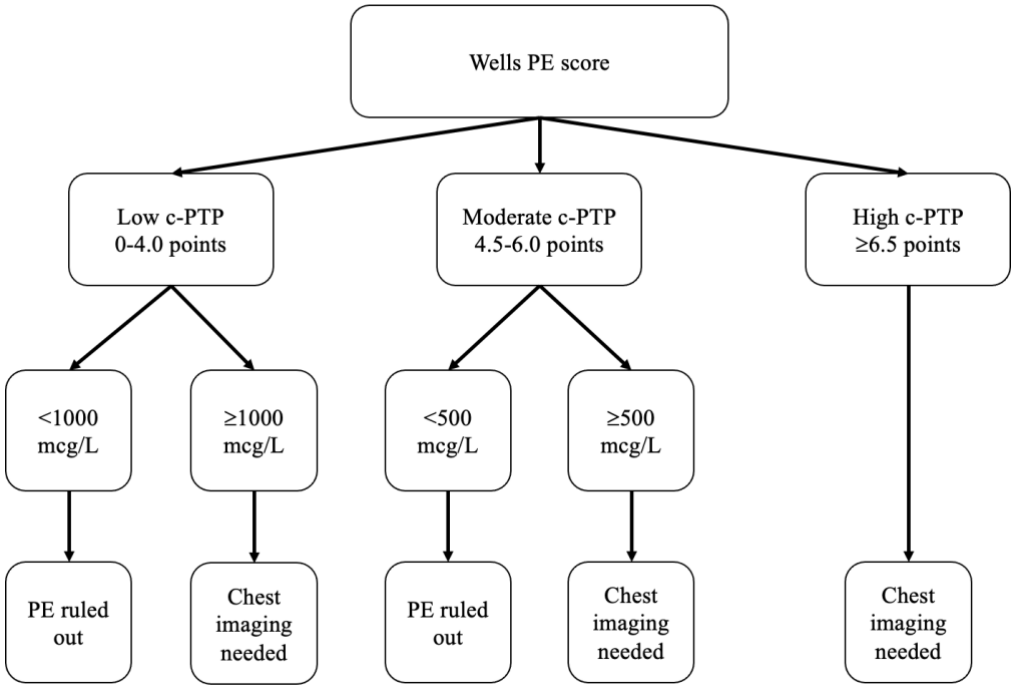

Figure 4. PEGeD algorithm

The 4PEPS algorithm consists of c-PTP assessment using the 4PEPS score combined with D-dimer testing with various cut-offs depending on the c-PTP. The criteria of the 4PEPS score include age, chronic respiratory disease, heart rate < 80 beats per minute, chest pain and acute dyspnea, male, hormonal estrogenic treatment, personal history of VTE, syncope, immobility within the last 4 weeks, pulse oxygen saturation < 95%, calf pain and/or unilateral lower limb edema and PE is the most likely diagnosis. In the very low c-PTP group (< 0 point), PE is excluded without the need for D-dimer testing. In the low c-PTP group (0-5 points), PE is ruled out if D-dimer is < 1000 mcg/L. In the moderate c-PTP group (6-12 points), PE is rule out if D-dimer is < age-adjusted D-dimer cut-off. In the high c-PTP group (≥ 13 points), imaging to rule out PE is required(23) (**Figure 5**). In the general population, these new PE diagnostic strategies showed their safety in addition to being more efficient than conventional diagnostic strategies (Wells PE and revised Geneva score combined with fixed D-dimer cut-off)(20-23).

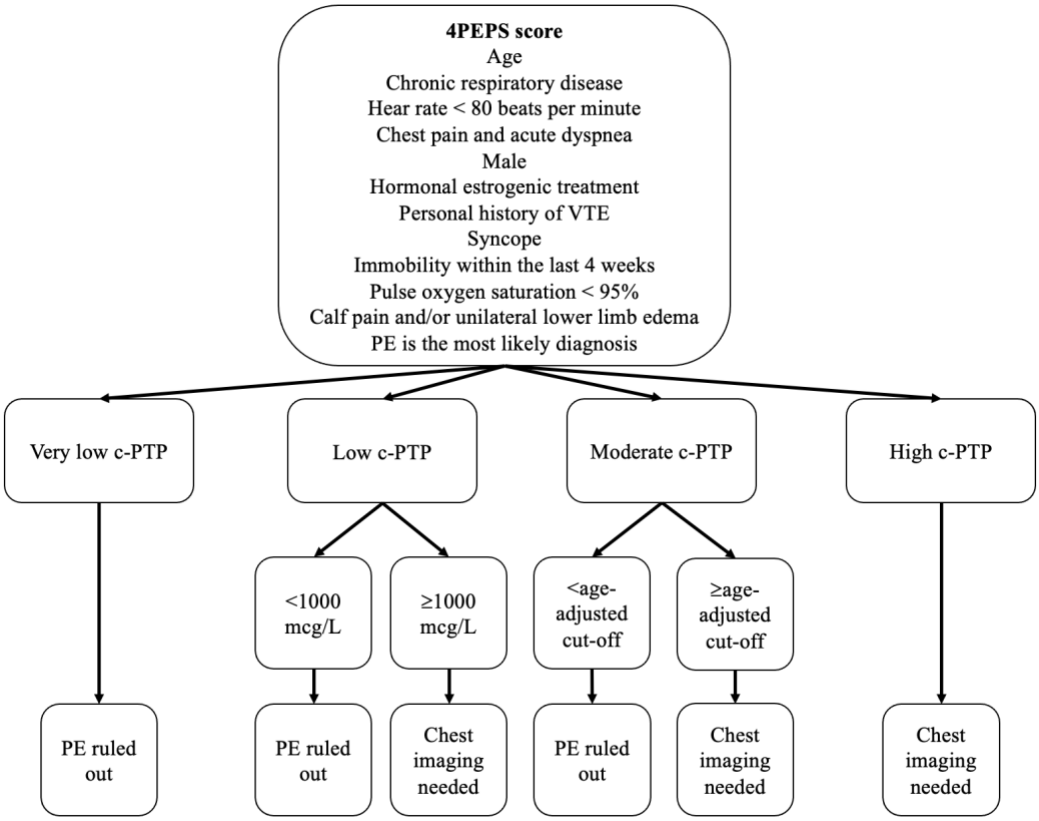

Figure 5. 4PEPS algorithm

1.1.7. Summary of available PE diagnostic strategies

There are many PE diagnostic strategies that have been derived and validated in the general population. In brief, standard diagnostic algorithms are the Wells PE or the revised Geneva scores combined with D-dimer using a fixed cut-off of 500 mcg/L and computed tomography pulmonary angiography (CTPA)-sparing diagnostic strategies are ADJUST-PE, YEARS, PEGeD and 4PEPS algorithms.

1.1.8 Radiological imaging to diagnose PE

CTPA or ventilation/perfusion (V/Q) scan are the 2 most common radiological modalities used to diagnose a PE(6). With a CTPA, the diagnosis of PE is confirmed when an intraluminal filling defect is seen, representing a thrombus in a pulmonary artery(24). Planar V/Q scan can be used to diagnose a PE and a diagnosis of PE is confirmed if the planar V/Q scan shows a high probability for PE defined as ≥ 2 large mismatched segmental defects(25, 26). More recently, V/Q single-photon emission computerized tomography (SPECT) is used and PE is diagnosed in the presence

of at least one segmental mismatch or two subsegmental mismatches (EANM criteria)(27). Although CTPA comes with radiation, possible contrast-induced allergy or nephropathy and incidental findings, this radiological imaging can be performed very quickly and can help with the differential diagnosis since other structures such as the heart and the lung parenchyma are visualized. On the other hand, V/Q scan is associated with less radiation, but takes more time, exposes patients to a radioactive product, and interpretation of a V/Q scan may be more challenging in patients with respiratory disease.

1.2 Chronic obstructive pulmonary disease

1.2.1 COPD and its epidemiology

Chronic obstructive pulmonary disease (COPD) is a heterogenous chronic lung disease and can be divided into chronic bronchitis, when airways are affected, and into emphysema, when alveoli are damaged. COPD is a significant burden worldwide. It is estimated that 480 million people are currently affected by COPD across the globe and it is projected that in 2050, there will be approximately 600 million patients with COPD(28). COPD has now become the third leading cause of mortality in the world(29).

1.2.2 Risk factors

Many factors can increase the risk or predispose a patient of developing COPD. The most common environmental risk factor is tobacco smoking. Other risk factors include biomass exposure, air pollution, occupational exposure (e.g. organic and inorganic dusts), vaping, cannabis inhalation, genetic factors (e.g. alpha-1 antitrypsin deficiency caused by SERPINA1 gene mutation), undeveloped lungs, asthma, infections (e.g. childhood infections, tuberculosis, human immunodeficiency virus) and low socioeconomic status(30).

1.2.3 Clinical presentation and diagnosis

Patients with COPD have chronic respiratory symptoms, such as dyspnea, cough, sputum production and recurrent lower respiratory tract infections. To diagnose COPD, patient should have a compatible clinical presentation and a persistent airflow obstruction on spirometry defined by a forced expiratory volume in 1 second (FEV1) / forced vital capacity (FVC) ratio < 0.70(31). According to the American Thoracic Society (ATS) and European Respiratory Society (ERS), the

severity of COPD is classified as mild (FEV1 ≥ 70%), moderate (FEV1 60%-69%), moderately severe (FEV1 50%-59%), severe (FEV1 35%-49%) and very severe (FEV1 < 35%)(32).

1.2.4 Definition and differential diagnosis of acute exacerbation of COPD

Acute exacerbation of COPD (AECOPD) is a common event seen in the natural history of COPD. AECOPD are characterized by worsening dyspnea and/or cough and sputum within 14 days. AECOPD tend to occur at a rate of 0.5 to 3.5 exacerbations/person/year(33) and the frequency of AECOPD increases as the severity of the COPD progresses(34). However, it may sometimes be challenging to diagnose AECOPD since increased respiratory symptoms can represent a broad range of respiratory diseases. Differential diagnoses that need to be kept in mind when assessing patients with COPD and increased respiratory symptoms include: heart failure, ischemic heart disease, arrythmia, PE, pneumonia, bronchiectasis, asthma, interstitial lung disease, anxiety/depression, pneumothorax, pleural effusion and anemia(35). Moreover, when AECOPD occurs, the most frequent etiology is infection. However, in up to 30% of the cases, the etiology is unknown and PE has been suggested as a potential explanation in those cases of AECOPD from unknown etiology(36).

1.2.5 PE and AECOPD

Recent meta-analyses showed a pooled prevalence of PE in patients with AECOPD varying between 11.0% and 17.2%(37-40). However, the prevalence of PE was highly variable across studies, varying from 0.3% to 36.1% and various subgroup analyses were not able to explain this high heterogeneity across studies(37-40). Moreover, the diagnosis of PE in patients with AECOPD seems to be a prognostic factor with a five-fold increase in mortality compared to patients without PE(37). Since PE and AECOPD share similar symptoms, it is challenging to diagnose PE in this population(35). When standard CDR is computed in patients with AECOPD, most of the patients are categorized in the intermediate c-PTP group as opposed to the general population where most of the patients are categorized in low-risk groups(41). Moreover, D-dimer tend to be higher in this population probably due to concomitant inflammation and/or infection which can result in a lower diagnostic yield(42). Also, as seen in the PEP trial, a multicenter prospective study of 740 patients with COPD admitted with acutely worsening respiratory symptoms, when a standard PE diagnostic strategy was systematically applied (revised Geneva score combined with D-dimer at a fixed cut-

off of 500 mcg/L), 67% of the patients needed a CTPA and only 8.7% of the CTPA were positive for PE(41). Also, the prevalence of PE in the PEP trial among patients in whom PE was not suspected was 4.3% (95%CI 2.8%-6.6%) which is too high to rule out PE according to clinical gestalt only(41-43). The SLICE trial, a multicenter randomized controlled trial, compared usual care to usual care combined with an active search strategy in 746 patients admitted for AECOPD. The active search strategy was characterized by D-dimer performed within 12 hours of randomization and if positive, a CTPA was performed. This study showed no difference on the primary composite outcome (non-fatal symptomatic VTE, readmission for COPD or death within 90 days)(44).

1.3 Thesis objectives and proposed methods

1.3.1 General objective

PE is a significant health burden in patients with AECOPD. In the context of confounding symptoms between PE and AECOPD and the absence of a validated diagnostic strategy specifically in patients with AECOPD, there is a need to improve PE diagnostic management in this population. Thus, the overall objective of my research program was to determine the optimal management of patients with suspicion of PE among patients with AECOPD. My doctoral research program consists of 6 specific projects.

1.3.2 Specific objectives for each project and the proposed methods

Project 1: From recent published meta-analyses evaluating the prevalence of PE in patients with AECOPD(37-40), no study reported on the prevalence of PE in patients with AECOPD in North America in the era of CTPA. A retrospective cohort study was conducted at the Ottawa Hospital to determine the prevalence of PE patients with AECOPD. The mortality associated with PE was also assessed.

Project 2: Since currently available CDR had not been evaluated specifically in patients with AECOPD, a sub-analysis of an individual participant data meta-analysis (IPDMA) was conducted to evaluate currently available CDR (revised Geneva and Wells PE scores in combination with D-dimers [fixed or age-adjusted] and YEARS) in patients with chronic respiratory disease.

Project 3: A post-hoc analysis of the PEP trial(41) was conducted to evaluate the performance of standard diagnostic algorithms (revised Geneva and Wells PE score combined with a fixed D-

dimer cut-off) and CTPA-sparing diagnostic strategies (ADJUST-PE, YEARS, PEGeD and 4PEPS).

Project 4: A systematic review with meta-analysis was conducted to evaluate the association between PE and the type of AECOPD.

Project 5: Predictors of PE in patients with AECOPD are not well defined. A post-hoc analysis of the PEP trial(41) was conducted to evaluate predictors of PE and to develop a new PE diagnostic algorithm specifically for patients with AECOPD.

Project 6: A pilot study was conducted to evaluate the feasibility of conducting a prospective study aiming at evaluating prospectively the prevalence of PE in North America.

CHAPTER 2: Manuscript 1 – Prevalence of diagnosed pulmonary embolism in patients with chronic obstructive pulmonary disease exacerbation presenting at the emergency department of a large North American academic hospital center

2.1 Preface to manuscript 1

To better understand the burden of PE in patients with AECOPD, I conducted a retrospective cohort study aiming at evaluating the prevalence of PE in patients with AECOPD in Canada. No contemporary data was available in North America and it is known that the prevalence of PE varies across the globe. Previous studies showed a lower proportion of confirmed PE among patients enrolled in PE diagnostic studies in North America vs. Europe. I worked on the literature review, study conception, data collection data analysis, interpretation of the data and manuscript drafting. Co-authors of this paper helped with the data extraction, supervised the project and revised the manuscript.

The results of this project were presented as an oral presentation at the International Society of Thrombosis and Haemostasis (ISTH) annual conference 2023 in Montreal.

The manuscript was published in the Canadian Journal of Respiratory, Critical Care and Sleep Medicine: Mai, V., Pradier, M., Mulpuru, S., Thiruganasambandamoorthy, V., Code, C., Fergusson, D., & Le Gal, G. (2024). Prevalence of diagnosed pulmonary embolism in patients with chronic obstructive pulmonary disease exacerbation presenting at the emergency department of a large North American academic hospital center. Canadian Journal of Respiratory, Critical Care, and Sleep Medicine, 8(5), 208–215.

2.2 Manuscript 1

Prevalence of diagnosed pulmonary embolism in patients with chronic obstructive pulmonary disease exacerbation presenting at the emergency department of a large North American academic hospital center

Running head: Pulmonary embolism in patients with chronic obstructive pulmonary disease exacerbation

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ABSTRACT

Background: The real prevalence of pulmonary embolism (PE) in patients with chronic obstructive pulmonary disease exacerbation (COPDe) remains largely unknown, especially in North America. Our aim was to evaluate the prevalence of PE in patients with COPDe at a large academic Canadian hospital.

Methods: This is a retrospective cohort study of all adult patients with COPDe seen at the emergency department (ED) of The Ottawa Hospital, Ontario, Canada (June 2019-January 2022). The primary outcome was the prevalence of PE during the initial assessment and at 3 months. Secondary outcomes included prevalence of venous thromboembolism and mortality. Subgroup analyses based on the type of COPDe and the post-ED clinical setting were conducted.

Results: Of 1158 patients seen in the ED with COPDe, PE was diagnosed in 13 patients (1.1%; 95%CI 0.6%-1.9%). Five patients (5/1158; 0.4%) had a diagnosis of PE during initial assessment and 8/1141 (0.7%) patients were diagnosed with PE during the 3-month follow-up. The prevalence of PE did not differ based on the type of COPDe (p=0.27) and was higher in patients admitted to the hospital compared to patients discharged from the ED (1.1% vs 0.0%; p=0.01). Mortality was clinically but not statistically higher in patients with PE compared to patients without PE (15.4% vs 6.0%; p=0.19).

Conclusion: Among patients with COPDe evaluated in the ED, the prevalence of diagnosed PE was low, but more than 60% of the PE were diagnosed during the 3-month follow-up. Further studies are needed to determine an appropriate diagnostic algorithm in this population.

Keywords: chronic obstructive airway disease, chronic obstructive lung disease, chronic obstructive pulmonary disease, pulmonary embolism, venous thromboembolism

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic, incurable, inflammatory lung disease that affects more than 200 million people worldwide and is the third leading cause of mortality[1]. Patients with COPD experience periodic exacerbations, which are characterized by worsening dyspnea and/or cough and sputum, and often lead patients to seek hospital care[2]. COPD exacerbation (COPDe) occurs at a rate of 0.5 to 3.5 exacerbations/patient/year and is associated with an increased risk of mortality, lung function decline and reduced health-related quality of life[3,4]. The most frequent cause of exacerbation is viral or bacterial infection[5]. However, the cause remains unknown in 30% of cases[6].

Pulmonary embolism (PE) is also associated with COPDe[7], but it can be difficult to make the diagnosis of PE among patients experiencing COPDe, as the symptom presentations can be similar[8]. Respiratory failure has been categorized as being a moderate risk factor for venous thromboembolism (VTE), within the range observed with estrogen use or cancer[9,10]. Moreover, it is important to diagnose PE in this context since it is a potentially fatal condition[11]. Compared to the general population, PE is more frequent than deep venous thrombosis (DVT) in patients with COPDe[12,13], however, the true prevalence among patients with COPDe, especially in North America, is not well known.

The challenge in understanding the prevalence of PE in this specific population is that COPDe and PE have confounding symptoms. A recent meta-analysis of 20 studies, including 4942 patients, suggested a prevalence of PE of 12% among patients with COPDe, with a 5-fold increased risk of mortality[14]. However, the prevalence of PE varied highly across studies and its heterogeneity was not fully explained by various subgroups analyses. Moreover, the prevalence of PE in emergency

department (ED) patients varies significantly across countries in non-COPD patients and is usually lower in North America compared to Europe[15]. No previous study has reported the prevalence of PE among patients with COPDe in North American settings in the era of computed tomography pulmonary angiogram (CTPA).

The aim of the study was to estimate the prevalence of PE in patients presenting to the ED with COPDe in a large academic Canadian center as well as the mortality of patients with COPDe and PE compared to patients with COPDe and no PE.

METHOD

Study design

A retrospective cohort study was conducted at the Ottawa Hospital which provides tertiary-level care, especially in respirology and thrombosis, includes 1420 beds and has ≈160,000 ED visits per year. The protocol (20220357-01H) was approved by the Ottawa Health Science Network Research Ethics Board.

Study participants

All adult patients with COPD presenting to the two EDs of The Ottawa Hospital with increasing respiratory symptoms and a discharge diagnosis of COPDe from June 1, 2019, to January 1, 2022, were included. The diagnosis of COPD was determined by spirometry with forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) ratio <0.70[16], supported by imaging (i.e hyperinflation or emphysema seen on chest x-ray or emphysema seen on CTPA)[17] or by the treating physicians' impression in the patients' chart. Post-bronchodilator FEV1 spirometry was used.

When post-bronchodilator spirometry was not available, pre-bronchodilator (or unspecified) spirometry was used. Patients already treated with anticoagulants at the initial assessment were excluded.

Data collection

Data were extracted from the electronic medical record system (Epic software, Epic Systems, Verona, WI, United States) at the study hospital. Patients were identified in the medical record system if they had a discharge diagnosis of COPD with acute exacerbation, unspecified (International Classification of Disease-10 diagnosis code J44.1) in the primary, secondary, or tertiary diagnosis fields during the study period. Only the first visit for COPDe was counted as index visit for each participant. Baseline characteristics and demographics of the patients and data related to the outcomes were extracted using a standardized data extraction form. The type of COPDe was extracted. Patients were categorized as having purulent COPDe if the exacerbation was described as purulent or if the patient had new yellow or green phlegm, non-purulent COPDe if it was described as non-purulent or if the patient had same or increased quantity of phlegm with usual color or white/transparent phlegm and unknown purulence status COPDe was attributed if no information was available on the purulence status. Patients were considered lost to follow-up if no information was available after the initial assessment at the ED or if no information was available after 60 days of follow-up.

Outcomes

The primary outcome was PE in patients with COPDe at the initial ED visit and at 3 months follow-up. The prevalence of PE at 3 months was used since PE diagnostic studies rely on the 3-month

failure rate of PE+DVT with the underlying rationale that a missed, hence untreated PE at presentation is likely to recur or worsen during the following weeks and would thus be captured during this time period[18]. In patients in whom thoracic imaging was performed, PE was diagnosed if there was a filling defect in a segmental or more proximal pulmonary artery on a CTPA, a high-probability finding on a ventilation-perfusion (V/Q) scan, or indeterminate results on CTPA or V/Q scan but a documented proximal DVT on leg ultrasonography. In patients without chest imaging performed at the initial assessment, any subsequent diagnosis of DVT or PE during the 3 months following the initial ED visit was captured by the same methods as described above. Secondary outcomes included VTE (PE and/or proximal lower extremity DVT) at enrollment and during the 3-month follow-up, mortality during the entire study period and diagnostic yield of D-dimers.

Statistical analyses

Descriptive analyses were performed for baseline characteristics of the patients. Continuous variables were presented with their mean values and standard deviation if normally distributed. Dichotomous variables were presented by count and proportion. The prevalence of PE and/or DVT was calculated with its 95% confidence interval (CI) at the initial assessment and during the 3-month follow-up. 95%CI were calculated using the binomial exact method[19]. Subgroup analyses on the prevalence of PE based on the type of COPDe (purulent vs non-purulent vs unknown purulence status COPDe) and clinical setting (hospitalized vs discharged from the ED) were conducted using Pearson Chi-Square test or Fisher's Exact test. Survival analyses were performed using Kaplan-Meier and log-rank test was used to compared mortality between patients with PE and patients without PE. Since we were interested in the crude prevalence rates, we did not adjust for known risk factors. A p-value < 0.05 was considered statistically significant. Analyses were

performed with SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Mac, Version 27.0. Armonk, NY: IBM Corp).

RESULTS

Baseline characteristics of the patients

A total of 1,158 patients were included of which 479 patients had a diagnosis of COPD confirmed by spirometry, 509 patients had a diagnosis of COPD supported by imaging and 170 patients had a diagnosis of COPD documented in their chart without confirmation by spirometry or supported by imaging. Six patients were lost to follow-up and 6 patients died on the same day of the initial assessment at the ED (**Figure 1**). The mean age was 69.9 ± 11.3 years and 53.5% were female. Current tobacco dependence was present in 626/1158 (54.1%) patients and 740/1158 (63.9%) patients had no exacerbation in the last year. The mean FEV1 was 1.38L ± 0.62L. Purulent COPDe was confirmed in 390 patients (33.7%) and hospitalization following the initial visit at the ED was required for 464 patients (40.1%) (**Table 1**). Diagnostic yield of D-dimers was not evaluated due to significant number of missing data for this variable. Data on D-dimers could be extracted only for 137 (11.8%) patients. One hundred and sixty-nine (14.6%) patients had a CTPA, 13 (1.1%) patients had a computed tomography of the chest with intravenous contrast, 3 (0.3%) patients had a V/Q scan and 41 (3.5%) patients had lower extremity doppler ultrasound.

Prevalence of PE

PE was diagnosed in 13/1158 patients (1.1%; 95%CI 0.6%-1.9%). At initial assessment, 5/1158 (0.4%) patients had a diagnosis of PE, resulting in a chest imaging positivity of 2.7% (5/185). Another 8/1141 (0.7%) patients were diagnosed with PE during the 3-month follow-up. Proximal

lower extremity DVT was diagnosed in only 1 patient who had a concomitant diagnosis of PE at the initial assessment. No patient had a diagnosis of isolated proximal lower extremity DVT. Among patients with confirmed COPD by spirometry, 2/479 (0.4%) and 3/477 (0.6%) patients were diagnosed with PE at the initial assessment and during the 3-month-follow-up, respectively. In patients with a diagnosis of COPD based on imaging, no PE was diagnosed at the initial assessment, but 4 PE (0.8%) were diagnosed during the 3-month follow-up. Among patients with COPD not confirmed by spirometry or not supported by imaging, PE was diagnosed in 3/170 (1.8%) patients at the initial assessment and 1/163 (0.6%) patients during the 3-month follow-up. Although the prevalence of PE at ED presentation did not differ based on the type of exacerbation (p=0.27), no PE was diagnosed in 390 patients with purulent COPDe, whereas 3/465 (0.6%) patients with non-purulent COPDe and 2/303 (0.7%) patients with unknown purulence status COPDe were diagnosed with PE. Out of 8 patients diagnosed with PE during follow-up, 6 patients had non-purulent COPDe and 2 patients had unknown purulence status COPDe at the recurrent visit that led to the diagnosis of PE. At the initial assessment, in the entire cohort, all the PE were diagnosed in patients who were hospitalized whereas no thromboembolic event was diagnosed in patients who were discharged from the ED (1.1% vs 0.0%; p=0.01) (**Table 2**).

Mortality

During the entire study period, 71 (6.1%) patients died, of which 6 patients died on the same day of the initial visit and 65 patients died during the 3-month follow-up. Respiratory insufficiency was the most common cause of death. No confirmed fatal PE occurred. Mortality was numerically but not statistically higher in patients with PE compared to patients without PE [2/13 (15.4%) patients vs 69/1145 (6.0%) patients; p=0.19] (**Table 3 and Figure 2**).

DISCUSSION

In our retrospective cohort study among patients presenting to a large academic ED with COPDe, the prevalence of diagnosed PE was 1.1%, of which more than 60% were diagnosed during the 3-month follow-up period. PE was also more frequently diagnosed in patients who were hospitalized compared to patients discharged directly from the ED. However, PE was associated with a clinically, but not statistically significant increased risk of mortality compared to patients without PE in patients with COPDe.

In our cohort, the prevalence of PE is lower than the average prevalence of PE in the literature[7,14] and is mostly consistent with the lower ranges seen[20,21]. Some elements may have explained the lower rate of PE. First, the majority of the patients were discharged from the ED without the need for hospitalization which may have put them at lower risk of VTE. It is consistent with the findings from the meta-analysis of Rizkallah et al.[22] showing that the prevalence of PE varied across settings, being lowest in the ED and highest in hospitalized patients. Second, the prevalence of PE may have been underestimated due to the lost to follow-up and to the absence of systematic follow-up due to the design of the study. Some venous thromboembolic events may have been missed. Third, subsegmental PE and distal DVT were not counted as an event for the outcomes whereas most of the prior studies included these thromboembolic events. At initial assessment, one brachial vein thrombosis, one isolated subsegmental PE and one superficial vein thrombosis were diagnosed in 3 different patients and during the 3-month follow-up, one patient was diagnosed with multiple subsegmental PE. These VTE were not included since there is still controversy in the management of these types of clots and some of these VTE are sometimes not treated with

anticoagulation[23-25]. Fourth, it is concordant with prior studies in the general population demonstrating that the prevalence of PE is lower in North America compared to Europe[15]. Fifth, no systematic search for PE was performed which could have reduced the prevalence of diagnosed PE. Hence, a low clinical suspicion, explained by imaging performed in 16% of the patients, could explain this low prevalence of diagnosed PE. This is consistent with the meta-analysis of Sato et al.[14] showing that the prevalence of PE was higher in studies that systematically performed CTPA in all patients compared to studies that did not (23% vs 6%). Moreover, it is possible that an underlying PE explaining the initial COPDe was missed and that it may not have been diagnosed afterwards. Some exacerbations, respiratory failures or deaths related to COPDe may have, in fact, been due to an undiagnosed PE. In this study, the number of PE diagnosed during follow-up was higher than the number of PE diagnosed at enrollment, which is the opposite of diagnostic studies in the general population. Therefore, it emphasizes the difficulty of diagnosing PE in patients with COPDe and it is not clear in which patients imaging should be performed to rule out PE.

It is concerning to see that more than 60% of the PE were diagnosed during the 3-month follow-up. Indeed, a high proportion of PE was possibly missed at the initial assessment at the ED, mainly due to the confounding symptoms. It is also hypothesis generating that some of the PE diagnosed during follow-up could be attributed to another risk factor (i.e., re-hospitalization, acute illness) that occurred during this time period as patients with COPD often have many comorbidities. Therefore, a clinical follow-up after being discharged with a diagnosis of COPDe may be of clinical value, although it may not capture all VTE occurring subsequently. In the real-world setting, perhaps too few CTPA are performed. Only 16% of this cohort had a chest imaging that could rule out PE and the chest imaging positivity was only 2.7%. In opposition, in the PEP trial

where a predefined diagnostic algorithm based on the revised Geneva score combined with D-dimers was used in a cohort of hospitalized patients with COPDe, two thirds of the patients needed a CTPA and only 9% of these investigations were positive for PE[13]. The counterpart is that CTPA comes with costs, radiation, possible kidney injury and incidental findings that require further investigations and increase patients' anxiety. Because of these elements, risks and benefits of CTPA should be balanced out, especially in patients with COPD who tend to have more frequent exacerbations as the disease progresses. Moreover, a randomized controlled trial comparing usual care to usual care with active strategy (D-dimers +/- imaging) did not show a reduction in the composite outcome of nonfatal symptomatic VTE, readmission for COPD or death within 90 days[26]. Thus, it is still unclear which patients among those with COPDe would most benefit from having imaging to rule out PE and among those, which diagnostic algorithm should be used.

In patients with COPDe, PE is more frequent than DVT. In this study, all the venous thromboembolic events were PE and one DVT was concomitantly diagnosed in a patient with PE. This is concordant with the literature of studies performed outside North America showing a higher prevalence of PE compared to DVT in patients with COPDe[14]. Diagnostic bias could explain part of this finding. Patients with COPDe have increased respiratory symptoms which are confounding symptoms for PE and thus, imaging of the chest is performed more frequently in these patients. On the other hand, in-situ thrombus may have a tendency to form more frequently in the lungs because of local inflammation generated by the inflammation and/or infection related to the exacerbation similarly to PE due to vascular endothelialitis related to COVID-19 infection[27].

Subgroup analyses conducted on the prevalence of PE are hypotheses generating. Even if our study was not powered to show a difference in the prevalence of PE based on the type of exacerbation, PE was more frequent in patients with non-purulent or unknown purulence status COPDe whereas no PE was diagnosed in patients with purulent COPDe. It is in line with some studies in the literature showing a higher prevalence of PE in patients with non-purulent COPDe compared to patients with purulent COPDe[28-30]. In addition, PE was also more frequently diagnosed among patients who were hospitalized with no PE than among patients discharged directly from the ED. It is concordant with prior studies showing a higher prevalence of PE among hospitalized patients[22]. Patients admitted to the hospital are usually more comorbid and have a higher risk of PE.

Moreover, concordant with results from recent meta-analyses[14,31,32], in patients with COPDe in North America, PE seemed to be associated with an increased risk of mortality. The number of PE in our study was too low to demonstrate such a difference. For the association between PE and mortality, it is difficult to determine if PE increases the risk of mortality or if developing a venous thromboembolic event is a reflection of a patient who has more comorbidities and is sicker. Although the direct causal effect of PE on mortality is not demonstrated, diagnosing PE in patients with COPDe may be important due its prognostic value.

Our study has strengths. It is the first study evaluating the prevalence of PE in a North American center in the era of CTPA. Thirty years ago, Lesser et al. evaluated the prevalence of PE in patients with COPDe diagnosed by V/Q scan in North America, but the sample size was limited[33]. We did not identify any Canadian data. Moreover, due to abnormal ventilation in patients with COPD,

interpreting V/Q scan is challenging. Also, this study includes one of the largest cohort of patients with COPDe in whom prevalence of PE was evaluated. We also acknowledge limitations. First, due to its design being a retrospective study, some patients were lost to follow-up and some VTE during the follow-up period may have been missed which could have underestimated the prevalence of PE. Second, nearly half of the patients had a diagnosis of COPD confirmed by spirometry. Since some patients were included as having COPD supported by imaging only or by physicians' impression, some included patients may have been misclassified as having COPD but, it is not clear what impact this information misclassification can have on the results. Third, even if no fatal PE was diagnosed, some deaths attributed to respiratory failure could have been caused by an unconfirmed PE since COPDe and PE have similar symptoms. Finally, patients did not undergo a systematic PE diagnostic strategy or an active search strategy for PE which could have underestimated the prevalence of diagnosed PE in this population.

CONCLUSION

In summary, among patients with COPDe evaluated in the ED, the prevalence of diagnosed PE during the study was low, but more than 60% of the PE were diagnosed during the 3-month follow-up. Further studies are needed to find an appropriate diagnostic algorithm in this specific population.

AUTHOR CONTRIBUTIONS

V. Mai, M. Pradier, S. Mulpuru, V. Thiruganasambandamoorthy, C. Code, D. Fergusson and G. Le Gal made a substantial contribution to the concept and design, analysis and interpretation of the data.

V. Mai drafted the initial work which was critically revised for intellectual content by M. Pradier, S. Mulpuru, V. Thiruganasambandamoorthy, C. Code, D. Fergusson and G. Le Gal.

V. Mai, M. Pradier, S. Mulpuru, V. Thiruganasambandamoorthy, C. Code, D. Fergusson and G. Le Gal approved the final version of the manuscript.

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CONFLICT OF INTEREST

V. Mai, M. Pradier, S. Mulpuru, V. Thiruganasambandamoorthy, C. Code, D. Fergusson and G. Le Gal do not have any conflicts of interest related to this study.

BIBLIOGRAPHY

1. WHO. Chronic obstructive pulmonary disease (COPD). June 21, 2021 2021;

2. Celli BR, Fabbri LM, Aaron SD, et al. An Updated Definition and Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbations: The Rome Proposal. *Am J Respir Crit Care Med*. Dec 1 2021;204(11):1251-1258. doi:10.1164/rccm.202108-1819PP

3. Seemungal TAR, Hurst JR, Wedzicha JA. Exacerbation rate, health status and mortality in COPD--a review of potential interventions. *Int J Chron Obstruct Pulmon Dis*. 2009;4:203-223. doi:10.2147/copd.s3385

4. Anzueto A. Impact of exacerbations on COPD. *European Respiratory Review*. 2010;19(116):113-118. doi:10.1183/09059180.00002610

5. Sapey E, Stockley RA. COPD exacerbations . 2: aetiology. *Thorax*. Mar 2006;61(3):250-8. doi:10.1136/thx.2005.041822

6. Connors AF, Jr., Dawson NV, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). *Am J Respir Crit Care Med*. Oct 1996;154(4 Pt 1):959-67. doi:10.1164/ajrccm.154.4.8887592

7. Aleva FE, Voets L, Simons SO, de Mast Q, van der Ven A, Heijdra YF. Prevalence and Localization of Pulmonary Embolism in Unexplained Acute Exacerbations of COPD: A Systematic Review and Meta-analysis. *Chest*. Mar 2017;151(3):544-554. doi:10.1016/j.chest.2016.07.034

8. Bertoletti L, Couturaud F, Sanchez O, Jimenez D. Pulmonary Embolism and Chronic Obstructive Pulmonary Disease. *Seminars in thrombosis and hemostasis*. Sep 15 2022;doi:10.1055/s-0042-1756190

9. Anderson FA, Jr., Spencer FA. Risk factors for venous thromboembolism. *Circulation*. Jun 17 2003;107(23 Suppl 1):I9-16. doi:10.1161/01.Cir.0000078469.07362.E6

10. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC)*. 2019:1901647. doi:10.1183/13993003.01647-2019

11. Tritschler T, Kraaijpoel N, Langlois N, et al. Development of a standardized definition of pulmonary embolism-related death: A cross-sectional survey of international thrombosis experts. *Journal of Thrombosis and Haemostasis*. 2020;18(6):1415-1420. doi:https://doi.org/10.1111/jth.14775

12. Bertoletti L, Quenet S, Mismetti P, et al. Clinical presentation and outcome of venous thromboembolism in COPD. *Eur Respir J*. Apr 2012;39(4):862-8. doi:10.1183/09031936.00058811

13. Couturaud F, Bertoletti L, Pastre J, et al. Prevalence of Pulmonary Embolism Among Patients With COPD Hospitalized With Acutely Worsening Respiratory Symptoms. *JAMA*. Jan 5 2021;325(1):59-68. doi:10.1001/jama.2020.23567

14. Sato R, Hasegawa D, Nishida K, Takahashi K, Schleicher M, Chaisson N. Prevalence of pulmonary embolism in patients with acute exacerbations of COPD: A systematic review and meta-analysis. *The American Journal of Emergency Medicine*. 2021/12/01/ 2021;50:606-617. doi:https://doi.org/10.1016/j.ajem.2021.09.041

15. Germini F, Zarabi S, Eventov M, Turcotte M, Li M, de Wit K. Pulmonary embolism prevalence among emergency department cohorts: A systematic review and meta-analysis by country of study. *J Thromb Haemost*. Jan 2021;19(1):173-185. doi:10.1111/jth.15124

16. Venkatesan P. GOLD report: 2022 update. *Lancet Respir Med*. Feb 2022;10(2):e20. doi:10.1016/s2213-2600(21)00561-0

17. Müller NL, Coxson H. Chronic obstructive pulmonary disease • 4: Imaging the lungs in patients with chronic obstructive pulmonary disease. *Thorax*. 2002;57(11):982-985. doi:10.1136/thorax.57.11.982

18. Dronkers CEA, van der Hulle T, Le Gal G, et al. Towards a tailored diagnostic standard for future diagnostic studies in pulmonary embolism: communication from the SSC of the ISTH. *J Thromb Haemost*. 2017;15(5):1040-1043. doi:https://doi.org/10.1111/jth.13654

19. Kohn MA SJ. Sample Size Calculators (website). UCSF CTSI. 20 December 2021 2021;

20. Rutschmann OT, Cornuz J, Poletti P-A, et al. Should pulmonary embolism be suspected in exacerbation of chronic obstructive pulmonary disease? *Thorax*. 2007;62(2):121-125. doi:10.1136/thx.2006.065557

21. Pang H, Wang L, Liu J, et al. The prevalence and risk factors of venous thromboembolism in hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease. *The Clinical Respiratory Journal*. 2018;12(11):2573-2580. doi:https://doi.org/10.1111/crj.12959

22. Rizkallah J, Man SFP, Sin DD. Prevalence of Pulmonary Embolism in Acute Exacerbations of COPD: A Systematic Review and Metaanalysis. *CHEST*. 2009;135(3):786-793. doi:10.1378/chest.08-1516

23. Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report. *CHEST*. 2021;160(6):e545-e608. doi:10.1016/j.chest.2021.07.055

24. Carrier M, Klok FA. Symptomatic subsegmental pulmonary embolism: to treat or not to treat? *Hematology American Society of Hematology Education Program*. 2017;2017(1):237-241. doi:10.1182/asheducation-2017.1.237

25. Risk for Recurrent Venous Thromboembolism in Patients With Subsegmental Pulmonary Embolism Managed Without Anticoagulation. *Annals of Internal Medicine*. 2022;175(1):29-35. doi:10.7326/m21-2981 %m 34807722

26. Jiménez D, Agustí A, Tabernero E, et al. Effect of a Pulmonary Embolism Diagnostic Strategy on Clinical Outcomes in Patients Hospitalized for COPD Exacerbation: A Randomized Clinical Trial. *JAMA*. Oct 5 2021;326(13):1277-1285. doi:10.1001/jama.2021.14846

27. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *New England Journal of Medicine*. 2020;doi:10.1056/NEJMoa2015432

28. Choi KJ, Cha SI, Shin KM, et al. Prevalence and predictors of pulmonary embolism in Korean patients with exacerbation of chronic obstructive pulmonary disease. *Respiration*. 2013;85(3):203-9. doi:10.1159/000335904

29. Dentali F, Pomero F, Micco PD, et al. Prevalence and risk factors for pulmonary embolism in patients with suspected acute exacerbation of COPD: a multi-center study. *European journal of internal medicine*. Oct 2020;80:54-59. doi:10.1016/j.ejim.2020.05.006

30. Liu X, Jiao X, Gong X, et al. Prevalence, Risk Factor and Clinical Characteristics of Venous Thrombus Embolism in Patients with Acute Exacerbation of COPD: A Prospective Multicenter Study. *Int J Chron Obstruct Pulmon Dis*. 2023;18:907-917. doi:10.2147/copd.S410954

31. Fu X, Zhong Y, Xu W, et al. The prevalence and clinical features of pulmonary embolism in patients with AE-COPD: A meta-analysis and systematic review. *PLoS One*. 2021;16(9):e0256480. doi:10.1371/journal.pone.0256480

32. Wang J, Ding YM. Prevalence and risk factors of pulmonary embolism in acute exacerbation of chronic obstructive pulmonary disease and its impact on outcomes: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci*. Mar 2021;25(6):2604-2616. doi:10.26355/eurrev_202103_25424

33. Lesser BA, Leeper KV, Jr., Stein PD, et al. The diagnosis of acute pulmonary embolism in patients with chronic obstructive pulmonary disease. *Chest*. Jul 1992;102(1):17-22. doi:10.1378/chest.102.1.17

Table 1. Baseline characteristics of the patients

Characteristics	Entire cohort (n=1158)	Confirmed COPD by spirometry (n=479)	Diagnosis of COPD supported by imaging only (n=509)	Diagnosis of COPD written in the chart only (n=170)
Age (mean ± SD)	69.9 ± 11.3	70.6 ± 9.9	68.9 ± 11.9	70.9 ± 13.0
Female – n (%)	620 (53.5)	260 (54.3)	269 (52.8)	91 (53.5)
Weight (kg) (mean ± SD)	71.6 ± 23.2[1]	69.7 ± 22.8[2]	66.0 ± 20.5[3]	89.1 ± 21.5[4]
Body mass index (kg/m^2) (mean ± SD)	25.8 ± 7.9[5]	25.3 ± 8.1[6]	24.1 ± 6.7[7]	31.5 ± 7.4[8]
Tobacco use – n (%)				
Current	626 (54.1)	230 (48.0)	311 (61.1)	85 (50.0)
Prior	433 (37.4)	227 (47.4)	155 (30.5)	51 (30.0)
Never	45 (3.9)	16 (3.3)	13 (2.6)	16 (9.4)
Unknown	54 (4.7)	6 (1.3)	30 (5.9)	18 (10.6)
Exacerbations in the last year – n (%)				
0	740 (63.9)	276 (57.6)	354 (69.5)	110 (64.7)
1	209 (18.0)	95 (19.8)	81 (15.9)	33 (19.4)
2	115 (9.9)	58 (12.1)	46 (9.0)	11 (6.5)
3	43 (3.7)	22 (4.6)	12 (2.4)	9 (5.3)
4	17 (1.5)	10 (2.1)	6 (1.2)	1 (0.6)
≥ 5	32 (2.8)	17 (3.5)	9 (1.8)	6 (3.5)
Unknown	2 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)
Antiplatelets – n (%)	313 (27.0)	143 (29.9)	121 (23.8)	49 (28.8)
Cancer – n (%)				
Active	143 (12.3)	90 (18.8)	46 (9.0)	7 (4.1)
Prior	113 (9.8)	69 (14.4)	30 (5.9)	14 (8.2)
Prior venous thromboembolic event – n (%)	37 (3.2)	23 (4.8)	12 (2.4)	2 (1.2)
FEV1 - liters (mean ± SD)	1.38 ± 0.62[9]	1.34 ± 0.59[10]	1.91 ± 0.79[11]	1.58 ± 0.71[12]
%FEV1 (mean ± SD)	54 ± 19[13]	53 ± 19[14]	59 ± 25[15]	64 ± 13[16]
GOLD stage – n (%)				
1	46/530 (8.7)	40/476 (8.4)	4/34 (11.8)	2/20 (10.0)
2	258/530 (48.7)	227/476 (47.7)	17/34 (50.0)	14/20 (70.0)
3	165/530 (31.1)	152/476 (31.9)	9/34 (26.5)	4/20 (20.0)
4	61/530 (11.5)	57/476 (12.0)	4/34 (11.8)	0/20 (0.0)
Purulent COPD exacerbation – n (%)	390 (33.7)	180 (37.6)	155 (30.5)	55 (32.4)

Hospitalization after the visit at the emergency department – n (%)	464 (40.1)	236 (49.3)	157 (30.8)	71 (41.8)

COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; FEV1/FVC: forced expiratory volume in 1 second / forced vital capacity;
[1]322 participants; [2]173 participants; [3]99 participants; [4]50 participants; [5]299 participants; [6]166 participants; [7]92 participants; [8]41 participants; [9]508 participants; [10]467 participants; [11]24 participants; [12]17 participants; [13]530 participants; [14]476 participants; [15]34 participants; [6]20 participants;

Table 2. Prevalence of PE at the initial assessment and during the 3-month follow-up

	Entire cohort No./Total (%) [95%CI]	Confirmed COPD by spirometry No./Total (%) [95%CI]	Diagnosis of COPD supported by imaging only No./Total (%) [95%CI]	Diagnosis of COPD written in the chart only No./Total (%) [95%CI]
PE at initial assessment– n (%)	5/1158[1] (0.4) [0.1-1.0]	2/479[1] (0.4) [0.1-1.5]	0/509 (0.0) [0.0-0.0]	3/170 (1.8) [0.4-5.1]
PE at initial assessment based on type of exacerbation – n (%)				
Purulent exacerbation	0/390 (0.0)	0/180 (0.0)	0/155 (0.0)	0/55 (0.0)
Non-purulent exacerbation	3/465 (0.6)	0/185 (0.0)	0/214 (0.0)	3/66 (4.5)
Unknown	2/303 (0.7)	2/114 (1.8)	0/140 (0.0)	0/49 (0.0)
	p=0.27	p=0.06		p=0.11
PE at initial assessment based on clinical setting - n (%)				
Hospitalized	5/464 (1.1)	2/236 (0.8)	0/157 (0.0)	3/71 (4.2)
Discharged from the ED	0/694 (0.0)	0/243 (0.0)	0/352 (0.0)	0/99 (0.0)
	p=0.01	p=0.24		p=0.07
PE during follow-up – n (%)	8/1141 (0.7) [0.3-1.4]	3/477 (0.6) [0.1-1.8]	4/501 (0.8) [0.2-2.0]	1/163 (0.6) [0.0-3.4]

COPD: chronic obstructive pulmonary disease; DVT: deep venous thrombosis; ED: emergency department; PE: pulmonary embolism; [1]Concomitant DVT and PE in one patient;

Table 3. Mortality

	Entire cohort (n=1158)	Confirmed COPD by spirometry (n=479)	Diagnosis of COPD supported by imaging only (n=509)	Diagnosis of COPD written in the chart only (n=170)
Mortality – n (%)	71 (6.1)	29 (6.1)	25 (4.9)	17 (10.0)
Fatal PE – n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mortality amongst patients with PE	2/13 (15.4)	0/5 (0.0)	0/4 (0.0)	2/4 (50.0)
Mortality amongst patients without PE	69/1145 (6.0)	29/474 (6.1)	25/505 (5.0)	15/166 (9.0)
	p=0.19	p=1.00	p=1.00	p=0.05

COPD: chronic obstructive pulmonary disease; PE: pulmonary embolism.

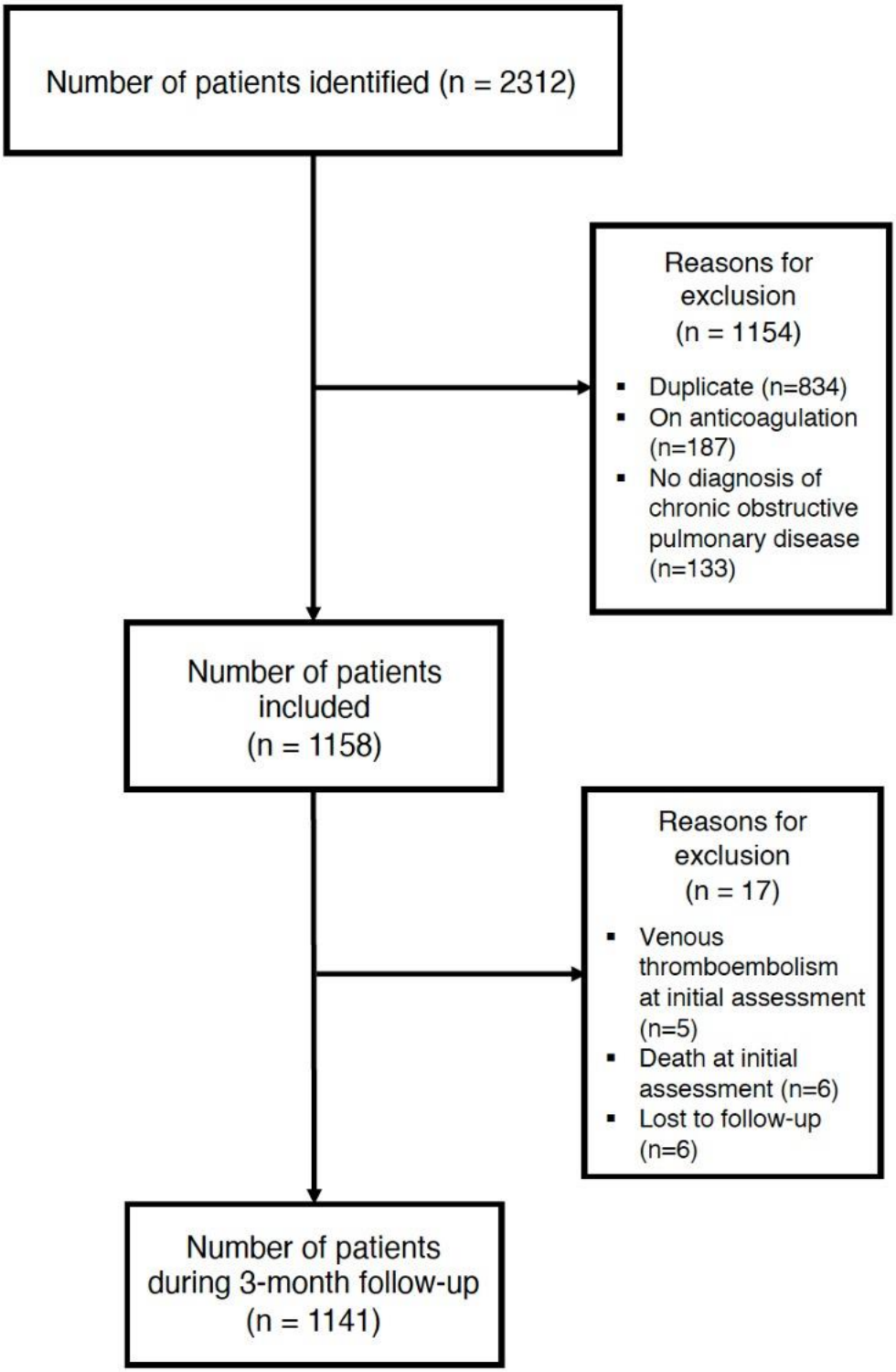

Figure 1. Patients flow diagram.

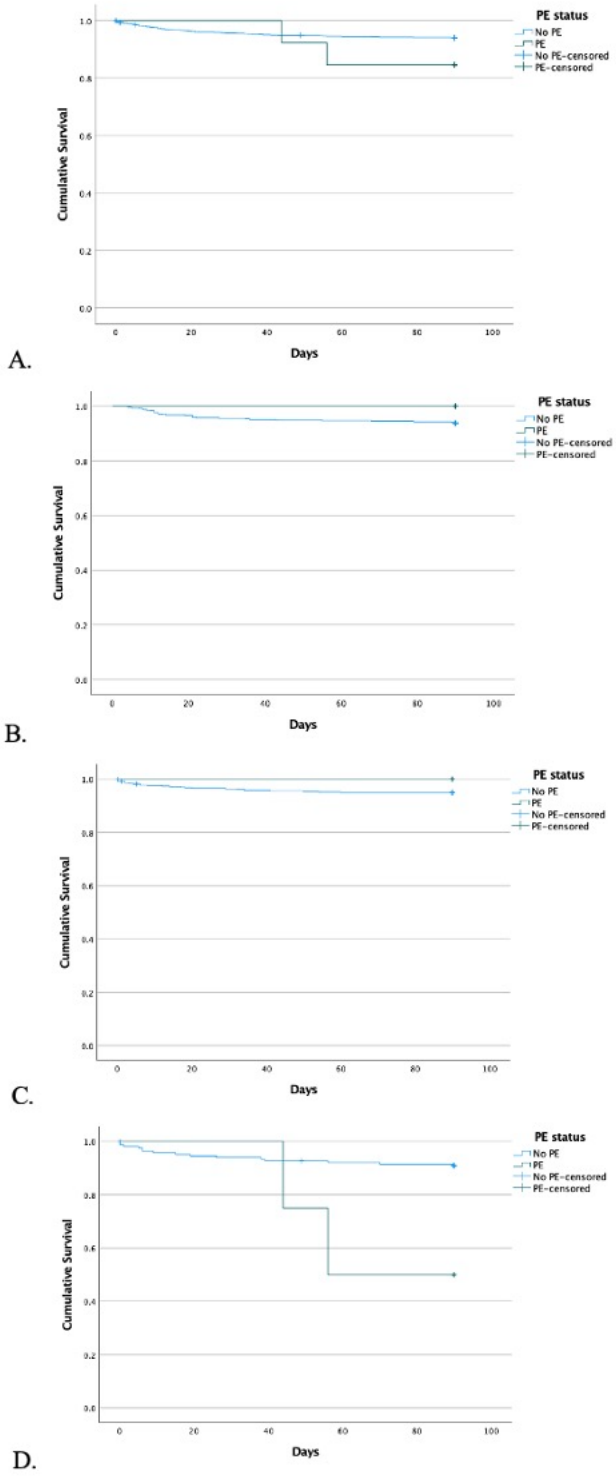

Figure 2. Mortality in patients with chronic obstructive pulmonary disease (COPD) exacerbation and pulmonary embolism compared to those without pulmonary embolism.

A (entire cohort; p=0.18), B (diagnosis of COPD confirmed by spirometry; p=0.57), C (diagnosis of COPD supported by imaging; p=0.65) and D (diagnosis of COPD written in the chart only; p=0.01).

CHAPTER 3: Manuscript 2- Safety and efficiency of diagnostic strategies for ruling out pulmonary embolism in patients with chronic lung disease: an individual-patient data meta-analysis

3.1 Preface to manuscript 2

For this project, I had the opportunity to collaborate with well-established international authors in the field of thrombosis. Working on this project gave me the chance to explore furthermore another study design: an IPDMA. This study included 12 studies, representing 16,990 patients (2,201 patients with chronic lung disease and 14,789 patients without chronic lung disease). This IPDMA evaluated the safety and efficiency of the revised Geneva and Wells PE scores in combination with D-dimers (fixed or age-adjusted) and the YEARS and PEGeD algorithms in patients with chronic lung disease. I worked on the literature review, study conception, interpretation of the data and manuscript drafting. Co-authors participated in the screening and selection of studies, data extraction, data analysis, risk of bias assessment, supervision and revision of the manuscript.

The abstract has been accepted for a poster presentation at ISTH annual conference 2025 in Washington.

The manuscript has been submitted to a peer-reviewed journal.

3.2 Manuscript 2

Safety and Efficiency of Diagnostic Strategies for Ruling Out Pulmonary Embolism in Patients with Chronic Lung Disease: An Individual-Patient Data Meta-Analysis.

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Abstract: 282 words
Manuscript: 2371 words

ABSTRACT

Introduction: The appropriate diagnostic management of patients with chronic lung disease and a suspicion of pulmonary embolism (PE) is unclear. Limited data exist on currently available PE diagnostic strategies, which have not been validated in patients with chronic lung disease. The aim of this study is to compare the performance of currently available PE diagnostic strategies between patients with and without chronic lung disease.

Methods: This is an individual-patient data meta-analysis. MEDLINE was searched from January 1, 1995 to January 1, 2021 for prospective or cross-sectional studies evaluating diagnostic strategies for PE. Studies for which information on chronic lung disease was not available were excluded. The main outcomes were safety (as defined by the diagnostic failure rate) and efficiency of each PE diagnostic strategy. Efficiency was defined as the number of patients in whom PE was considered excluded based on the diagnostic strategy among all patients.

Results: Twelve studies, representing 16,990 patients (2,201 patients with chronic lung disease and 14,789 patients without chronic lung disease), were included. The pooled prevalence of venous thromboembolism was 21.0% and 14.8% in patients without and with chronic lung disease, respectively. The safety of each PE diagnostic strategy was largely similar in patients with chronic lung disease compared to patients without chronic lung disease. PE diagnostic strategies were more efficient in patients without chronic lung disease compared to patients with chronic lung disease with the PEGeD algorithm being the most efficient (46.8%; 95%CI 41.1%-52.6%).

Conclusion: In patients with chronic lung disease, the Wells and revised Geneva scores combined with D-dimer (fixed or age-adjusted) were the safest diagnostic strategies, but their efficiency was low. Further studies are needed to improve PE diagnostic strategies in patients with chronic lung disease.

INTRODUCTION

In the general population, clinical decision rules (CDRs), such as the Wells PE(1) and revised Geneva(2) scores, have been derived and validated to help the clinician evaluate clinical pre-test probability (c-PTP) of a patient suspected of having a pulmonary embolism (PE). Moreover, PE diagnostic strategies have been refined by combining c-PTP assessment using CDRs with D-dimer testing, which help decide if imaging is needed to rule out PE(3). Computed tomography pulmonary angiography (CTPA) is the most frequently used radiological modality to rule out PE. However, it is associated with radiation exposure, costs, a climate impact due to use of energy and natural resources, possible contrast-induced allergy or nephropathy and incidental findings that are of unknown relevance. To reduce the need for imaging, newer PE diagnostic strategies have been developed, such as the ADJUST-PE(4) and YEARS algorithms(5). ADJUST-PE consists of c-PTP assessment using a CDR, either the Wells score or the revised Geneva score, combined with D-dimer testing using an age-adjusted cut-off(4). The YEARS algorithm consists of a 3-item score (clinical signs of deep venous thrombosis (DVT), hemoptysis and PE is the most likely diagnosis) combined with D-dimer testing using two different cut-offs depending on the number of items (<1000 ng/ml in patients with no item and <500 ng/ml in patients with at least one item)(5).

Patients with chronic lung disease are a challenging population because, in the context of an exacerbation, they tend to present with symptoms similar to those of a PE, making it difficult to differentiate between the two diseases. Chronic obstructive pulmonary disease (COPD) is one of the most common causes of chronic lung disease among patients included in PE diagnostic studies. Patients with COPD most often tend to have other risk factors for PE, and the acute exacerbation of COPD (AECOPD) is also a risk factor for PE in itself(6). Since current PE diagnostic strategies

have not been specifically derived and validated in this special population and approximately 10% of patients in PE diagnostic studies had COPD(2, 3, 5), it is currently unclear how current PE diagnostic strategies perform in these patients. A recent study evaluated current PE diagnostic strategies in a cohort of 740 patients with COPD hospitalized with acute worsening respiratory symptoms and showed that the Wells PE and revised Geneva scores combined with fixed D-dimer cut-off had a low (and thus safe) diagnostic failure rate, but that a high proportion of patients would need a CTPA to rule out PE, making this approach relatively inefficient. Recent PE diagnostic strategies, such as the ADJUST-PE, YEARS, PEGeD and 4PEPS algorithms, would reduce the need for imaging by up to 32%, but at the expense of an increase in the diagnostic failure rate(7).

However, no study has evaluated PE diagnostic strategies specifically in patients with chronic lung disease. Thus, it remains unclear how patients with chronic lung disease and a clinical suspicion of PE should be approached for appropriate diagnostic management. The aim of this study is to compare the performance of currently available CDRs (Wells PE and revised Geneva scores in combination with D-dimer testing [fixed or age-adjusted], YEARS and PEGeD algorithms) between patients with and without chronic lung disease.

METHODS

This is a secondary analysis of a published individual-patient data meta-analysis (IPDMA) (8). This article followed the guidance from the PRISMA-IPD (PRISMA for Individual Data systematic reviews)(9) and PRISMA-DTA (PRISMA for Diagnostic Test Accuracy)(10) statements.

Individual patient-data meta-analysis of PE diagnostic studies

The systematic search of the main IPDMA was conducted in MEDLINE from January 1, 1995 to January 1, 2021 for studies evaluating diagnostic strategies for PE. Eligible studies were prospective cohort studies or cross-sectional studies including patients with a suspicion of PE and available data to calculate at least one predefined CDR of interest. Studies with qualitative D-dimer measurements only or with patients at low c-PTP only were excluded. Study selection was performed independently by two pairs of authors (N.K. and G.J.G., and N.v.E. and F.A.K.). Patient-level data of each included study was requested from the principal investigators. Quality assessment of each included study was evaluated independently using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) tool(11) by 3 pairs of authors (G.J.G. and T.T., N.v.E. and N.K., and F.A.K. and M.A.M.S). Further details on the main IDPMA can be found elsewhere(8).

Eligibility criteria

In addition to the exclusion criteria stated above, we excluded studies that did not collect data on chronic lung diseases(12-15).

Outcomes

The main outcomes of our analysis were safety and efficiency of each PE diagnostic strategy. Safety was defined as the failure rate, which was the proportion of patients diagnosed with venous thromboembolism (VTE) at baseline or during follow-up among patients in whom PE would have been considered ruled out at baseline according to each assessed PE diagnostic strategy. Efficiency was defined as the number of patients in whom PE would have been considered excluded based

on each assessed PE diagnostic strategy among all patients. Assessed PE diagnostic strategies were the Wells PE(1) and revised Geneva(2) scores (combined with fixed and age-adjusted D-dimer cut-offs(4)), YEARS algorithm(5) and PEGeD algorithm(12) (using the Wells PE and revised Geneva scores) (**Tables S1-S3**). Secondary outcomes included the diagnostic yield of D-dimer, all-cause mortality and PE-related mortality. Diagnostic yield of D-dimer was defined as the proportion of patients with a diagnosis of PE based on positivity of D-dimer (fixed and age-adjusted). All-cause mortality and PE-related mortality were planned a priori but could not be assessed since data on mortality was not available.

Data synthesis and analysis

Baseline characteristics of the studies are presented without imputation. To handle partially missing data, imputation was performed in the dataset of the included 16 studies(3-5, 12-24) of the main IPDMA(8) by using 1-stage multilevel chained equations. Ten datasets were created and the Rubin rule was used to combine the results of the analyses performed separately in these 10 datasets(25). The analyses were performed using the 12 studies included (3-5, 16-24) in this secondary analysis. The safety and efficiency of each PE diagnostic strategy was calculated with their 95% confidence interval (95%CI) using random-effects model in the overall cohort, in patients with chronic lung disease and in patients without chronic lung disease. Heterogeneity was assessed by calculating 95% prediction interval and tau coefficient. Crosshair figures were created. The diagnostic yield of D-dimer was also calculated and presented with its 95%CI for the overall cohort, for patients with chronic lung disease and for patients without chronic lung disease. Analyses were performed using using R, version 4.3.1 (R Foundation for Statistical Computing; www.R-project.org) and SAS software (Copyright © [9.4] SAS Institute Inc.).

RESULTS

Study selection and included patients

Twelve studies(3-5, 16-24) met eligibility and were included in this analysis, representing 16,990 patients. Characteristics of the 12 included studies(3-5, 16-24) can be found in **Table 1**. The proportion of patients with chronic lung disease per study varied between 9.3% and 36.0%. Baseline characteristics of patients included in the overall cohort of this secondary analysis can be found in **Table 2**. Among 16,990 included patients, 2,201 (13.0%) patients had chronic lung disease. Patients with chronic lung disease were older and a higher proportion were inpatients (**Table 2**). The overall pooled prevalence of VTE was 20.2% (95%CI 19.6%-20.9%). The pooled prevalence of VTE was 21.0% (95%CI 20.3%-21.8%) and 14.8% (95%CI 13.2%-16.6%) in patients without chronic lung disease and in patients with chronic lung disease, respectively. The study-level risk of bias can be found in **Figure S1**.

Safety and efficiency

In patients with chronic lung disease, the failure rate was 0.60% (95%CI 0.14%-2.50%) with the Wells score with fixed D-dimer, 1.06% (95%CI 0.44%-2.53%) with the Wells score with age-adjusted D-dimer, 0.58% (95%CI 0.10%-3.20%) with the revised Geneva score with fixed D-dimer, 0.87% (95%CI 0.30%-2.50%) with the revised Geneva score with age-adjusted D-dimer, 2.96% (95%CI 1.79%-4.86%) with the YEARS algorithm, 3.12% (95%CI 2.04%-4.74%) with the PEGeD algorithm (Wells) and 2.54% (95%CI 1.45%-4.39%) with the PEGeD algorithm (revised Geneva). In patients without chronic lung disease, the failure rate was comparable or lower than in patients with chronic lung disease for each PE diagnostic strategy (**Table 3** and **Figure 1**).

For each PE diagnostic strategy, efficiency was lower in patients with chronic lung disease compared to patients without chronic lung disease (**Table 4** and **Figure 1**). In patients with chronic lung disease, the PEGeD algorithm (Wells) was the most efficient (43.9%; 95%CI 37.9%-50.0%) and the Wells score with fixed D-dimer was the least efficient (19.0%; 95%CI 14.8%-24.2%) (**Table 4** and **Figure 1**).

For the safety and efficiency, tau coefficients and large prediction intervals demonstrated considerable between-study heterogeneity (**Tables 3-4**).

Diagnostic yield of using only D-dimer

When using fixed D-dimer cut-off, PE was diagnosed in 0.7% (95%CI 0.5%-1.0%) and in 1.1% (95%CI 0.5%-2.6%) patients with negative D-dimer without and with chronic lung disease, respectively, and PE was diagnosed in 31.4% (95%CI 30.4%-32.4%) and in 19.6% (95%CI 17.7%-21.6%) patients with positive D-dimer without and with chronic lung disease, respectively. When using the age-adjusted D-dimer cut-off, PE was diagnosed in 1.2% (95%CI 1.0%-1.5%) and in 1.6% (95%CI 1.0%-2.7%) patients with negative D-dimer without and with chronic lung disease, respectively, and PE was diagnosed in 34.1% (95%CI 33.0%-35.2%) and in 22.9% (95%CI 20.7%-25.4%) patients with positive D-dimer without and with chronic lung disease, respectively (**Table S4**).

DISCUSSION

In this IPDMA of 16,990 patients, the safety of each PE diagnostic strategy was largely similar in patients with and without chronic lung disease. The failure rate was the lowest with the Wells PE and revised Geneva scores combined with fixed D-dimer, followed by the Wells PE and revised

Geneva scores combined with age-adjusted D-dimer. However, failure rates were higher with the YEARS and PEGeD algorithms. In terms of efficiency, PE diagnostic strategies were more efficient in patients without chronic lung disease compared to patients with chronic lung disease. The PEGeD algorithm (Wells) was the most efficient and the Wells score combined with fixed D-dimer was the least efficient. Moreover, the diagnostic yield of D-dimer was lower in patients with chronic lung disease than in patients without chronic lung disease.

For new PE diagnostic algorithms, the International Society of Thrombosis and Haemostasis (ISTH) recommended using a safety threshold calculated based on the prevalence of PE in the cohort(26). With a prevalence of VTE of 20.2%, the calculated safety threshold, defined as the 95%CI upper limit of the failure rate, would be approximately 1.93%. However, these recommendations were made based on studies evaluating PE diagnostic strategies in the general population(26). Since patients with chronic lung disease have a higher baseline risk of PE(27), some venous thromboembolic events diagnosed during follow-up could be incident events rather than events missed at the initial evaluation, and thus, we used a slightly higher upper margin for the safety threshold, i.e. in the range of 2.0%-3.0%, instead of the calculated safety threshold according to the prevalence of PE. When considering the safety threshold of 2.0%-3.0%, the Wells score combined with fixed or age-adjusted D-dimer and the revised Geneva score combined with fixed D-dimer would be safe in patients with chronic lung disease. However, up to 81.0% of the patients would need imaging to rule out PE which is not optimal, considering that patients with COPD have 0.5-3.5 exacerbations/patient/year and that exacerbations become more frequent as the severity of the COPD progresses(28, 29). Consequently, using these PE diagnostic strategies might expose these patients to a high number of CTPA and with its inconveniences such as

radiation, cost, a climate impact, possible contrast-induced allergy or nephropathy and incidental findings. On the other hand, using CTPA-sparing diagnostic strategies, such as the YEARS or PEGeD algorithms, would avoid unnecessary imaging, but at the expense of an increase in the diagnostic failure rate, higher than usually accepted.

The results on the diagnostic yield of D-dimer are also of interest. In patients with positive D-dimer, either with fixed or age-adjusted cut-offs, the percentage of diagnosed VTE was lower in patients with chronic lung disease than in patients without chronic lung disease. Suspicion bias can partly explain the lower rate of VTE diagnosed in patients with chronic lung disease compared to patients without chronic lung disease. Indeed, it is well known from physicians that respiratory failure is a risk factor for PE that it is not major, which leads to more investigations in these patients which can explain why the confirmation rate is lower among these patients. Moreover, these results support data demonstrating that D-dimer level is higher in patients with AECOPD than normally expected(30-32), possibly due to concomitant inflammation/infection. In addition, it is also reassuring to see that the percentage of VTE diagnosed in patients with chronic lung disease and negative D-dimer was reasonably low and might be even lower if restricted to patients with non-high c-PTP, considering that some included patients had high c-PTP.

This study presents some limitations. First, chronic lung disease is a broad term and specifications on the included respiratory diseases were not available in the primary studies. Second, misclassification according to the chronic lung disease status could be present since the diagnosis of chronic lung disease was not made according to predefined diagnostic criteria such as spirometry confirmation of a forced expiratory volume in 1 second/forced vital capacity <0.70 for

patients with COPD. The effect of the misclassification on the results is unknown but may have been limited since these results are in line with a recent study conducted specifically in patients with COPD(7). Third, heterogeneity was considerable for the analyses on safety and efficiency, which could reduce the confidence we have in the estimates. This study also has some strengths. To our knowledge, current PE diagnostic strategies were assessed in the largest cohort of patients with chronic lung disease. With this large sample size (>16,000 participants, including over 2,200 patients with chronic lung disease), CIs are narrow which increase the confidence we have in the results. This is also an international population with patients from Europe and North America. Moreover, most available PE diagnostic strategies except the 4PEPS algorithm(33) were evaluated in this study.

In conclusion, in patients with chronic lung disease, the Wells and revised Geneva scores combined with D-dimer (fixed or age-adjusted) were the safest diagnostic strategies, but the efficiency was low. Further studies are needed to improve PE diagnostic strategies in patients with chronic lung disease.

REFERENCES

1. Wells PS, Anderson DR, Rodger M, Stiell I, Dreyer JF, Barnes D, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. Ann Intern Med. 2001;135(2):98-107.

2. Le Gal G, Righini M, Roy PM, Sanchez O, Aujesky D, Bounameaux H, et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Ann Intern Med. 2006;144(3):165-71.

3. van Belle A, Büller HR, Huisman MV, Huisman PM, Kaasjager K, Kamphuisen PW, et al. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. Jama. 2006;295(2):172-9.

4. Righini M, Van Es J, Den Exter PL, Roy PM, Verschuren F, Ghuysen A, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. JAMA. 2014;311(11):1117-24.

5. van der Hulle T, Cheung WY, Kooij S, Beenen LFM, van Bemmel T, van Es J, et al. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. Lancet. 2017;390(10091):289-97.

6. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing G-J, Harjola V-P, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). 2019:1901647.

7. Rambaud G, Mai V, Motreff C, Sanchez O, Roy PM, Auffret Y, et al. Pulmonary embolism diagnostic strategies in patients with COPD exacerbation: Post-hoc analysis of the PEP trial. Thrombosis Research. 2023;231:58-64.

8. Stals MAM, Takada T, Kraaijpoel N, van Es N, Büller HR, Courtney DM, et al. Safety and Efficiency of Diagnostic Strategies for Ruling Out Pulmonary Embolism in Clinically Relevant Patient Subgroups : A Systematic Review and Individual-Patient Data Meta-analysis. Ann Intern Med. 2022;175(2):244-55.

9. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. Jama. 2015;313(16):1657-65.

10. Salameh JP, Bossuyt PM, McGrath TA, Thombs BD, Hyde CJ, Macaskill P, et al. Preferred reporting items for systematic review and meta-analysis of diagnostic test accuracy studies (PRISMA-DTA): explanation, elaboration, and checklist. Bmj. 2020;370:m2632.

11. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529-36.

12. Kearon C, de Wit K, Parpia S, Schulman S, Afilalo M, Hirsch A, et al. Diagnosis of Pulmonary Embolism with d-Dimer Adjusted to Clinical Probability. New England Journal of Medicine. 2019;381(22):2125-34.

13. Galipienzo J, Garcia de Tena J, Flores J, Alvarez C, Garcia-Avello A, Arribas I. Effectiveness of a diagnostic algorithm combining clinical probability, D-dimer testing, and computed tomography in patients with suspected pulmonary embolism in an emergency department. Romanian Journal of Internal Medicine. 2012;50(3):195-202.

14. Ghanima W, Almaas V, Aballi S, Dorje C, Nielssen BE, Holmen LO, et al. Management of suspected pulmonary embolism (PE) by D-dimer and multi-slice computed tomography in outpatients: an outcome study. Journal of Thrombosis & Haemostasis. 2005;3(9):1926-32.

15. Penaloza A, Soulie C, Moumneh T, Delmez Q, Ghuysen A, El Kouri D, et al. Pulmonary embolism rule-out criteria (PERC) rule in European patients with low implicit clinical probability (PERCEPIC): a multicentre, prospective, observational study. The Lancet Haematology. 2017;4(12):e615-e21.

16. Kline JA, Hogg MM, Courtney DM, Miller CD, Jones AE, Smithline HA. D-dimer threshold increase with pretest probability unlikely for pulmonary embolism to decrease unnecessary computerized tomographic pulmonary angiography. Journal of Thrombosis & Haemostasis. 2012;10(4):572-81.

17. Douma RA, Mos IC, Erkens PM, Nizet TA, Durian MF, Hovens MM, et al. Performance of 4 clinical decision rules in the diagnostic management of acute pulmonary embolism: a prospective cohort study. Annals of Internal Medicine. 2011;154(11):709-18.

18. Goekoop RJ, Steeghs N, Niessen RW, Jonkers GJ, Dik H, Castel A, et al. Simple and safe exclusion of pulmonary embolism in outpatients using quantitative D-dimer and Wells' simplified decision rule. Thrombosis & Haemostasis. 2007;97(1):146-50.

19. Schouten HJ, Geersing GJ, Oudega R, van Delden JJ, Moons KG, Koek HL. Accuracy of the Wells clinical prediction rule for pulmonary embolism in older ambulatory adults. Journal of the American Geriatrics Society. 2014;62(11):2136-41.

20. Mos IC, Douma RA, Erkens PM, Kruip MJ, Hovens MM, van Houten AA, et al. Diagnostic outcome management study in patients with clinically suspected recurrent acute pulmonary embolism with a structured algorithm. Thromb Res. 2014;133(6):1039-44.

21. Wicki J, Perneger TV, Junod AF, Bounameaux H, Perrier A. Assessing clinical probability of pulmonary embolism in the emergency ward: a simple score. Archives of Internal Medicine. 2001;161(1):92-7.

22. Perrier A, Roy PM, Aujesky D, Chagnon I, Howarth N, Gourdier AL, et al. Diagnosing pulmonary embolism in outpatients with clinical assessment, D-dimer measurement, venous ultrasound, and helical computed tomography: a multicenter management study. American Journal of Medicine. 2004;116(5):291-9.

23. Righini M, Le Gal G, Aujesky D, Roy PM, Sanchez O, Verschuren F, et al. Diagnosis of pulmonary embolism by multidetector CT alone or combined with venous ultrasonography of the leg: a randomised non-inferiority trial. Lancet. 2008;371(9621):1343-52.

24. Perrier A, Roy PM, Sanchez O, Le Gal G, Meyer G, Gourdier AL, et al. Multidetector-row computed tomography in suspected pulmonary embolism. N Engl J Med. 2005;352(17):1760-8.

25. Marshall A, Altman DG, Holder RL, Royston P. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. BMC Medical Research Methodology. 2009;9(1):57.

26. Dronkers CEA, van der Hulle T, Le Gal G, Kyrle PA, Huisman MV, Cannegieter SC, et al. Towards a tailored diagnostic standard for future diagnostic studies in pulmonary embolism: communication from the SSC of the ISTH. J Thromb Haemost. 2017;15(5):1040-3.

27. Keramidas G, Gourgoulianis KI, Kotsiou OS. Venous Thromboembolic Disease in Chronic Inflammatory Lung Diseases: Knowns and Unknowns. Journal of Clinical Medicine. 2021;10(10):11.

28. Seemungal TAR, Hurst JR, Wedzicha JA. Exacerbation rate, health status and mortality in COPD--a review of potential interventions. Int J Chron Obstruct Pulmon Dis. 2009;4:203-23.

29. Anzueto A. Impact of exacerbations on COPD. European Respiratory Review. 2010;19(116):113-8.

30. Kampolis CF, Moschos C, Loukeri AA, Spithakis P-D, Stratos E, Papapetrou D, et al. D-dimer testing in patients with acute exacerbation of COPD and suspected pulmonary embolism. European Respiratory Journal. 2015;46(suppl 59):PA3772.

31. Akpinar E, Hosgun D, Doganay B, Gulhan M. Cut-off value of D-dimer in diagnosis of pulmonary embolism in patients with chronic obstructive lung disease. European Respiratory Journal Conference: European Respiratory Society Annual Congress. 2013;42(SUPPL. 57).

32. Sadeghi S, Ardestani ME, Raofi E, Jalaie Esfandabadi A. Diagnostic value of d-dimer in detecting pulmonary embolism in patients with acute copd exacerbation. Tanaffos. 2020;19(4):371-9.

33. Roy P-M, Friou E, Germeau B, Douillet D, Kline JA, Righini M, et al. Derivation and Validation of a 4-Level Clinical Pretest Probability Score for Suspected Pulmonary Embolism to Safely Decrease Imaging Testing. JAMA Cardiology. 2021;6(6):669-77.

Table 1. Characteristics of included studies[+]

Study, year	Number of patients provided by the authors	Main objective of the study	Median age (IQR), years	Female, n (%)	Inpatients, n (%)	Previous VTE, n (%)	Chronic lung disease, n (%)	Patients with VTE diagnosed at baseline or during follow-up, n (%)
Kline et al, 2012 (16)	333	To measure the effect of doubling the D-dimer threshold in patients with "PE unlikely" with the revised Geneva or Wells scores.	57 (47-66)	199 (59.8)	333 (100.0)	50 (15.0)	120 (36.0)	77 (23.1)
Douma et al, 2011(17)	807	To compare the performance of 4 CDRs[ϕ] combined with D-dimer testing.	54 (40-67)	487 (60.3)	163 (20.2)	39 (4.8)	75 (9.3)	192 (23.8)[*]
Goekoop et al, 2007(18)	876	To evaluate the safety and efficiency of the simplified Wells score combined with D-dimer testing.	50 (38-65)	549 (62.7)	0 (0.0)	83 (9.5)	113 (12.9)	110 (12.6)[*]
Righini et al, 2014(4)	3324	To evaluate the diagnostic yield of an age-adjusted D-dimer cut-off.	63 (53-73)	1887 (56.8)	0 (0.0)	466 (14.0)	523 (15.7)	639 (19.2)
Schouten et al, 2014(19)	294	To determine if the Wells score combined with normal D-dimer testing can be used in older unhospitalized adults.	76 (67-84)	195 (66.3)	0 (0.0)	51 (17.3)	54 (18.4)	83 (28.2)
van Belle et al, 2006(3)	3296	To assess the clinical effectiveness of the simplified Wells score combined with D-dimer testing. .	52 (39-68)	1891 (57.4)	605 (18.4)	425 (12.9)	341 (10.3)	699 (21.2)

van der Hulle et al, 2017(5)	3448	To evaluate the YEARS algorithm.	54 (40-67)	2142 (62.1)	468 (13.6)	359 (10.4)	423 (12.3)	473 (13.7)
Mos et al, 2014(20)	279	To evaluate the safety of the Wells score combined with D-dimer testing in patients with clinically suspected acute recurrent PE.	54 (42-68)	163 (58.4)	36 (12.9)	279 (100.0)	36 (12.9)	114 (40.9)
Wicki et al, 2001(21)	1089	To develop a simple standardized clinical score assessing clinical pre-test probability of emergency ward patients (Geneva score).	62 (46-76)	597 (54.8)	0 (0.0)	202 (18.5)	132 (12.1)	296 (27.2)
Perrier et al, 2004(22)	965	To evaluate the Geneva score combined with D-dimer testing and lower limb compression ultrasound.	63 (45-77)	562 (58.2)	0 (0.0)	166 (17.2)	99 (10.3)	229 (23.7)
Righini et al, 2008(23)	755	To compare two strategies: 1) revised Geneva score with D-dimer testing; 2) revised Geneva score with D-dimer testing and venous compression ultrasound of the leg (if D-dimer > 500 ng/mL or high clinical probability.	63 (45-76)	453 (60.0)	0 (0.0)	142 (18.8)	79 (10.5)	197 (26.1)
Perrier et al, 2005(24)	1692	To evaluate Geneva score combined with D-dimer testing.	61 (45-75)	923 (54.6)	0 (0.0)	300 (17.7)	206 (12.2)	361 (21.3)

[+]Dataset without imputation; [*]Only patients in whom PE was excluded at baseline based on a low clinical probability and low D-dimer (i.e., without imaging) were followed over time; [ϕ]Wells rule and revised Geneva score (original and simplified); CDR: clinical decision rule; IQR: interquartile range; PE: pulmonary embolism; VTE: venous thromboembolism;

Table 2. Baseline characteristics of patients in the overall cohort[+]

Characteristics	Overall (n=16,990)	Absence of chronic lung disease (n=14,789)	Presence of chronic lung disease (n=2201)
Age, years (mean ± SD)	57.0 ± 18.3	55.6 ± 18.5	66.0 ± 13.8
Female, n (%)	9963 (58.6)	8828 (57.0)	1135 (51.6)
Body mass index, kg/m^2 (mean ± SD)	30.6 ± 8.4	30.7 ± 8.5	30.4 (8.4)
Previous VTE, n (%)	2506 (14.7)	2165 (14.6)	341 (15.5)
Cancer, n (%)	1829 (10.8)	1569 (10.6)	260 (11.8)
Inpatients, n (%)	1596 (9.4)	1292 (8.7)	304 (13.8)

[+]Dataset without imputation; SD: standard deviation

Table 3. Safety of each PE diagnostic strategy in the overall cohort and according to chronic lung disease status

PE diagnostic strategies	Overall	Chronic Lung Disease	
	n=16,990	No n=14,789	Yes n=2,201
Wells score (fixed D-dimer), %	0.45	0.43	0.60
95% CI	0.26-0.76	0.25-0.75	0.14-2.50
95% PI	0.18-1.08	0.18-1.07	0.10-3.48
τ Coefficient	0.28	0.28	
Wells score (age-adjusted D-dimer), %	0.79	0.77	1.06
95% CI	0.54-1.16	0.51-1.15	0.44-2.53
95% PI	0.38-1.65	0.36-1.63	0.32-3.38
τ Coefficient	0.26	0.27	
Revised Geneva score (fixed D-dimer), %	0.61	0.62	0.58
95% CI	0.35-1.06	0.35-1.08	0.10-3.20
95% PI	0.21-1.80	0.21-1.84	0.06-5.10
τ Coefficient	0.38	0.38	
Revised Geneva score (age-adjusted D-dimer), %	1.16	1.22	0.87
95% CI	0.77-1.75	0.80-1.85	0.30-2.50
95% PI	0.44-3.02	0.46-3.20	0.19-3.86
τ Coefficient	0.37	0.37	
YEARS algorithm, %	2.14	2.05	2.96
95% CI	1.61-2.83	1.52-2.74	1.79-4.86
95% PI	0.90-5.00	0.86-4.80	1.10-7.68
τ Coefficient	0.36	0.36	
PEGeD algorithm (Wells), %	3.12	3.15	3.12
95% CI	2.52-3.85	2.54-3.91	2.04-4.74

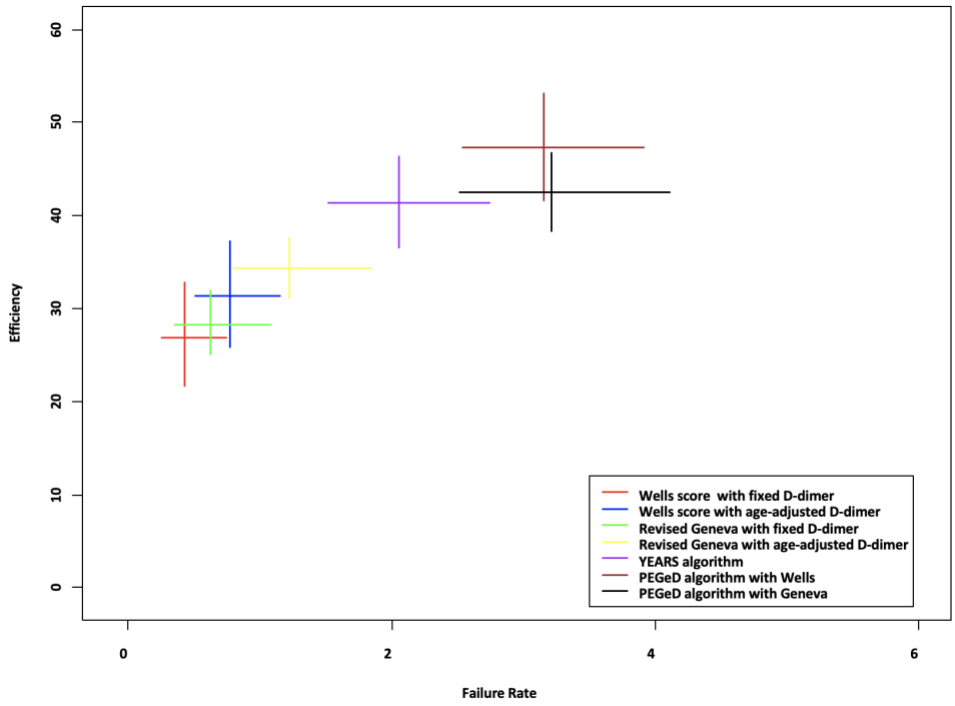
95% PI	1.62-5.90	1.65-5.95	1.43-6.63
τ Coefficient	0.27	0.27	
PEGeD algorithm (revised Geneva), %	3.10	3.21	2.54
95% CI	2.43-3.95	2.51-4.11	1.45-4.39
95% PI	1.51-6.27	1.55-6.52	0.99-6.32
τ Coefficient	0.29	0.30	

CI: confidence interval; PE: pulmonary embolism; PI: prediction interval;

Table 4. Efficiency* of each PE diagnostic strategy in the overall cohort and according to chronic lung disease status

PE diagnostic strategies	Overall	Chronic Lung Disease	
	n=16,990	No n=14,789	Yes n=2,201
Wells score (fixed D-dimer), %	25.8	26.9	19.0
95% CI	20.6-31.7	21.7-32.8	14.8-24.2
95% PI	9.9-51.8	10.7-52.7	7.0-41.9
τ Coefficient	0.50	0.49	
Wells score (age-adjusted D-dimer), %	30.8	31.4	27.3
95% CI	25.4-36.7	25.9-37.3	22.1-33.2
95% PI	13.4-55.8	13.8-56.2	11.5-51.6
τ Coefficient	0.46	0.49	
Revised Geneva score (fixed D-dimer), %	27.5	28.3	22.4
95% CI	24.1-31.1	25.1-31.9	19.2-26.0
95% PI	16.6-41.8	17.6-42.2	13.4-35.0
τ Coefficient	0.27	0.25	
Revised Geneva score (age-adjusted D-dimer), %	34.1	34.3	33.2
95% CI	30.9-37.4	31.1-37.6	29.5-37.1
95% PI	23.6-46.4	23.8-46.5	22.8-45.6
τ Coefficient	0.21	0.21	
YEARS algorithm, %	40.8	41.4	37.4
95% CI	36.0-45.9	36.6-46.4	32.4-42.6
95% PI	23.7-60.4	24.3-60.8	21.2-56.8
τ Coefficient	0.34	0.34	
PEGeD algorithm (Wells), %	46.8	47.3	43.9
95% CI	41.1-52.6	41.6-53.1	37.9-50.0
95% PI	26.0-68.7	26.6-69	23.9-66.0
τ Coefficient	0.40	0.40	
PEGeD algorithm (revised Geneva), %	41.5	42.5	35.8
95% CI	37.2-45.9	38.3-46.8	31.4-40.5
95% PI	26.6-58.1	27.8-58.6	22.4-51.9
τ Coefficient	0.28	0.27	

*Defined as the predicted probability of ruling out PE based on the CDR and D-dimer testing alone; CI: confidence interval; PE: pulmonary embolism; PI: prediction interval;



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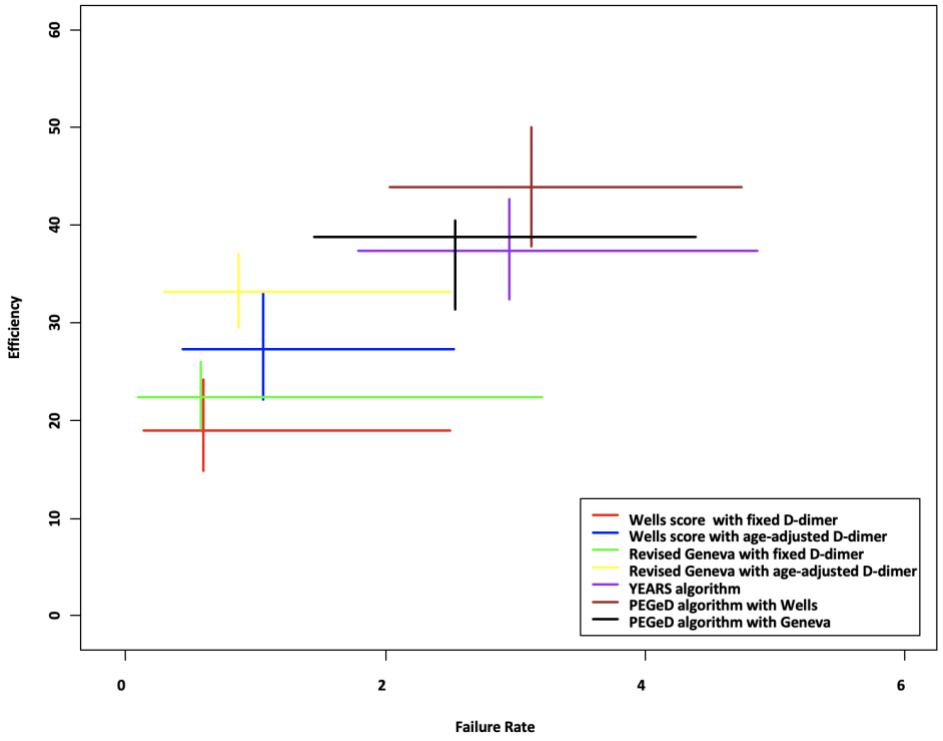

B.

Figure 1. Crosshair figures presenting the failure rate (safety) and efficiency of each PE diagnostic strategies A) in patients without chronic lung disease and B) in patients with chronic lung disease.

CHAPTER 4: Manuscript 3- Pulmonary embolism diagnostic strategies in patients with COPD exacerbation: Post-hoc analysis of the PEP trial

4.1 Preface to manuscript 3

To better understand the performance of all current PE diagnostic strategies specifically in patients with AECOPD, we conducted this post-hoc analysis of the PEP trial. The aim of this study was to evaluate the safety and efficacy of standard diagnostic strategies (revised Geneva and Wells PE score combined with fixed D-dimer cut-off) and CTPA-sparing diagnostic strategies (ADJUST-PE, YEARS, PEGeD and 4PEPS) in patients with COPD admitted for acutely worsening respiratory symptoms. I worked on the literature review, study conception, data analysis, interpretation of the data and manuscript drafting. Co-authors contributed to the patients' recruitment, data collection, supervision and revision of the manuscript.

Results of this study were presented at the ISTH annual conference 2023 in Montreal.

The paper was published in Thrombosis Research: Rambaud G*, Mai V*, Motreff C, Sanchez O, Roy PM, Auffret Y, Le Mao R, Gagnadoux F, Paleiron N, Schmidt J, Pastre J, Nonent M, Tromeur C, Salaun PY, Mismetti P, Girard P, Lacut K, Lemarié CA, Meyer G, Leroyer C, Le Gal G, Bertoletti L, Couturaud F; "PEP" investigators. Pulmonary embolism diagnostic strategies in patients with COPD exacerbation: Post-hoc analysis of the PEP trial. Thromb Res. 2023 Nov;231:58-64. *equal contributions

4.2 Manuscript 3

Pulmonary embolism diagnostic strategies in patients with COPD exacerbation: post-hoc analysis of the PEP trial

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*Members of The frequency of symptomatic **P**ulmonary embolism in patients with an acute **E**xacerbation of chronic obstructive **P**ulmonary disease (PEP) study Group are listed at the end of the article.

Manuscript word count: 2821
Abstract word count: 247
Tables: 2
Figure: 1

ABSTRACT

Background: The prevalence of pulmonary embolism (PE) is approximately 11-17% in patients with an acute exacerbation of chronic obstructive pulmonary disease (AE-COPD). The optimal diagnostic strategy for PE in these patients remains undetermined.

Aims: To evaluate the safety and efficacy of standard (revised Geneva and Wells PE scores combined with fixed D-dimer cut-off) and computed tomography pulmonary angiogram (CTPA)-sparing diagnostic strategies (ADJUST-PE, YEARS, PEGeD, 4PEPS) in patients with AE-COPD.

Method: *Post-hoc* analyses of data from the multicenter prospective PEP study were performed. The primary outcome was the diagnostic failure rate of venous thromboembolism (VTE) during the entire study period. Secondary outcomes included diagnostic failure rate of PE and deep venous thrombosis (DVT), respectively, during the entire study period and the number of CTPA needed per diagnostic strategy.

Results: 740 patients were included. The revised Geneva and Wells PE scores combined with fixed D-dimer cut-off had a diagnostic failure rate of VTE of 0.7% (95%CI 0.3%-1.7%), but >70.0% of the patients needed imaging. All CTPA-sparing diagnostic algorithms reduced the need for CTPAs (-10.1% to -32.4%, depending on the algorithm), at the cost of an increased VTE diagnosis failure rate of up to 2.1% (95%CI 1.2%-3.4%).

Conclusion: Revised Geneva and Wells PE scores combined with fixed D-dimer cut-off were safe, but a high number of CTPA remained needed. CTPA-sparing algorithms would reduce imaging, at the cost of an increased VTE diagnosis failure rate that exceeds the safety threshold. Further studies are needed to improve diagnostic management in this population.

Keywords list: chronic obstructive airway disease, chronic obstructive pulmonary disease, deep venous thrombosis, pulmonary embolism, venous thromboembolism

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) has an estimated global prevalence of >200 million cases [1] and is the third leading cause of mortality worldwide [2]. The occurrence of an acute exacerbation of COPD (AE-COPD), characterized by worsening respiratory symptoms, represents a leading cause of hospitalization and is associated with reduced quality of life and death [3]. The most frequent cause of AE-COPD is infection [4]. However, recent meta-analyses found a prevalence of pulmonary embolism (PE) of approximately 11-17% in AE-COPD patients [5-8]. Diagnosing PE in these patients is challenging due to confounding symptoms.

In a recent large prospective cohort of patients hospitalized for AE-COPD in which a standard diagnostic algorithm including pre-test probability assessment with the revised Geneva score was used, the overall prevalence of PE was 5.9% (95% confidence (CI) 4.5%-7.9%); when PE was not suspected clinically, the prevalence was lower at 3.2%, but not low enough (i.e. not <1.4%) to safely exclude the possibility of PE based on clinical grounds only [9, 10]. A high proportion of patients needed computed tomography pulmonary angiogram (CTPA) to rule out PE. Furthermore, the mortality was 27% in patients with PE, compared to 5% in patients without PE [9]. Therefore, the question was raised as to whether PE should be systematically searched in AE-COPD patients.

In a recent randomized trial evaluating usual care plus active search strategy over usual care only in patients admitted with AE-COPD without an initial clinical suspicion of PE, introducing an active diagnostic strategy for PE failed to show its superiority over usual care on a composite health outcome [11]. However, the prevalence of PE at admission was 4.6% in the active strategy group, confirming a non-negligible prevalence of PE even when it is not suspected in this population.

Consequently, the best PE diagnostic management for patients with AE-COPD is still unknown. Using standard diagnostic algorithm requires a high number of CTPA which is associated with cost, radiation and a risk for contrast-induced nephropathy, while ruling out PE based only on clinical judgement does not appear safe. Recently, CTPA-sparing diagnostic algorithms have been derived and validated in the general population to reduce the need for imaging [12-15]. How these new PE diagnostic strategies perform in patients with AE-COPD and whether they could reduce imaging in this population remains unclear [16].

In a post-hoc analysis, data from the prospective PEP study were used to evaluate the safety and efficacy of diagnostic strategies using pre-test probability assessment with the revised Geneva and Wells PE scores as well as CTPA-sparing diagnostic strategies (ADJUST-PE, YEARS, PEGeD and 4PEPS) in patients with COPD presenting with acute worsening of respiratory symptoms.

METHODS

We performed *post-hoc* analyses of the PEP study (NCT02035293). Its design and main results have been previously described [9]. Briefly, this multicenter prospective study (7 French hospitals) of patients with documented COPD admitted for acute worsening of respiratory symptoms was conducted from January 2014 to May 2017 with a 3-month follow-up. This study has been approved by the institutional review boards (IRB Ouest 6-797) and all patients gave consent to participate in the PEP study. All patients underwent a predefined PE diagnostic algorithm, which included pre-test probability assessment with the revised Geneva score, D-dimer levels and CTPA plus leg compression ultrasound (**e-Figure 1**). All clinical events of interest (i.e., PE, distal and proximal deep venous thrombosis [DVT] and all-cause mortality) were adjudicated by an independent committee. Amongst 740 patients included, 44 patients (5.9%; 95%CI 4.5%-7.9%)

were diagnosed with PE and 10 patients had an isolated DVT (1.4%, 95%CI 0.7%-2.5%; proximal n=4; distal n=6) at admission [9]. At 3 months, PE was diagnosed in 5/670 patients (0.7%; 95%CI 0.3%-1.7%) of which 3 (60.0%; 95%CI 23%-88%) were fatal; no isolated DVT was diagnosed (**e-Table 1**) [9].

Outcome measures

The primary outcome of this *post-hoc* analysis was the safety of PE diagnostic strategies using pre-test probability assessment with the revised Geneva and Wells PE scores as well as of the CTPA-sparing diagnostic strategies (ADJUST-PE, YEARS, PEGeD and 4PEPS scores). Safety was defined as the diagnostic failure rate of venous thromboembolism (VTE) during the entire study period (i.e., diagnostic failure rate of PE and isolated DVT at admission and at 3 months). Each diagnostic strategy is described in the appendix (**e-Tables 2-3**). All the data required to compute the pre-test probability assessment with the revised Geneva score, Wells PE score and the CTPA-sparing diagnostic strategies (ADJUST-PE, YEARS, PEGeD and 4PEPS) were predefined in the original protocol, prospectively collected and were available for all the patients [9]. Secondary outcomes included diagnostic failure rate of PE during the entire study period, diagnostic failure rate of isolated DVT during the entire study period and the efficacy of the CTPA-sparing diagnostic strategies defined by the number of CTPA needed with each diagnostic strategy.

Statistical methods

Baseline clinical characteristics of the patients are provided. For continuous variables, mean value with its standard deviation and median value with its interquartile ranges were calculated if normally and not normally distributed, respectively. Categorical variables were presented as proportions (n, %). CTPA-sparing diagnostic strategies were computed for all the patients with data that had been collected prospectively as part of the PEP study [9]. The safety of each CTPA-

sparing diagnostic strategies was evaluated by the diagnostic failure rate of VTE during the entire study period which was calculated by dividing the number of patients in whom VTE was missed at admission (amongst those would not have had CTPA) and the number of patients diagnosed with VTE during the 3-month follow-up by the number of patients from the entire cohort (excluding patients who had a diagnosis of VTE at admission, who were lost to follow-up (n=2)[9] and who were started on anticoagulation for another reason other than VTE). In addition, patients in whom D-dimer results were not available were excluded from this safety analysis. We used the diagnostic failure rate of VTE during the entire study period as a surrogate of the diagnostic failure rate at 3 months to capture all VTE missed if the CTPA-sparing diagnostic strategy had been used, assuming that VTE missed at admission would be captured during the 3-month follow-up. Diagnostic failure rate of PE and diagnostic failure rate of isolated DVT were calculated with the same method. Based on the recommendations from the International Society of Thrombosis and Haemostasis (ISTH), the 95%CI upper limit for diagnostic failure rate of VTE at 3 months in this population with a prevalence of PE of 5.9% would be 1.85% [17]. The efficacy of each CTPA-sparing diagnostic strategies was evaluated by the number of CTPA needed with each diagnostic strategy. The relative difference between the proportion of CTPA needed for each CTPA-sparing diagnostic strategy and the proportion of CTPA needed for the standard diagnostic strategy (revised Geneva score combined with fixed D-dimer cut-off) was also calculated. For this secondary outcome, some patients were excluded since they would have required D-dimer based on the CTPA-sparing diagnostic strategies, but D-dimer result was not available. Subgroup analysis was performed for the safety and efficacy of standard and CTPA-sparing diagnostic strategies based on the suspicion of PE (PE suspected vs PE not suspected). Statistical analyses were performed using

SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Mac, Version 27.0. Armonk, NY: IBM Corp).

RESULTS

For this *post-hoc* analysis, all 740 patients from the PEP trial were included. The mean age was 68.2 ± 10.9 years and 37% were female. The mean forced expiratory volume in first second was 53.0 ± 16.7% and most patients were categorized as Global Initiative for Obstructive Lung Disease stage II-III (**Table 1**).

Safety of diagnostic strategies using pre-test probability assessment with the revised Geneva and Wells PE scores

When the revised Geneva score with fixed D-dimer cut-off was used, 5 VTE (5 PE and 0 isolated DVT) were diagnosed during the 3-month follow-up. The diagnostic failure rate of VTE during the entire study period with this algorithm was 0.7% (95%CI 0.3%-1.7%). When using Wells PE score combined with fixed D-dimer threshold, 5 VTE (5 PE and 0 isolated DVT) would have been missed during the entire study period, resulting in a diagnostic failure rate of VTE of 0.7% (95%CI 0.3%-1.7%) (**Table 2**). Details of all PE, DVT and VTE occurring at admission and at three months according to pre-test clinical assessment with Geneva or Wells PE score are reported in **e-Table 1.**

Safety of CTPA-sparing diagnostic strategies

When the ADJUST-PE algorithm (revised Geneva or Wells scores) was computed, 9 VTE (6 PE and 3 isolated DVT) would have been missed during the entire study period, resulting in a diagnostic failure rate of VTE of 1.3% (95%CI 0.7%-2.5%). If the YEARS algorithm would have been used, 10 VTE (8 PE and 2 isolated DVT) would have been missed during the entire study period, resulting in a diagnostic failure rate of VTE of 1.5% (95%CI 0.8%-2.7%). When the

PEGeD algorithm was computed, 12 VTE (9 PE and 3 isolated DVT) would have been missed during the entire study period, resulting in a diagnostic failure rate of VTE of 1.8% (95%CI 1.0%-3.1%). If the 4PEPS algorithm would have been used, 14 VTE (10 PE and 4 isolated DVT) would have been missed during the entire study period, resulting in a diagnostic failure rate of VTE of 2.1% (95%CI 1.2%-3.4%) (**Table 2**). Details of diagnostic failure rates of PE, isolated DVT and VTE at admission and at 3 months according to CTPA-sparing diagnostic strategies are reported in **e-Table 4**. Details of all PE, DVT and VTE occurring at admission and at 3 months according to pre-test clinical probability assessment of each PE diagnostic algorithm are reported in **e-Table 5**. Subgroup analysis showed that the safety of CTPA-sparing diagnostic strategies was similar whether PE was suspected or not (**e-Table 6**).

Efficacy of CTPA-sparing diagnostic strategies

When the revised Geneva and the Wells PE scores combined with fixed D-dimer threshold were computed, 70.9% and 71.0% of the patients, respectively, would have needed a CTPA. When ADJUST-PE (revised Geneva score), ADJUST-PE (Wells PE score), YEARS, PEGeD and 4PEPS algorithms were computed, 55.8%, 60.8%, 45.8%, 42.2% and 38.5% of the patients, respectively, would have needed a CTPA which corresponds to a an absolute reduction of 15.1%, 10.1%, 25.1%, 28.7% and 32.4% in the number of CTPA needed, respectively, when compared to the proportion of patients requiring a CTPA with the revised Geneva score combined with fixed D-dimer cut-off (**Table 2 and Figure 1**). When CTPA-sparing diagnostic strategies were computed, the number of CTPA needed was lower when PE was not suspected compared to when PE was suspected (**e-Table 6**).

DISCUSSION

This *post-hoc* analysis of the PEP study, including 740 hospitalized patients for AE-COPD, showed that standard diagnostic strategies (revised Geneva or Wells PE combined with fixed D-dimer cut-off) were safe, but 71% of the patients would have needed a CTPA to confirm or rule out PE. As opposed, CTPA-sparing diagnostic strategies (ADJUST-PE, YEARS, PEGeD and 4PEPS algorithms) reduced up to 32% the need for CTPA, however at the cost of an increased diagnostic failure rate of VTE.

Based on ISTH recommendations on the failure rate of VTE safety threshold for diagnostic strategy, a calculated 95%CI upper limit based on the prevalence of PE should be used. In the PEP study, with a prevalence of PE of 5.9%, the "safe" 95%CI upper limit of the failure rate is 1.85%. Although the revised Geneva and Wells PE scores have not been specifically derived and validated in patients with COPD, they appear safe with a low diagnostic failure rate of VTE at 3 months (0.7%; 95%CI 0.3%-1.7%), with a 95%CI upper limit lower than the safety threshold recommended by ISTH (i.e. 1.85%) [17]. Nonetheless, when the revised Geneva score was used in this population, more patients were categorized in the intermediate clinical probability group compared to the princeps study, at the expense of the low clinical probability group [18]. This could explain why 71% of the patients needed a CTPA [9], which is higher than in the general population [14, 15]. Although the Wells PE score categorized more patients in the low probability group compared to the revised Geneva score in patients with AE-COPD, the proportion of CTPA needed would be similar. The high proportion of CTPA required is concerning since CTPA is associated with radiation [19], possible contrast-induced nephropathy [20] or allergic reaction [21], incidental findings [22] and cost [23]. Also, as the severity of COPD progresses, these patients tend to have more frequent exacerbations [3] and may subsequently require more CTPA.

In the recent years, CTPA-sparing diagnostic strategies have been developed in the general population to reduce the need for CTPA while maintaining their safety. When ADJUST-PE, YEARS, PEGeD and 4PEPS algorithms were computed in patients with AE-COPD, there was a reduction of up to 32% of the CTPA required. However, as the reduction of CTPA increases, the diagnostic failure rate of VTE also increases with a 95%CI upper limit as high as 3.4% which is more than 1.5% higher than the safety threshold of 1.85% [17]. The VTE diagnostic failure rate during the entire study period was used as a surrogate of the diagnostic failure rate at 3 months to take into account VTE missed at admission. Moreover, ISTH recommendations stipulate that it could be arguable to use a fixed threshold of 1.85% or 2.00% [17]. Even if these fixed upper limits were used, the diagnostic failure rate of VTE with CTPA-sparing diagnostic algorithms would have exceeded the safety threshold. Therefore, these diagnostic strategies do not seem safe enough for patients with AE-COPD, which is concordant with the *post-hoc* study of Rodriguez et al.[16] that compared a conventional strategy, an age-adjusted strategy, and the YEARS algorithm. Moreover, when each diagnostic strategy was computed in the PEP cohort, the proportion of patients and the prevalence of VTE in each risk group were different from the princeps studies (**e-Table 7**). Patients with AE-COPD have clinical characteristics that are different from the general population, which may explain why clinical probability stratifications and diagnostic strategies do not perform as well as in the general population.

Although the absolute number of PE missed seems low, the consequences of these diagnostic failures are high. In patients with AE-COPD who were diagnosed with PE during the 3-month follow-up, 60% of the patients died[9]. Moreover, the risk of mortality was 5 times higher in patients with PE compared to those without PE [9]. These elements emphasize the importance in diagnosing appropriately PE at admission. Moreover, studies that systematically performed CTPA

in patients with AE-COPD showed a higher prevalence of PE compared to studies that did not systematically investigate for PE. A recent trial evaluating systematic search for PE in AE-COPD patients failed to show its superiority over usual care on a clinical composite outcome [11]. However, this study was possibly underpowered. These elements reinforce the need to improve PE diagnostic management in patients with AE-COPD.

In patients with COPD, PE is more frequent than DVT [5, 24] and this was confirmed in this study. As part of the diagnostic algorithm in the PEP study [9], bilateral leg doppler ultrasound was performed in patients with high clinical pre-test probability or with positive D-dimers. Ten DVT were confirmed of which 40% were proximal and most were asymptomatic. DVT requires similar treatment as PE and a high proportion would have been missed by current diagnostic strategies since bilateral leg doppler ultrasound is not routinely performed when investigating for PE. Therefore, the questions on the optimal VTE diagnostic management in AE-COPD patients remains open. Whether performing systematic bilateral leg doppler ultrasound to all patients who need CTPA would reduce the number of CTPA and the diagnostic failure rate of VTE could be investigated.

Our study presents some limitations. First, this is a *post-hoc* analysis of a prospective study where patients were not actually managed according to CTPA-sparing diagnostic strategies. Second, the number of VTE was low, which can reduce the confidence in the observed estimates, especially the 95%CI upper limits. Consequently, these results should be viewed as exploratory. Third, we failed to identify an optimal diagnostic strategy in these patients that balances adequately the need for CTPA with the failure rate of PE diagnosis. This study main strengths include the ability to compute all available diagnostic strategies in one of the largest prospective cohort of patients with

documented COPD hospitalized for AE-COPD, the adjudication of all events by an independent committee, and the fact that only two patients were lost to follow-up.

CONCLUSION

In conclusion, in this *post-hoc* analysis of patients with AE-COPD, whether PE was clinically suspected or not, the revised Geneva and Wells PE scores combined with fixed D-dimer cut-off were safe but required a large number of CTPA. In contrast, ADJUST-PE, YEARS, PEGeD and 4PEPS algorithms reduced the need for CTPA at the cost of an increased diagnostic failure rate of VTE. Thus, further studies are needed to improve PE diagnostic management of COPD patients presenting with worsening respiratory symptoms.

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REFERENCES

[1] S. Safiri, K. Carson-Chahhoud, M. Noori, S.A. Nejadghaderi, M.J.M. Sullman, J. Ahmadian Heris, K. Ansarin, M.A. Mansournia, G.S. Collins, A.-A. Kolahi, J.S. Kaufman, Burden of chronic obstructive pulmonary disease and its attributable risk factors in 204 countries and territories, 1990-2019: results from the Global Burden of Disease Study 2019, BMJ 378 (2022) e069679.

[2] WHO, Chronic obstructive pulmonary disease (COPD), (2021).

[3] A. Anzueto, Impact of exacerbations on COPD, European Respiratory Review 19(116) (2010) 113-118.

[4] E. Sapey, R.A. Stockley, COPD exacerbations . 2: aetiology, Thorax 61(3) (2006) 250-8.

[5] R. Sato, D. Hasegawa, K. Nishida, K. Takahashi, M. Schleicher, N. Chaisson, Prevalence of pulmonary embolism in patients with acute exacerbations of COPD: A systematic review and meta-analysis, The American Journal of Emergency Medicine 50 (2021) 606-617.

[6] W. Han, M. Wang, Y. Xie, H. Ruan, H. Zhao, J. Li, Prevalence of Pulmonary Embolism and Deep Venous Thromboembolism in Patients With Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis, Frontiers in cardiovascular medicine 9 (2022) 732855.

[7] J. Wang, Y.M. Ding, Prevalence and risk factors of pulmonary embolism in acute exacerbation of chronic obstructive pulmonary disease and its impact on outcomes: a systematic review and meta-analysis, Eur Rev Med Pharmacol Sci 25(6) (2021) 2604-2616.

[8] X. Fu, Y. Zhong, W. Xu, J. Ju, M. Yu, M. Ge, X. Gu, Q. Chen, Y. Sun, H. Huang, L. Shen, The prevalence and clinical features of pulmonary embolism in patients with AE-COPD: A meta-analysis and systematic review, PLoS One 16(9) (2021) e0256480.

[9] F. Couturaud, L. Bertoletti, J. Pastre, P.M. Roy, R. Le Mao, F. Gagnadoux, N. Paleiron, J. Schmidt, O. Sanchez, E. De Magalhaes, M. Kamara, C. Hoffmann, L. Bressollette, M. Nonent, C. Tromeur, P.Y. Salaun, S. Barillot, F. Gatineau, P. Mismetti, P. Girard, K. Lacut, C.A. Lemarié, G. Meyer, C. Leroyer, Prevalence of Pulmonary Embolism Among Patients With COPD Hospitalized With Acutely Worsening Respiratory Symptoms, JAMA 325(1) (2021) 59-68.

[10] A.L. Lessler, J.A. Isserman, R. Agarwal, H.I. Palevsky, J.M. Pines, Testing low-risk patients for suspected pulmonary embolism: a decision analysis, Ann Emerg Med 55(4) (2010) 316-326.e1.

[11] D. Jiménez, A. Agustí, E. Tabernero, L. Jara-Palomares, A. Hernando, P. Ruiz-Artacho, G. Pérez-Peñate, A. Rivas-Guerrero, M.J. Rodríguez-Nieto, A. Ballaz, R. Agüero, S. Jiménez, M. Calle-Rubio, R. López-Reyes, P. Marcos-Rodríguez, D. Barrios, C. Rodríguez, A. Muriel, L. Bertoletti, F. Couturaud, M. Huisman, J.L. Lobo, R.D. Yusen, B. Bikdeli, M. Monreal, R. Otero, Effect of a Pulmonary Embolism Diagnostic Strategy on Clinical Outcomes in Patients Hospitalized for COPD Exacerbation: A Randomized Clinical Trial, JAMA 326(13) (2021) 1277-1285.

[12] M. Righini, J. Van Es, P.L. Den Exter, P.M. Roy, F. Verschuren, A. Ghuysen, O.T. Rutschmann, O. Sanchez, M. Jaffrelot, A. Trinh-Duc, C. Le Gall, F. Moustafa, A. Principe, A.A. Van Houten, M. Ten Wolde, R.A. Douma, G. Hazelaar, P.M. Erkens, K.W. Van Kralingen, M.J. Grootenboers, M.F. Durian, Y.W. Cheung, G. Meyer, H. Bounameaux, M.V. Huisman, P.W. Kamphuisen, G. Le Gal, Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study, JAMA 311(11) (2014) 1117-24.

[13] T. van der Hulle, W.Y. Cheung, S. Kooij, L.F.M. Beenen, T. van Bemmel, J. van Es, L.M. Faber, G.M. Hazelaar, C. Heringhaus, H. Hofstee, M.M.C. Hovens, K.A.H. Kaasjager, R.C.J. van Klink, M. Kruip, R.F. Loeffen, A.T.A. Mairuhu, S. Middeldorp, M. Nijkeuter, L.M. van der Pol,

S. Schol-Gelok, M. Ten Wolde, F.A. Klok, M.V. Huisman, Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study, Lancet 390(10091) (2017) 289-297.

[14] C. Kearon, K. de Wit, S. Parpia, S. Schulman, M. Afilalo, A. Hirsch, F.A. Spencer, S. Sharma, F. D'Aragon, J.-F. Deshaies, G. Le Gal, A. Lazo-Langner, C. Wu, L. Rudd-Scott, S.M. Bates, J.A. Julian, Diagnosis of Pulmonary Embolism with d-Dimer Adjusted to Clinical Probability, New England Journal of Medicine 381(22) (2019) 2125-2134.

[15] P.-M. Roy, E. Friou, B. Germeau, D. Douillet, J.A. Kline, M. Righini, G. Le Gal, T. Moumneh, A. Penaloza, Derivation and Validation of a 4-Level Clinical Pretest Probability Score for Suspected Pulmonary Embolism to Safely Decrease Imaging Testing, JAMA Cardiology 6(6) (2021) 669-677.

[16] C. Rodríguez, L. Jara-Palomares, E. Tabernero, A. Tenes, S. González, W. Briceño, J.L. Lobo, R. Morillo, B. Bikdeli, D. Jiménez, Adjusted D-dimer cutoff levels to rule out pulmonary embolism in patients hospitalized for COPD exacerbation: results from the SLICE trial, Thrombosis journal 20(1) (2022) 10.

[17] C.E.A. Dronkers, T. van der Hulle, G. Le Gal, P.A. Kyrle, M.V. Huisman, S.C. Cannegieter, F.A. Klok, Towards a tailored diagnostic standard for future diagnostic studies in pulmonary embolism: communication from the SSC of the ISTH, J Thromb Haemost 15(5) (2017) 1040-1043.

[18] G. Le Gal, M. Righini, P.M. Roy, O. Sanchez, D. Aujesky, H. Bounameaux, A. Perrier, Prediction of pulmonary embolism in the emergency department: the revised Geneva score, Ann Intern Med 144(3) (2006) 165-71.

[19] M.K. Kalra, A.D. Sodickson, W.W. Mayo-Smith, CT Radiation: Key Concepts for Gentle and Wise Use, RadioGraphics 35(6) (2015) 1706-1721.

[20] T.G. Gleeson, S. Bulugahapitiya, Contrast-Induced Nephropathy, American Journal of Roentgenology 183(6) (2004) 1673-1689.

[21] M.J. Cha, D.Y. Kang, W. Lee, S.H. Yoon, Y.H. Choi, J.S. Byun, J. Lee, Y.-H. Kim, K.S. Choo, B.S. Cho, K.N. Jeon, J.-W. Jung, H.-R. Kang, Hypersensitivity Reactions to Iodinated Contrast Media: A Multicenter Study of 196 081 Patients, Radiology 293(1) (2019) 117-124.

[22] J. van Es, R.A. Douma, S.M. Schreuder, S. Middeldorp, P.W. Kamphuisen, V.E.A. Gerdes, L.F.M. Beenen, Clinical Impact of Findings Supporting an Alternative Diagnosis on CT Pulmonary Angiography in Patients With Suspected Pulmonary Embolism, CHEST 144(6) (2013) 1893-1899.

[23] A. Perrier, M.R. Nendaz, F.P. Sarasin, N. Howarth, H. Bounameaux, Cost-Effectiveness Analysis of Diagnostic Strategies for Suspected Pulmonary Embolism Including Helical Computed Tomography, American Journal of Respiratory and Critical Care Medicine 167(1) (2003) 39-44.

[24] L. Bertoletti, S. Quenet, P. Mismetti, L. Hernández, J.J. Martín-Villasclaras, C. Tolosa, M. Valdés, M. Barrón, J.A. Todolí, M. Monreal, Clinical presentation and outcome of venous thromboembolism in COPD, Eur Respir J 39(4) (2012) 862-8.

[25] P.S. Wells, D.R. Anderson, M. Rodger, J.S. Ginsberg, C. Kearon, M. Gent, A.G. Turpie, J. Bormanis, J. Weitz, M. Chamberlain, D. Bowie, D. Barnes, J. Hirsh, Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer, Thromb Haemost 83(3) (2000) 416-20.

Table 1. Baseline characteristics of the patients

Characteristics	Entire cohort (n=740)	PE (n=44)	Isolated DVT (n=10)	No VTE (n=686)
Age, years (mean ± SD)	68.2 ± 10.9	70.8 ± 10.3	77.7 ± 8.3	67.9 ± 10.9
Female – n/N (%)	274/740 (37)	12/44 (27)	3/10 (30)	259/686 (38)
Body mass index, kg/m^2 (mean ± SD)*	25.7 ± 6.7 [n=735]	25.5 ± 7.1 [n=43]	26.2 ± 4.8 [n=10]	25.7 ± 6.7 [n=682]
%FEV1 (mean ± SD)ϕ	53.0 ± 16.7 [n=677]	54.1 ± 16.0 [n=41]	52.9 ± 15.0 [n=9]	52.9 ± 16.7 [n=627]
GOLD stage - n (%) 1 2 3 4	 80 (11.9) 239 (35.4) 265 (39.3) 91 (13.5) [n=675]	 5 (12.2) 14 (34.1) 17 (41.5) 5 (12.2) [n=41]	 1 (11.1) 4 (44.4) 3 (33.3) 1 (11.1) [n=9]	 74 (11.8) 221 (35.4) 245 (39.2) 85 (13.6) [n=625]
Tobacco use – n/N (%) Current smoker Ex-smoker	 263/736 (35.7) 416/736 (56.5)	 11/43 (25.6) 27/43 (62.8)	 2/10 (20.0) 6/10 (60.0)	 250/683 (36.6) 383/683 (56.1)
Number of exacerbations in the last year - (median, IQR)	1.0 (0-3.0) [n=668]	1.0 (0-3.0) [n=39]	2.5 (1.0-4.0) [n=10]	1.0 (0-3.0) [n=619]
Prolonged immobilization - n (%)	133/739 (18.0)	10/44 (22.7)	4 (40.0)	119/685 (17.4)
Familial history – n/N (%)	66/695 (9.5)	4/42 (9.5)	0/8 (0)	62/645 (9.6)
Cancer in the past 2 years – n/N (%)	59/738 (8.0)	7/44 (15.9)	2/10 (20.0)	50/684 (7.3)
Previous VTE – n/N (%)	55/740 (6.9)	5/44 (11.4)	3/10 (30.0)	47/686 (6.9)
Surgery – n/N (%)	24/738 (3.3)	0/44 (0)	1/10 (10.0)	23/684 (3.4)
Trauma – n/N (%)	15/740 (2.0)	2/44 (4.5)	0/10 (0)	13/686 (1.9)
PE suspected – n/N (%)	299/740 (40.4)	30/44 (68.2)	5/10 (50.0)	264/686 (38.5)

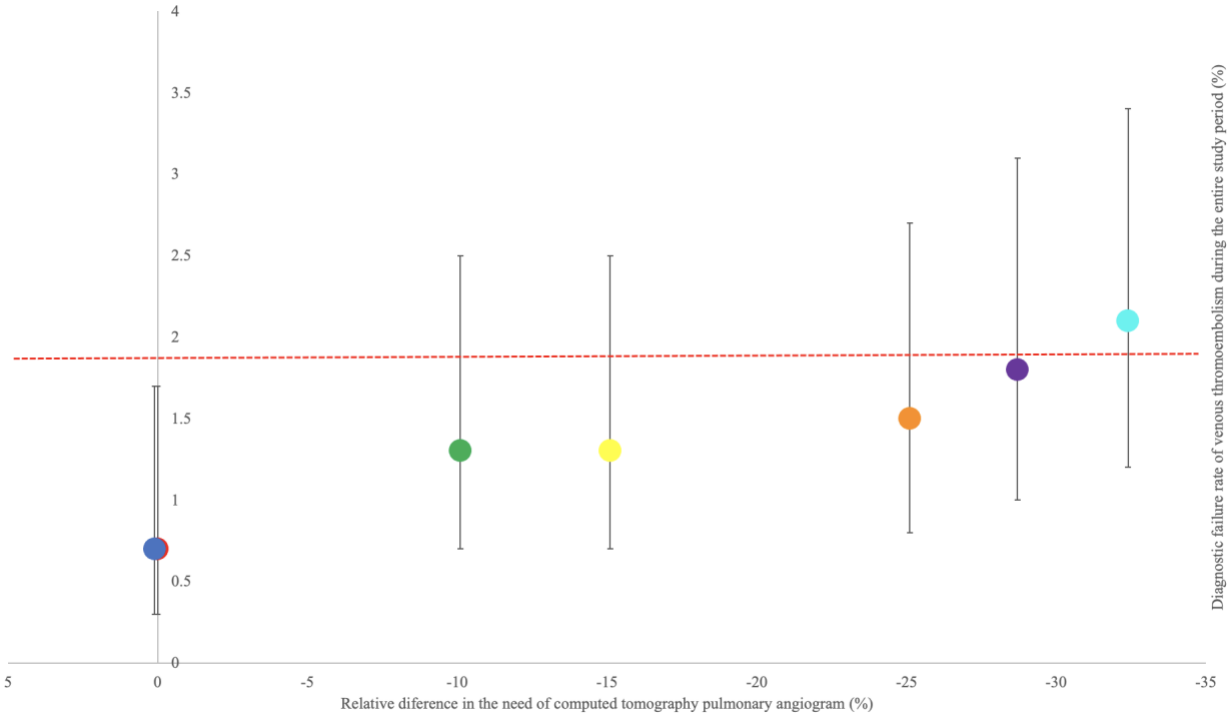
DVT: deep venous thrombosis; FEV1: forced expiratory volume in 1 second; GOLD: Global Initiative for Obstructive Lung Disease; PE: pulmonary embolism; SD: standard deviation; VTE: venous thromboembolism

Table 2. Comparison of the diagnostic failure rate of venous thromboembolism and the number of computed tomography pulmonary angiograms needed depending on the pulmonary embolism diagnostic strategies used

Diagnostic strategies	Estimated diagnostic failure rate of VTE during the entire study period in the entire cohort n/N (% [95% CI])	Number of PE missed during the entire study period	Number of DVT missed during the entire study period	Number of CTPA needed n/N (% [95% CI])	Relative difference in CTPA compared to standard diagnostic strategy*
Revised Geneva + fixed D-dimer cut-off [18]	5/670 (0.7 [0.3-1.7])	5	0	517/729 (70.9 [67.5-74.1])	NA
Wells PE + fixed D-dimer cut-off [25]	5/670 (0.7 [0.3-1.7])	5	0	518/730 (71.0 [67.6-74.1])	+0.1%
ADJUST-PE (revised Geneva)[12]	9/674 (1.3 [0.7-2.5])	6	3 (proximal:1; distal:2)	407/729 (55.8 [52.2-59.4])	-15.1%
ADJUST-PE (Wells PE)[12]	9/674 (1.3 [0.7-2.5])	6	3 (proximal:1; distal:2)	446/734 (60.8 [57.2-64.2])	-10.1%
YEARS[13]	10/675 (1.5 [0.8-2.7])	8	2 (distal:2)	332/725 (45.8 [42.2-49.4])	-25.1%
PEGeD[14]	12/677 (1.8 [1.0-3.1])	9	3 (proximal:1; distal:2)	308/730 (42.2 [38.7-45.8])	-28.7%
4PEPS[15]	14/679 (2.1 [1.2-3.4])	10	4 (proximal:1; distal:3)	280/728 (38.5 [35.0-42.1])	-32.4%

CI: confidence interval; CTPA: computed tomography pulmonary angiogram; DVT: deep venous thrombosis; NA: not applicable; PE: pulmonary embolism; VTE: venous thromboembolism;
**Revised Geneva score with fixed D-dimer cut-off was considered the standard diagnostic strategy.*

Figure 1. Relative difference in the need of computed tomography pulmonary angiogram at admission and diagnostic failure rate of venous thromboembolism during the entire study period based on different pulmonary embolism diagnostic strategies compared to standard diagnostic strategy (revised Geneva score combined with fixed D-dimer cut-off)



Red: Revised Geneva score combined with fixed D-dimer cut-off; Blue: Wells pulmonary embolism (PE) score combined with fixed D-dimer cut-off; Green: ADJUST-PE (Wells PE score) algorithm; Yellow: ADJUST-PE (revised Geneva score) algorithm; Orange: YEARS algorithm; Purple: PEGeD algorithm; Turquoise: 4PEPS algorithm; Dotted red line: 95% confidence interval upper limit of 1.85.

CHAPTER 5: Manuscript 4- Chronic obstructive pulmonary disease exacerbation purulence status and its association with pulmonary embolism: a systematic review with meta-analysis

5.1 Preface to manuscript 4

This study was not planned initially and was not part of my thesis proposal. However, by working on this topic, I found some information which made me think that an association between PE and the type of AECOPD could be possible. To help the clinician better predict the presence of PE in patients with AECOPD, we conducted a systematic review with meta-analysis aiming to evaluate the association between PE and the type of AECOPD (purulent AECOPD vs non-purulent or unknown purulent status AECOPD). I worked on the literature review, study conception, screening and selection of studies, data extraction, data analysis, risk of bias assessment, interpretation of the data and manuscript drafting. Co-authors helped with screening and selection of studies, data extraction, risk of bias assessment, supervision and revision of the manuscript.

The protocol of this meta-analysis is accessible via PROSPERO (CRD42023459429). Also, the protocol has been published in BMJ Open: Mai V, Girardi L, de Wit K, Castellucci L, Aaron S, Couturaud F, Fergusson DA, Le Gal G. Chronic obstructive pulmonary disease exacerbation purulence status and its association with pulmonary embolism: protocol for a systematic review with meta-analysis. BMJ Open. 2024 Jun 19;14(6):e085328.

We submitted the manuscript to a peer-reviewed journal.

5.2 Manuscript 4

Chronic obstructive pulmonary disease exacerbation purulence status and its association with pulmonary embolism: a systematic review with meta-analysis

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ABSTRACT

Background: Diagnosing pulmonary embolism (PE) in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is challenging due to similar symptoms. Finding predictors of PE could help improve diagnostic management of patients with AECOPD. The aim of this systematic review with meta-analysis was to evaluate the association between AECOPD purulence status and the presence of PE.

Methods: A systematic review with meta-analysis was conducted. MEDLINE, EMBASE and CENTRAL were searched from inception to April 2024 for randomized trials, cohort or cross-sectional studies reporting on the prevalence of PE according to AECOPD purulence status. Relative risks (RR) with 95% confidence intervals (CI) of PE according to AECOPD purulence status were calculated and pooled proportions of PE with their 95%CI were calculated based on the AECOPD purulence status.

Results: From 7059 unique citations identified by the literature search, 14 studies (5,056 participants) met eligibility and were included. The prevalence of PE varied between 0.4% and 33.2% across studies. The risk of PE was not statistically significantly lower in patients with purulent AECOPD compared to patients with non-purulent/unknown etiology AECOPD (RR 0.64; 95%CI 0.26-1.55; I^2=88.0%). The pooled proportion of PE was 7.3% (95%CI 2.4%-14.7%; I^2=94.7%) and 13.3% (95%CI 8.0%-19.7%; I^2=96.0%) in studies including patients with purulent AECOPD and non-purulent/unknown etiology AECOPD.

Conclusion: The risk of PE was clinically lower in patients with purulent AECOPD compared to patients with non-purulent/unknown etiology AECOPD. However, a diagnosis of purulent AECOPD is not sufficient to rule out PE diagnosis. Further studies are needed to confirm the

association between PE and AECOPD purulence status and to assess the potential role of this predictor in combination with other clinical variables for diagnosing PE in patients with AECOPD.

INTRODUCTION

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a risk factor for pulmonary embolism (PE)(1). Patients with chronic obstructive pulmonary disease (COPD) have chronic inflammation, either systemic and/or affecting the airways, and this inflammation increases in the context of AECOPD(2) which contributes to the increased risk of thrombosis. As the severity of COPD progresses, the risk of AECOPD also increases, with an estimated rate of 0.5-3.5 exacerbations/person/year(3, 4). With a 5-fold increase in mortality when PE is diagnosed in patients with AECOPD(5), it is critical to diagnose PE in these patients.

However, diagnosing PE in patients with AECOPD is challenging since the two diseases share similar symptoms. Moreover, it is unclear when PE should be suspected or when imaging should be performed to rule out PE in patients with COPD presenting with increased respiratory symptoms. PE should not be ruled out by using clinical gestalt only, since the prevalence of PE is not low enough to safely exclude it in patients with COPD presenting with acutely worsening respiratory symptoms(6, 7). When standard PE diagnostic strategies, such as the revised Geneva or Wells PE scores combined with D-dimer at a fixed cut-off, a high proportion of patients needs imaging to rule out PE(6, 8). Computed tomography pulmonary angiography (CTPA) is the diagnostic modality most frequently used to rule out PE, but this radiological test comes with radiation, cost, possible contrast-induced allergy or nephropathy as well as incidental findings.

Therefore, identifying predictors of PE diagnosis could help improve diagnostic management of patients with AECOPD. Some studies showed a lower rate of PE or VTE in patients with purulent AECOPD as compared with patients with non-purulent or unknown etiology AECOPD(9-11).

Since the cause of non-purulent and unknown etiology AECOPD is most often unclear, PE could account for those types of exacerbations. Thus, the aim of this systematic review with meta-analysis was to evaluate the association between the AECOPD purulence status and the presence of PE.

METHODS

Protocol and registration

The protocol of this systematic review with meta-analysis has been published previously(12) and was also registered in PROSPERO (CRD42023459429).

Eligibility criteria

Inclusion criteria were randomized trials, cohort studies (retrospective or prospective) or cross-sectional studies that reported on the prevalence of PE according to the AECOPD purulence status. AECOPD purulence status was categorized as 1) definitive purulent AECOPD (purulent AECOPD or purulent sputum), 2) possible purulent AECOPD (clinical and/or radiological evidence of tracheobronchial infection or pneumonia), 3) non-purulent AECOPD or unknown etiology AECOPD. The term unknown etiology AECOPD was used instead of unknown purulence status (as published in the protocol) to reflect more precisely this group of patients with AECOPD. There was no restriction on language. Published manuscripts and conference abstracts were included. Studies were excluded if the prevalence of PE according to the AECOPD purulence status was not provided in the paper or by the authors.

Information sources and search strategy

From inception to April 1st, 2024, MEDLINE, EMBASE and CENTRAL were searched. Conference abstracts from the American Thoracic Society, American College of Chest Physicians,

European Respiratory Society, British Thoracic Society, American Society of Hematology, International Society on Thrombosis and Haemostasis were hand searched from January 2000 to April 2024. Studies were translated when needed. The search strategy was reviewed by a research librarian with expertise in knowledge synthesis and translation. The search strategy can be found in the supplemental file (**Appendix 1**).

Study selection

Screening of citations was conducted using Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. All titles and abstracts for potential inclusion in this study were screened by two independent reviewers (V.M. and L.G.). Full texts of potentially eligible studies were screened independently by two reviewers (V.M. and L.G.). Disagreements were resolved by consensus or by consulting a third reviewer (G.L.G.). If the same cohort was published in multiple articles, the article with the largest cohort reporting on the information needed was included. For two studies(6, 7) where the prevalence of PE was described but not available according to the AECOPD purulence status, the corresponding authors were contacted to have the information since we knew it was available in their database.

Data extraction

A standardized collection form was used by two reviewers (V.M. and L.G.) for independent data extraction. Disagreements were resolved with a discussion between the two reviewers (V.M. and L.G.) or with the third reviewer's (G.L.G) input. Data on baseline characteristics of the studies and outcomes in each study were extracted.

Outcome measures

The primary outcome was PE at initial assessment. PE was defined as either symptomatic, incidental or fatal and was involving subsegmental branches or more proximal arteries on CTPA,

high probability on a planar ventilation/perfusion (V/Q) scan or at least one segmental mismatch or two subsegmental mismatches on a V/Q SPECT (EANM criteria)(13), when available. Studies in which the localization of PE was not specified in the text were included, and subgroup analyses were performed. Secondary outcomes included VTE [i.e. DVT (either proximal or distal) and/or PE] and DVT (either proximal or distal), respectively, at initial assessment. Distal and proximal DVT were not presented separately as planned in the protocol since many included studies did not specify the localization of the DVT. DVT could be either symptomatic or incidental and was localized in the lower extremity. Initial assessment was defined as the first 48 hours from hospital admission or initial medical evaluation if the patient was admitted or managed as an outpatient, respectively, or as defined by individual studies.

Risk of bias

The risk of bias of each included study was assessed independently by two reviewers (V.M. and L.G.) by using the ROBINS-E tool(14). The risk of bias of each study was evaluated by using AECOPD purulence status as the exposure. Publication bias was assessed visually with a funnel plot for the primary outcome. Absence of publication bias was considered if the funnel plot was symmetrical.

Data synthesis and statistical analysis

The prevalence of PE, DVT and VTE at initial assessment for each study was calculated with 95% confidence intervals (CI) by using the binomial exact method(15). For the prevalence of VTE, if PE and DVT were diagnosed in a same patient, only one thromboembolic event was counted. The association between the risk of PE and the AECOPD purulence status was assessed by calculating relative risks (RR) with 95%CI using a Mantel-Haenszel random-effects model. Events were categorized in the definitive purulent AECOPD group if it was mentioned purulent AECOPD or

the sputum was described as purulent. Events were categorized in the possible purulent AECOPD group if there was clinical and/or radiological evidence of tracheobronchial infection or pneumonia. If two definitions were found in a same study, the definitive purulent AECOPD definition was used for the main analysis and sensitivity analyses were conducted by using alternative definitions of purulent AECOPD. Since some studies could not be pooled in the evaluation of the RR evaluating the association between PE and AECOPD purulence status, pooled proportions of PE according to the type of AECOPD (purulent AECOPD and non-purulent/unknown etiology AECOPD) were calculated using random-effects model using StatsDirect statistical software. To evaluate heterogeneity, I^2 was calculated. Significant heterogeneity was considered if I^2 was > 50%. Subgroup analyses were conducted for type of study (randomized trials vs prospective cohort studies vs retrospective cohort studies vs cross-sectional studies), systematic search of PE vs no systematic search of PE and localization of PE (segmental and more proximal PE vs subsegmental and more proximal PE vs unknown). Since the definition of purulent AECOPD was heterogenous across studies and some studies included various definitions of purulent AECOPD, post-hoc sensitivity analyses were conducted according to the definition of purulent AECOPD (possible purulent AECOPD definition was used primarily instead of the definitive purulent AECOPD definition and clinical purulent AECOPD definition was used in combination with possible purulent AECOPD definition used primarily) and by using fixed-effects model. Sensitivity analyses according to the risk of bias were planned. Similar analyses for DVT and VTE, respectively, were planned. The manuscript was drafted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.

RESULTS

Studies selection

The systematic search identified 7059 citations, of which 191 full texts were evaluated for eligibility and 14 studies(6, 7, 9, 10, 16-25), representing 5,056 participants, were included. The reasons of exclusion can be found in **Figure 1**.

Characteristics of the studies

Out of the 14 included studies(6, 7, 9, 10, 16-25), 9 studies(6, 7, 9, 10, 16-20) included patients with purulent and non-purulent/unknown etiology AECOPD, whereas 5 studies(21-25) included only patients with non-purulent/unknown etiology AECOPD (**Table 1**). The definition of the AECOPD purulence status can be found in **Table S1**. We identified 1 randomized controlled trial, 8 prospective cohort studies, 4 retrospective cohort studies, and 1 cross-sectional study (**Table 1**). The proportion of purulent AECOPD varied from 0.0% to 65.4% across studies. The prevalence of PE per study varied between 0.4% to 33.2%. More precisely, the prevalence of PE varied between 0.4% and 17.6% in studies including patients with purulent AECOPD and non-purulent/unknown etiology AECOPD, whereas the prevalence of PE varied between 14.0% and 33.2% in studies including only patients with non-purulent/unknown etiology AECOPD. The prevalence of DVT per study varied between 0.1% and 20.7% (**Table 2**).

Risk of bias of included studies

When using the ROBINS-E tool(14), 3 studies were considered as having some concerns, 9 studies were considered at high risk and 2 studies were considered at very high risk of bias (**Table S2**). Publication bias was not present for the analysis on the relative risk of PE and AECOPD purulence

status (**Figure S1**), whereas publication bias was present for the analysis on pooled proportions of PE (**Figure S2**).

Association between the prevalence of PE and the AECOPD purulence status

Among the 9 studies(6, 7, 9, 10, 16-20) including patients with purulent and non-purulent/unknown etiology AECOPD, PE occurred in 76/1568 (4.8%) in patients with purulent AECOPD and in 238/2786 (8.5%) in patients with non-purulent/unknown etiology AECOPD. Although the risk of PE was lower in patients with purulent AECOPD compared to patients with non-purulent/unknown etiology AECOPD, it was not statistically significant (RR 0.64; 95%CI 0.26-1.55; p=0.32; I^2=88.0%) (**Figure 2**). No difference was seen in subgroup analyses according to study design, systematic search for PE and localization of PE (**Figures S3-S4-S5**). Post-hoc sensitivity analyses based on the definition of purulent AECOPD showed no difference when possible purulent AECOPD definition was used primarily instead of the definitive purulent AECOPD definition (RR 0.58; 95%CI 0.23-1.43; p=0.23; I^2=88.0%), but there was a reduction in PE in patients with purulent AECOPD compared to non-purulent/unknown etiology AECOPD when clinical purulent AECOPD definition was used in combination with possible purulent AECOPD definition used primarily (RR 0.44; 95%CI 0.20-0.97; p=0.04; I^2<0.01) (**Figures S6-S7**). Moreover, the risk of PE was also lower in patients with purulent AECOPD compared to patients with non-purulent/unknown etiology AECOPD when using fixed-effects model (RR 0.57; 95%CI 0.45-0.72; p<0.01; I^2=88.0%) (**Figure S8**). Sensitivity analyses according to the risk of bias could not be conducted since no study was considered at low risk of bias. These analyses were not conducted for DVT and VTE, respectively, since data on DVT in the included studies was not

available to allow the evaluation of the association between the risk of DVT and the AECOPD purulence status.

Pooled proportion of PE according to the AECOPD purulent status

In the 9 studies(6, 7, 9, 10, 16-20) including patients with purulent AECOPD, the pooled proportion of PE was 7.3% (95%CI 2.4%-14.7%; I^2=94.7%) and in the 14 studies(6, 7, 9, 10, 16-25) including patients with non-purulent/unknown etiology AECOPD, the pooled proportion of PE was 13.3% (95%CI 8.0%-19.7%; I^2=96.0%) (**Figure 3**). Subgroup analyses according to study design, systematic search for PE and localization of PE did not show any significant differences (**Table S3**).

DISCUSSION

This systematic review of 5,056 participants demonstrates that the risk of PE is lower in patients with purulent AECOPD compared to patients with non-purulent/unknown etiology AECOPD, although it was not statistically significant. Also, the prevalence of PE is not low enough to rule out PE based on clinical evaluation only in patients with purulent AECOPD and non-purulent/unknown etiology AECOPD, respectively.

These findings are a step forward in improving PE diagnostic management in patients with AECOPD. The risk of PE seems to be lower in patients with purulent AECOPD compared to patients with non-purulent/unknown etiology AECOPD. AECOPD purulence status could be further evaluated as a potential predictor of PE and if possible, be integrated in PE diagnostic strategy specifically for patients with AECOPD. This could help reduce the need for imaging to

rule out PE and consequently, reduce the negative effects of CTPA. Moreover, even if the risk of PE seems lower in patients with purulent AECOPD, the pooled proportion of PE of 7.3% in this group of patients is too high to safely exclude PE without further investigations(26). In the general population, PE is generally deemed ruled out when imaging is negative for PE or D-dimer is negative in patients with non-high c-PTP. Hence, in patients with COPD, purulent AECOPD could not exclude by itself the presence of PE but could rather be a predictor and help in the PE diagnostic algorithm. Although the most frequent cause of AECOPD is infection, in up to 30% of the cases the etiology of the exacerbation is unknown(27) and PE may explain a proportion of these AECOPD. The prevalence of PE was higher in patients with non-purulent/unknown etiology AECOPD compared to patients with purulent AECOPD. Thus, PE should still be kept in the mind of clinicians, no matter the type of AECOPD.

The definition of purulent AECOPD was highly variable across and within studies. This may explain why the main analysis and the subgroup analyses evaluating the RR of PE according to the AECOPD purulent status were not always statistically significant, although they were clinically significant, possibly due statistical power. To our knowledge, there is no standardized AECOPD purulent status definition which can explain this heterogeneity in the definition of purulent AECOPD. Moreover, the diagnosis of AECOPD can be difficult with potential misclassification(28). These elements support the need in clarifying which patients with COPD and symptoms compatible with AECOPD should be targeted for further investigations to rule out PE. Finding the subgroup of patients at higher risk of PE will help reduce unnecessary radiological testing and associated burden.

Moreover, given the clinical and methodological heterogeneity and potential bias, caution in the interpretation of findings is warranted and best considered hypothesis generating. Since the prevalence of PE varies according to the AECOPD purulent status, the inflammatory response could be different in non-purulent/unknown etiology AECOPD, which could explain this possible higher risk of PE. On the other hand, in some cases, PE could be the trigger for some of these unexplained AECOPD. Indeed, the causality is not demonstrated here.

We acknowledge that this study has limitations. First, the definition of purulent AECOPD was highly heterogenous across studies, which made it more challenging to pool data. Sensitivity analyses were conducted to further explore this element and did not show any difference in the clinical significance although some results were statistically significant according to the definition used, but this might rather be explained by the power and not necessarily by the definition of purulent AECOPD used. Second, most of the studies were at high risk of bias. In the majority of the studies, presence of detection bias could have partly explained a higher prevalence of PE among patients with non-purulent/unknown etiology AECOPD compared to patients with purulent AECOPD. Third, there was presence of publication bias for the analysis on pooled proportions of PE. This could be explained by studies on the prevalence of PE including only patients with non-purulent/unknown etiology AECOPD that tend to be more frequently published since the origin of the AECOPD is unknown. Fourth, heterogeneity was high and subgroup analyses were not able to explain it. Finally, only a small proportion of studies evaluating the prevalence of PE in patients with AECOPD reported this outcome according to the AECOPD purulence status. The main strength of this study is that to our knowledge, this is the first systematic review with meta-analysis evaluating the association between PE and AECOPD purulence status.

CONCLUSION

This systematic review demonstrates that the risk of PE is lower in patients with purulent AECOPD compared to patients with non-purulent/unknown etiology AECOPD but it was not statistically significant. AECOPD purulence status cannot exclude by itself the presence of PE since PE prevalence is not low enough to rule out PE in patients with either a purulent AECOPD or patients with a non-purulent/unknown etiology AECOPD. The definition of purulent AECOPD was highly heterogenous. Further studies are needed to confirm the association between PE and AECOPD purulence status to improve PE diagnostic management in this special population.

REFERENCES

1. Konstantinides SV, Meyer G. The 2019 ESC Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism. Eur Heart J. 2019;40(42):3453-5.

2. Celli BR, Barnes PJ. Exacerbations of chronic obstructive pulmonary disease. European Respiratory Journal. 2007;29(6):1224-38.

3. Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, et al. Susceptibility to Exacerbation in Chronic Obstructive Pulmonary Disease. New England Journal of Medicine. 2010;363(12):1128-38.

4. Seemungal TAR, Hurst JR, Wedzicha JA. Exacerbation rate, health status and mortality in COPD--a review of potential interventions. Int J Chron Obstruct Pulmon Dis. 2009;4:203-23.

5. Sato R, Hasegawa D, Nishida K, Takahashi K, Schleicher M, Chaisson N. Prevalence of pulmonary embolism in patients with acute exacerbations of COPD: A systematic review and meta-analysis. The American Journal of Emergency Medicine. 2021;50:606-17.

6. Couturaud F, Bertoletti L, Pastre J, Roy PM, Le Mao R, Gagnadoux F, et al. Prevalence of Pulmonary Embolism Among Patients With COPD Hospitalized With Acutely Worsening Respiratory Symptoms. JAMA. 2021;325(1):59-68.

7. Jiménez D, Agustí A, Tabernero E, Jara-Palomares L, Hernando A, Ruiz-Artacho P, et al. Effect of a Pulmonary Embolism Diagnostic Strategy on Clinical Outcomes in Patients Hospitalized for COPD Exacerbation: A Randomized Clinical Trial. JAMA. 2021;326(13):1277-85.

8. Rambaud G, Mai V, Motreff C, Sanchez O, Roy PM, Auffret Y, et al. Pulmonary embolism diagnostic strategies in patients with COPD exacerbation: Post-hoc analysis of the PEP trial. Thrombosis Research. 2023;231:58-64.

9. Choi KJ, Cha SI, Shin KM, Hwangbo Y, Yoo SS, Lee J, et al. Prevalence and predictors of pulmonary embolism in Korean patients with exacerbation of chronic obstructive pulmonary disease. Respiration. 2013;85(3):203-9.

10. Dentali F, Pomero F, Micco PD, La Regina M, Landini F, Mumoli N, et al. Prevalence and risk factors for pulmonary embolism in patients with suspected acute exacerbation of COPD: a multi-center study. European journal of internal medicine. 2020;80:54-9.

11. Liu X, Jiao X, Gong X, Nie Q, Li Y, Zhen G, et al. Prevalence, Risk Factor and Clinical Characteristics of Venous Thrombus Embolism in Patients with Acute Exacerbation of COPD: A Prospective Multicenter Study. Int J Chron Obstruct Pulmon Dis. 2023;18:907-17.

12. Mai V, Girardi L, de Wit K, Castellucci L, Aaron S, Couturaud F, et al. Chronic obstructive pulmonary disease exacerbation purulence status and its association with pulmonary embolism: protocol for a systematic review with meta-analysis. BMJ Open. 2024;14(6):e085328.

13. Bajc M, Schümichen C, Grüning T, Lindqvist A, Le Roux P-Y, Alatri A, et al. EANM guideline for ventilation/perfusion single-photon emission computed tomography (SPECT) for diagnosis of pulmonary embolism and beyond. European Journal of Nuclear Medicine and Molecular Imaging. 2019;46(12):2429-51.

14. ROBINS-E Development Group (Higgins J MR, Rooney A, Taylor K, Thayer K, Silva R, Lemeris C, Akl A, Arroyave W, Bateson T, Berkman N, Demers P, Forastiere F, Glenn B, Hróbjartsson A, Kirrane E, LaKind J, Luben T, Lunn R, McAleenan A, McGuinness L, Meerpohl J, Mehta S, Nachman R, Obbagy J, O'Connor A, Radke E, Savović J, Schubauer-Berigan M, Schwingl P, Schunemann H, Shea B, Steenland K, Stewart T, Straif K, Tilling K, Verbeek V, Vermeulen R, Viswanathan M, Zahm S, Sterne J). Risk Of Bias In Non-randomized Studies - of Exposure (ROBINS-E). 2022.

15. Kohn MA SJ. Sample Size Calculators (website). UCSF CTSI. 2021.

16. Bahloul M, Chaari A, Tounsi A, Baccouche N, Abid H, Chtara K, et al. Incidence and impact outcome of pulmonary embolism in critically ill patients with severe exacerbation of chronic obstructive pulmonary diseases. Clin Respir J. 2015;9(3):270-7.

17. Hassen MF, Tilouche N, Jaoued O, Elatrous S. Incidence and Impact of Pulmonary Embolism During Severe COPD Exacerbation. Respir Care. 2019;64(12):1531-6.

18. Li YX, Zheng ZG, Liu N, Wang XN, Wu LL, Chen RC. Risk factors for pulmonary embolism in acute exacerbation of chronic obstructive pulmonary disease. [Chinese]. Zhonghua jie he he hu xi za zhi = Zhonghua jiehe he huxi zazhi = Chinese journal of tuberculosis and respiratory diseases. 2016;39(4):298-303.

19. Mai Vicky PM, Mulpuru Sunita, Thiruganasambandamoorthy Venkatesh, Code Catherine, Le Gal Grégoire. Prevalence of Pulmonary Embolism in Patients with Chronic Obstructive Pulmonary Disease Exacerbation in North America – A Single Center Experience. .

20. Meitei SP, Tale S, Negi A, Dua R, Walia R, Saxena S. Prevalence and characteristics of venous thromboembolism in severe exacerbation of COPD in a tertiary care hospital in India. European Respiratory Journal Conference: International Congress of the European Respiratory Society, ERS. 2021;58(SUPPL 65).

21. Andrejak C, Poulet C, Hoguet E, Magois E, Gosset M, Jounieaux V. Prevalence of pulmonary embolism in COPD patients hospitalized for an unexplained wheezing COPD exacerbation. American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS. 2012;185(MeetingAbstracts).

22. Chaudhary N, Khan U, Shah T, Shaheen F, Mantoo S, Qadri S, et al. Prevalence and predictors of pulmonary embolism in patients with acute exacerbation of chronic obstructive pulmonary disease. Lung India. 2021;38(6):533-9.

23. Jindal A, Rathore Y, Joshi V, Jain S, Khippal N. A cross-sectional study for the evaluation of pulmonary embolism in unexplained dyspnea in acute exacerbation of chronic obstructive pulmonary disease. Indian Journal of Respiratory Care. 2020;9:191.

24. Tillie-Leblond I, Marquette CH, Perez T, Scherpereel A, Zanetti C, Tonnel AB, et al. Pulmonary embolism in patients with unexplained exacerbation of chronic obstructive pulmonary disease: prevalence and risk factors. Ann Intern Med. 2006;144(6):390-6.

25. Wang TS, Su XL, Mao YM, Sun YX. Pulmonary embolism in patients with chronic obstructive pulmonary disease and exacerbations of unknown origin. Asian Biomedicine. 2013;7(4):529-35.

26. Kline JA, Mitchell AM, Kabrhel C, Richman PB, Courtney DM. Clinical criteria to prevent unnecessary diagnostic testing in emergency department patients with suspected pulmonary embolism. J Thromb Haemost. 2004;2(8):1247-55.

27. Sapey E, Stockley RA. COPD exacerbations . 2: aetiology. Thorax. 2006;61(3):250-8.

28. Pratt AJ, Purssell A, Zhang T, Luks VPJ, Bauza X, Mulpuru S, et al. Complexity in clinical diagnoses of acute exacerbation of chronic obstructive pulmonary disease. BMC Pulm Med. 2023;23(1):298.

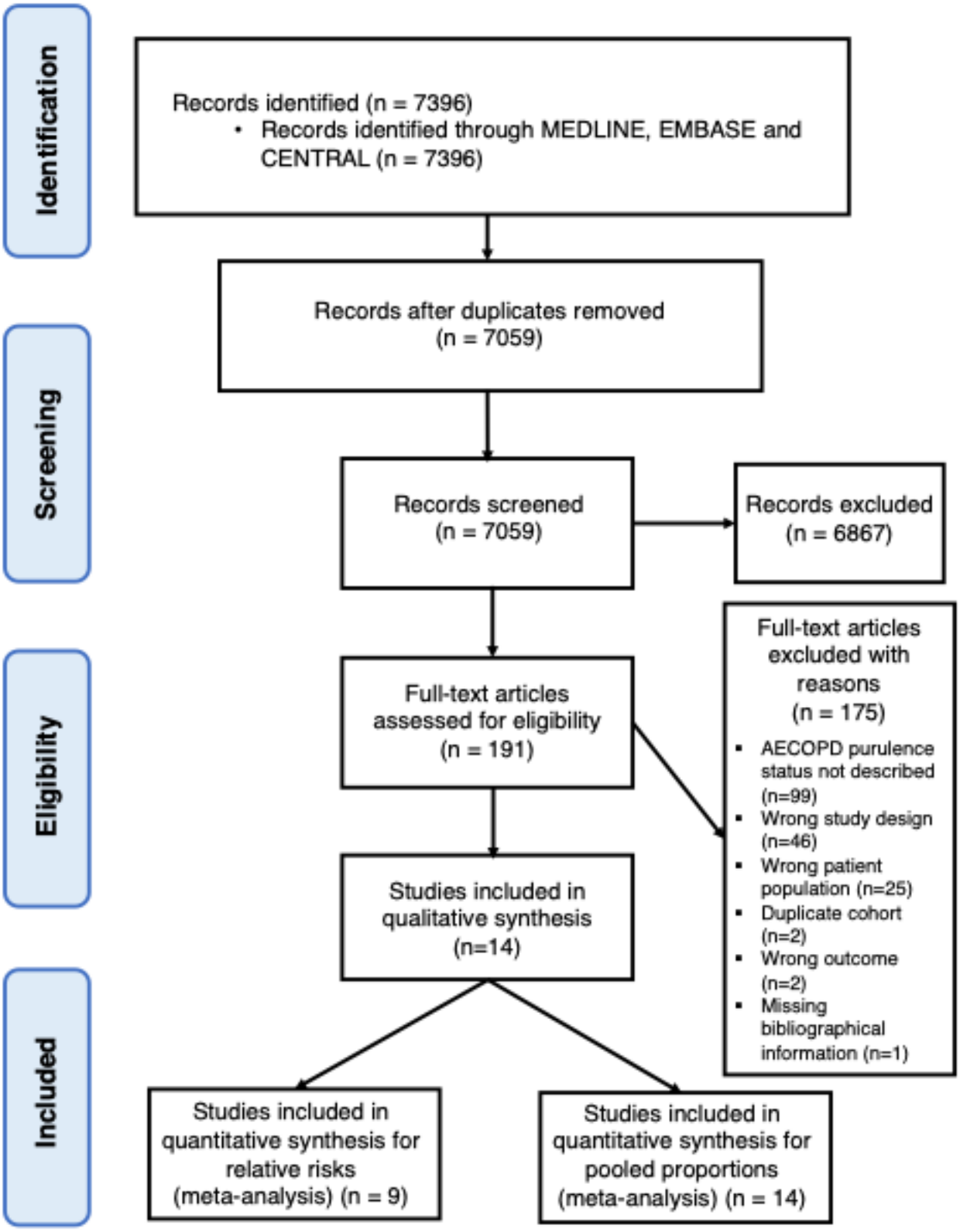


Figure 1. Flow chart.

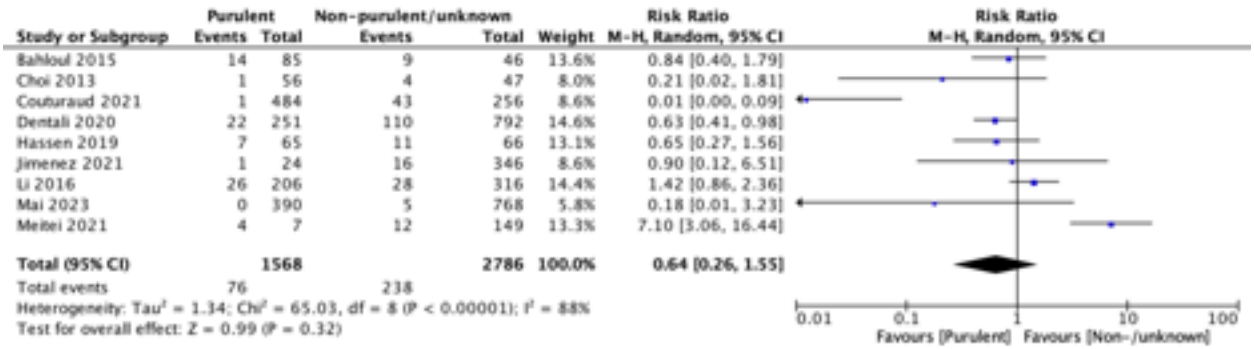
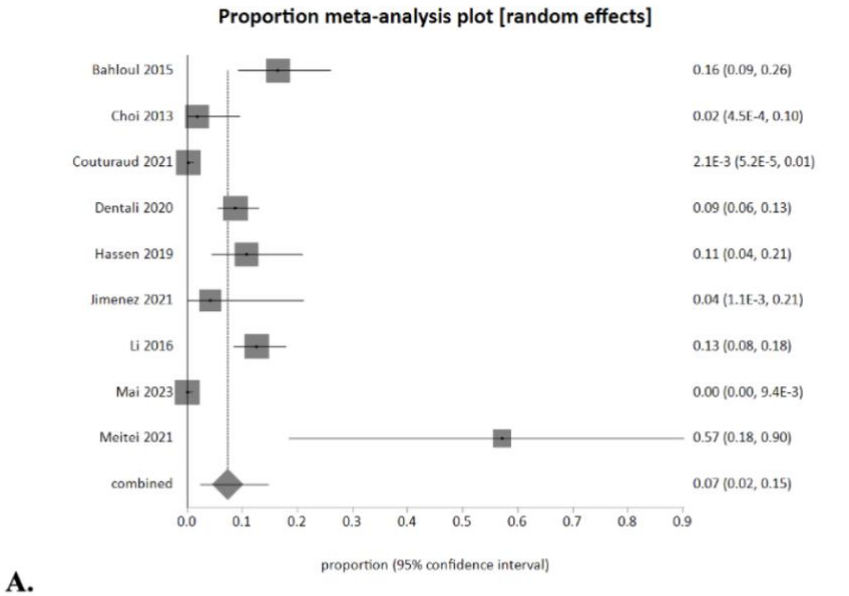
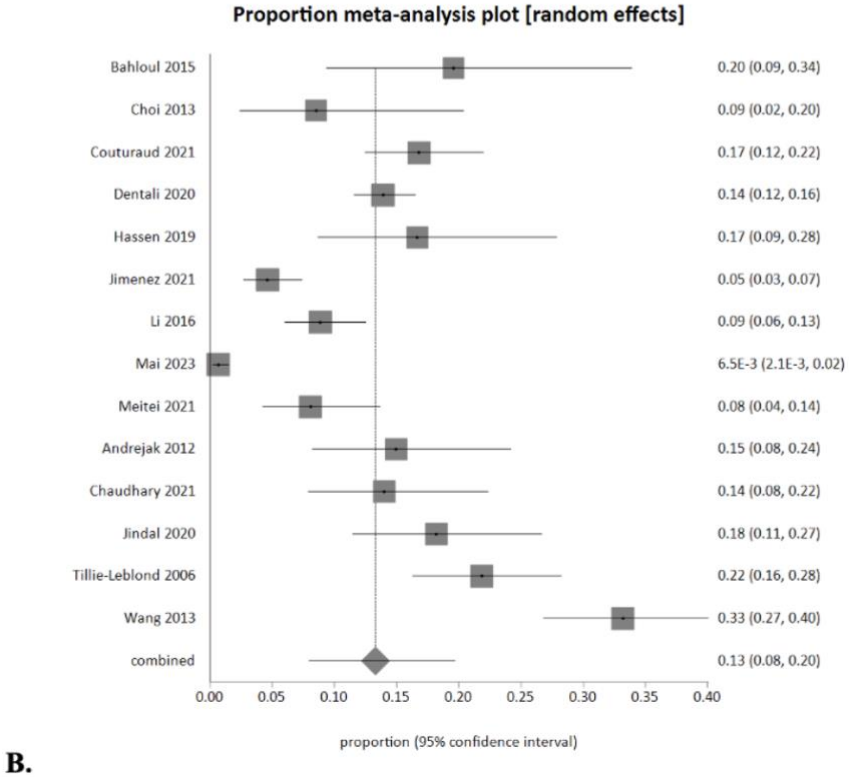


Figure 2. Forest plot and relative risk for the association between the risk of pulmonary embolism and the acute exacerbation of chronic obstructive pulmonary disease purulence status.



A.



B.

Figure 3. Pooled proportions of pulmonary embolism in patients A) with purulent acute exacerbation of chronic obstructive pulmonary disease and B) non-purulent/unknown etiology acute exacerbation of chronic obstructive pulmonary disease.

CHAPTER 6: Manuscript 5 - Derivation and validation of a COPD-specific pulmonary embolism diagnostic strategy for patients with COPD and acutely worsening respiratory symptoms

6.1 Preface to manuscript 5

This project is the core of my thesis. Moreover, this work gave me the opportunity to collaborate with well-established thrombosis physicians in France and Spain. I had the chance to work on the cohorts of the PEP trial and the SLICE trial, two prospective studies of patients with COPD admitted for an exacerbation. The aim of this study was to evaluate predictors of PE in patients with AECOPD, to derive and to attempt to validate a PE diagnostic strategy specifically for patients with AECOPD. I worked on the literature review, study conception, data analysis, interpretation of the data and manuscript drafting. Co-authors contributed to the patients' recruitment, data collection, supervision and revision of the manuscript.

The abstract has been accepted for an oral presentation at ISTH annual conference 2025 in Washington. The abstract has also been selected for a Travel Award.

This manuscript has been submitted in a peer-reviewed journal.

6.2 Manuscript 5

Derivation and validation of a COPD-specific pulmonary embolism diagnostic strategy for patients with COPD and acutely worsening respiratory symptoms

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Abstract: 288 words

Manuscript: 3325 words

ABSTRACT

Introduction: Diagnosing pulmonary embolism (PE) in patients with chronic obstructive pulmonary disease (COPD) exacerbation is challenging due to similarities in clinical symptoms. The aim of this study was to evaluate predictors of PE diagnosis in patients with COPD exacerbation and to derive and validate a COPD-specific PE diagnostic strategy.

Methods: A post-hoc analysis of the PEP trial, a prospective multicenter study of patients with COPD hospitalized with acutely worsening respiratory symptoms, was conducted. The outcome predicted was PE at admission. Isolated proximal DVT was also used as a surrogate of PE for the outcome predicted. Univariable and multivariable analyses were conducted to evaluate predictors of PE. Clinically and statistically significant independent variables were selected using multivariable logistic regression. Receiver operating characteristic curves were computed to determine the most discriminant D-dimer cut-offs. An attempt to validate the COPD-specific PE diagnostic strategy was made in the SLICE trial cohort.

Results: 734 patients were included. At admission, the prevalence of PE and/or proximal DVT was 6.5% (95%CI 5.0%-8.6%). A COPD-specific PE diagnostic strategy consisting of a 3-item score (type of COPD exacerbation, alternative diagnosis less likely than PE, and clinical signs of DVT) combined with D-dimer at specific cut-offs (1000 mcg/L if 0 score item and 500 mcg/L if 1 or 2 score items) was derived. The prevalence of PE (± proximal DVT) was 0.8%, 8.0%, 19.3% and 53.9% in the 0, 1, 2 and 3 item groups, respectively. The overall diagnostic failure rate was 0.9% (95%CI 0.4%-1.9%) and 392 patients (53.4%) would need imaging to rule out PE.

Conclusion: A COPD-specific PE diagnostic strategy was derived specifically for patients with COPD and acutely worsening respiratory symptoms. Prospective validation of this diagnostic algorithm is needed prior integrating it in clinical practice.

INTRODUCTION

The prevalence of pulmonary embolism (PE) in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is estimated at 11-17%(1-4). AECOPD represent 0.5-1.6% of all emergency department (ED) visits and one third to more than half of the ED visits for AECOPD results in a hospitalization(5-7). Since PE and AECOPD share similar symptoms, the diagnosis of PE is difficult to make in patients with AECOPD. Indeed, even when PE is not suspected, the prevalence of PE in patients with AECOPD is approximately 4%(8, 9). Therefore, excluding PE according to clinical gestalt may not be appropriate in this population(10). Moreover, it is important to diagnose PE in patients with AECOPD as it is associated with increased mortality (1, 8).

It is unclear how the diagnostic work-up of PE in patients with COPD should be conducted since clinical decision rules (CDR) have not been derived and validated specifically in patients with COPD and a systematic screening for PE with D-dimer ± computed tomography pulmonary angiogram (CTPA) does not seem to improve a composite health outcome (nonfatal symptomatic venous thromboembolism (VTE), readmission for COPD, or death at 90 days)(9). For patients with COPD presenting with acute worsening of dyspnea/chest discomfort and suspected PE, expert consensus from the American Thoracic Society (ATS) suggests a diagnostic algorithm using usual diagnostic strategies (i.e., Wells and revised Geneva scores) combined with fixed D-dimer cut-off at 500 mcg/L to guide physicians in performing further investigations(11). However, when Wells or revised Geneva scores combined with a fixed D-dimer cut-off were computed in patients enrolled in the PEP trial(8), 70% of the patients would require CTPA to rule out PE thus exposing a substantial proportion of patients to unnecessary radiation(12). CTPA-sparing diagnostic

strategies (i.e ADJUST-PE(13), YEARS(14), PEGeD(15) and 4PEPS(16)) reduced the need to perform chest imaging to rule out PE, however, the diagnostic failure rate seemed higher than the safety threshold in patients with AECOPD(12).

Thus, current CDR may not be adapted to patients with COPD who generally have more comorbidities than the general population and who already have respiratory symptoms at baseline. It is currently unclear which PE diagnostic management strategy would be most optimal to use in this population. The aim of this study was to evaluate predictors of PE in patients with COPD and acutely worsening respiratory symptoms to derive and validate a COPD-specific PE diagnostic strategy.

METHODS

Study design and derivation cohort

This is a post-hoc analysis of the PEP trial. The manuscript was drafted according to the TRIPOD+AI statement(17). The PEP trial which was a prospective multicenter cohort study aiming to evaluate the prevalence of PE in 740 patients with confirmed COPD hospitalized for acutely worsening respiratory symptoms managed according to the revised Geneva score combined with a fixed D-dimer cut-off at 500 mcg/L. This cohort was chosen to due to accessibility of the data and the PEP cohort being representative of this special population. This cohort is one of the largest cohort of patients with COPD hospitalized with acutely worsening respiratory symptoms in whom a PE diagnostic strategy was systematically applied, whether or not PE was suspected. The study was conducted in 7 centers in France from January 2014 to May 2017. All patients were followed for 3 months. In addition to the exclusion criteria of the main study(8), we

excluded patients with a diagnosis of isolated distal DVT at admission for this post-hoc analysis. The main exclusion criteria of the princeps study were contraindication to CTPA, creatinine clearance < 30 mL/min/1.73m^2, pregnancy, hospitalization for > 48 hours before inclusion, anticoagulation for a condition other than VTE, pneumothorax at admission, severe AECOPD making imaging tests unfeasible, life expectancy < 3 months and inability to give written informed consent. Further details on the derivation cohort can be found elsewhere(8).

Validation cohort

The external validation of the COPD-specific PE diagnostic strategy was attempted by using the cohort of the SLICE study. The SLICE study was a multicenter randomized controlled trial of 746 patients with COPD hospitalized for an exacerbation (in whom PE was not the initial clinical suspicion) comparing usual care to usual care plus an active screening strategy for PE on a composite health outcome (nonfatal symptomatic VTE, readmission for COPD, or death within 90 days). The active screening strategy for PE consisted of D-dimer testing, using the manufacturers assay threshold, and if positive, CTPA was performed. Only the 369 patients managed according to usual care combined with an active search strategy for PE and for which D-dimer level was available were used for validation since a PE diagnostic strategy was systematically applied to these patients. The rationale in using this cohort was the accessibility of the data and the representativeness of the cohort. The study was conducted in 18 centers in Spain from September 2014 to November 2020. Further details and exclusion criteria of the validation cohort can be found elsewhere(9).

Outcome

The outcome predicted was PE at admission. PE was defined as PE in a segmental or more proximal artery, multiple subsegmental PE, or single subsegmental PE (if associated with a DVT). Isolated proximal DVT was also included in the outcome predicted since isolated proximal DVT was considered as a surrogate for PE in patients with acutely worsening respiratory symptoms. In patients with new or worsening respiratory symptoms and a new diagnosis of proximal DVT, a potential diagnosis of PE was considered(18). Proximal DVT was defined as a thrombus affecting the popliteal vein or more proximal vein of the lower extremities. Outcomes were independently adjudicated in the derivation and validation cohorts.

Statistical analysis

Derivation

Our sample size was determined by the number of patients enrolled in the PEP study(8). The 734 included patients, 48 of them with outcome events, allowed us to derive a prediction model, considering that 5 to 10 outcome events per predictor in the model are needed(19). For missing data, imputation, using predictive mean matching method for continuous variables and discriminant function method for categorical variables, was performed for some variables in the dataset of the PEP cohort (n=740). All variables were evaluated as a potential predictor of PE and relevant variables were included in the univariable analysis. For the univariable analysis, 0.1 was the p-value threshold for a variable to be considered for the multivariable logistic regression. Variables with ≥ 15% missing data were excluded from the multivariable analysis. Variables to be included in the multivariable logistic regression model were chosen according to statistical significance and clinical importance. For the multivariate analysis, a p-value < 0.05 was considered statistically significant. Only clinically and statistically significant variables were kept in the

multivariable model. Continuous variables could be transformed into categorical variables by choosing the most discriminant cut-off point. Regression coefficients were calculated for each variable in the multivariable model and points were assigned for each variable according to the regression coefficient. One point was attributed to the smallest regression coefficient and other variables were assigned a number of points proportional to the regression coefficients. However, for the COPD-specific score (3-item score), type of AECOPD was given 1 point instead of 3 points to stay conservative since this variable is not found in current validated CDR(13-16, 20, 21). The variable "type of AECOPD" was divided as purulent AECOPD, defined as bronchial infection or pneumonia, and as non-purulent AECOPD when the AECOPD was neither bronchial infection nor pneumonia. The COPD-specific score was computed for each patient. Discrimination of the COPD-specific score was measured by computing a receiver operating characteristic (ROC) curve with its 95%CI. Calibration was measured with the Hosmer-Lemeshow test (chi-square and p-value)(22). Bootstrapping was performed to ensure stability of the results. The proportion of patients and the prevalence of PE was calculated and presented graphically. Cut-off points were chosen to determine the clinical pre-test probability (c-PTP) groups. Sensitivity analyses of the ROC curve were performed with the cohort without imputation as well as including the 3-month VTE events in the predicted events. For the COPD-specific PE diagnostic strategy, ROC curve was computed for D-dimer in each group to determine the most discriminative D-dimer cut-off of each group. The diagnostic failure rate [prevalence of VTE (PE and proximal DVT) diagnosed at admission and during the 3-month follow-up among patients who were considered negative for PE as per the PE diagnostic strategy] and the proportion of patients who would need imaging to rule out PE were calculated.

External validation

The COPD-specific PE diagnostic strategy was applied in an external cohort to ensure robustness of the diagnostic algorithm derived(9). Discrimination was measured with the ROC curve and its 95%CI and calibration was measured with the Hosmer-Lemeshow (chi-square and p-value)(22). Proportion of patients and prevalence of PE per c-PTP groups were calculated and presented graphically. The diagnostic failure rate and the proportion of patients requiring imaging to rule out PE were calculated.

RESULTS

Baseline characteristics

Baseline characteristics of the derivation and validation cohorts are presented in **Table 1**. The derivation cohort included 734 patients. At admission, 44 PE and 4 proximal DVT were diagnosed. As a result, the prevalence of PE and proximal DVT was 48/734 (6.5%; 95%CI 5.0%-8.6%). The counts and proportions of missing values for each variable are presented in **Table S1**. The validation cohort included 369 patients and the prevalence of PE at admission was 17/369 (4.6%; 95%CI 2.9%-7.3%).

Usual CDR (Wells PE and revised Geneva scores)

Before deriving a new score, we evaluated the discriminant ability of all items of the Wells PE and the revised Geneva scores in COPD patients with acutely worsening respiratory symptoms. The area under the ROC curve was 0.68 (95%CI 0.60-0.76) for the Wells PE score and was 0.62 (95%CI 0.54-0.70) for the revised Geneva score (**Figure S1-S2**).

Initial score derivation

All relevant variables for predicting PE were evaluated by univariable analysis. Several variables were statistically significant (**Table S1**). When assessed in the multivariable regression model, 4 variables were included based on clinical and statistical significance (**Table S2**). The 4 variables initially kept were the type of AECOPD, alternative diagnosis less likely than PE, pH and clinical signs of DVT. According to the regression coefficients of each variable, points attributed for each variable are presented in **Table S2**. This 4-item score was computed in all patients of the derivation cohort. The area under the ROC curve was 0.86 (95%CI 0.81-0.91) (**Figure S3**). Most of the patients had ≤ 0 points with very few patients with > 4 points and the prevalence of PE per c-PTP groups increased as the number of points per group increased (**Figure S4**). However, when this 4-item score was computed in the validation cohort, there was no trend in the distribution of patients and as well as in the prevalence of PE per c-PTP groups (**Figure S5**). When looking at the validation results, the variable pH did not validate as a good predictor of PE in this cohort. Thus, modification of the score was made by removing the item pH from the score and by modifying the number of points per item.

Derivation of the COPD-specific PE diagnostic strategy

Using available data as well as statistical significance and clinical importance of various variables, we explored the option to derive a COPD-specific PE diagnostic strategy instead of a score in isolation. We kept the 3 most significant variables (type of AECOPD, alternative diagnosis less likely than PE, and clinical signs of DVT) in the score and attributed 1 point to each item. The regression coefficients can be found in **Table S3**. We computed this 3-item score in the derivation cohort and the area under the ROC curve was 0.81 (95%CI 0.75-0.87) (**Figure 1**). The Hosmer-

Lemeshow test showed good calibration (chi-square=1.70 and p-value=0.64). Patients' distribution was as follows: 370 patients (50.4%) had 0 item, 263 patients (35.8%) had 1 item, 88 patients (12.0%) had 2 items and 13 patients (1.8%) had 3 items. PE (or isolated proximal DVT) at admission was diagnosed in 3/370 patients (0.8%; 95%CI 0.3%-2.4%) with 0 item, in 21/263 patients (8.0%; 95%CI 5.3%-11.9%) with 1 item, in 17/88 patients (19.3%; 95%CI 12.4%-28.8%) with 2 items and in 7/13 patients (53.9%; 95%CI 29.2%-76.8%) with 3 items (**Figures 2A-3A**). D-dimer was also incorporated in the algorithm. For patients categorized in the 0-item group, we used a D-dimer cut-off of 1000 mcg/L (**Figure S6A**). For patients categorized in the 1- or 2-items groups, the D-dimer cut-off was 500 mcg/L (**Figures S6B-S6C**). For patients categorized in the 3-items group, D-dimer was not needed, but chest imaging needed to be performed to rule out PE. This strategy aligns with other CTPA-sparing diagnostic strategies showing that it is safe to use higher D-dimer cut-offs in patients with a low c-PTP(14, 16, 23). The overall diagnostic failure rate was 6/687 patients (0.9%; 95%CI 0.4%-1.9%) and 392/734 patients (53.4%; 95%CI 49.8%-57.0%) needed imaging to rule out PE (**Figure 2A**). More specifically, the diagnostic failure rate in patients managed without imaging (i.e. with negative D-dimer) was 4/342 patients (1.2%; 95%CI 0.5%-3.0%) (**Figure 2A**). Sensitivity analysis including the 3-month VTE in the predicted events yielded similar accuracy (**Figure S7**). Sensitivity analysis in the cohort without imputation was not performed since the COPD-specific score only included variables without missing data.

External validation of the COPD-specific PE diagnostic strategy

An attempt to validate the COPD-specific PE diagnostic strategy was made by using the SLICE cohort of 369 patients(9). The 3-item COPD score was computed in all patients. The area under the ROC curve was 0.61 (95%CI 0.46-0.77) (**Figure S8**). The Hosmer-Lemeshow test showed

good calibration (chi-square=2.64 and p-value=0.10). The distribution of patients was as followed: 23 patients (6.2%) with 0 item, 291 patients (78.9%) with 1 item, 55 patients (14.9%) with 2 items and no patient had 3 items. PE at admission was diagnosed in 1/23 patients (4.4%; 95%CI 0.8%-21.0%) with 0 item, in 9/291 patients (3.1%; 95%CI 1.6%-5.8%) with 1 item and in 7/55 patients (12.7%; 95%CI 6.3%-24.0%) with 2 items (**Figures 2B-3B**). The overall diagnostic failure rate was 0.9% (95%CI 0.3%-2.5%) and 186/369 patients (50.4%; 95%CI 45.3%-55.5%) needed imaging to rule out PE (**Figure 2B**). More specifically, the diagnostic failure rate in patients managed without imaging (i.e. with negative D-dimer) was 2/183 patients (1.1%; 95%CI 0.3%-3.9%) (**Figure 2B**).

DISCUSSION

This post-hoc analysis of the PEP trial, including 734 patients with COPD hospitalized for acutely worsening respiratory symptoms, identified predictors of PE in this special population. Our study showed that the accuracy of the Wells PE and revised Geneva scores was poor in this population. Consequently, a COPD-specific PE diagnostic strategy was derived, which ultimately included a 3-item score (type of AECOPD, alternative diagnosis less likely than PE, and clinical signs of DVT) combined with D-dimer at various cut-offs depending on the number of items. This COPD-specific score showed satisfactory accuracy and the COPD-specific PE diagnostic strategy yielded low diagnostic failure rate with ≈50% of the patients needing chest imaging to rule out PE. An attempt to externally validate retrospectively this diagnostic algorithm was made and showed reasonable performance with a low overall diagnostic failure rate.

This COPD-specific PE diagnostic strategy is easy to apply. First, predictors in this diagnostic algorithm include major predictors of PE in the general population, such as clinical signs of DVT or an alternative diagnosis less likely than PE, two items included in the YEARS algorithm(14), and include a predictor specifically adapted to patients with COPD such as the type of AECOPD. Second, we chose predictors that were easily available by a clinical questionnaire or a common blood test, are not costly and could be measured with reasonable precision. We also chose to derive a diagnostic algorithm instead of a clinical score so that it can be more easily integrated in clinical practice. This COPD-specific PE diagnostic strategy would dictate if further imaging is needed to rule out PE. Being a 3-item score combined with D-dimer with 2 different cut-offs, this COPD-specific diagnostic strategy can be easily remembered and applied in a clinical setting, even in a busy area such as emergency rooms.

Moreover, this COPD-specific PE diagnostic strategy is clinically reliable. In the derivation cohort, the COPD-specific score including 3 items showed very good accuracy. Most of the patients were categorized in the 0 or 1 item groups and the prevalence of PE per risk group increases as the number of items increased which is what is expected for a CDR. In the validation cohort, accuracy of the COPD-specific score was adequate. Also, most of the patients were categorized in the 1 item group and there was a trend in increased prevalence of PE per risk group as the number of items increased. However, the validation cohort included only a part of the population used in the derivation cohort; by study design, in the SLICE trial there were no patients in whom PE was thought to be the most likely diagnosis and patients with signs or symptoms of DVT were excluded from the trial, which are 2 items of our COPD-specific score.

The safety and efficiency of the COPD-specific PE diagnostic strategy were also assessed. This diagnostic algorithm appeared safe and approximately 50% of the patients would not need imaging to rule out PE which is greater than when the Wells PE or revised Geneva scores combined with a fixed D-dimer cut-off were computed(8, 12). This new PE diagnostic strategy could help reduce unnecessary radiation and costs, as well as potential incidental findings that can bring anxiety to the patients. Since patients with COPD tend to have more frequent exacerbations as their pulmonary disease progresses(24), reducing the need for imaging is even more important. Furthermore, systematically applying a COPD-specific PE diagnostic strategy will target patients who need further investigations to rule out PE, a disease associated with increased mortality in this special population(1). This will help reduce unneeded investigations in patients who would have been investigated according to clinical decision or systematic imaging. This will also help diagnose PE in patients with COPD, which is challenging. When imaging or CDR are not systematically applied in this population, less patients are diagnosed with PE(25), but more importantly, it leads to potential missed PE, which can be fatal. Adequately diagnosing and treating the exact cause of AECOPD will also help reduce further medical visits and consequently, improve quality of life of patients with COPD.

We acknowledge that this study has limitations. First, the validation cohort was not entirely representative of the population in which the PE diagnostic strategy was derived. Patients in whom PE was the most likely diagnosis and patients with clinical signs of DVT were excluded from the validation cohort. Thus, the validation cannot be considered fully completed in that context. However, it was the prospective cohort that was most similar to our derivation cohort from which we could access data for validation. Second, the sample size of the validation cohort was relatively

small. Third, some variables could not be adequately evaluated as a predictor due to a high number of missing data, whereas some potential predictors may have not been captured in the case report form. Nevertheless, this study has some strengths. First, to our knowledge, this is the first PE diagnostic strategy specifically derived in patients with COPD and acutely worsening respiratory symptoms. Second, the sample size of the derivation cohort was reasonable to adequately derive a PE diagnostic strategy. Third, all VTE were adjudicated by an independent committee in the derivation and validation cohorts. Fourth, as opposed to a clinical score that help predicts the risk in having a PE, we are proposing a diagnostic algorithm that will help the clinician decide if further investigations are needed to exclude or to diagnose PE. Finally, the COPD-specific PE diagnostic strategy is simple and will be easy to apply in clinical practice.

CONCLUSION

A COPD-specific PE diagnostic strategy, consisting of a 3-item score combined with D-dimer testing, is a tool derived specifically for patients with COPD and acutely worsening respiratory symptoms to help in the management of these patients. Prospective validation of the COPD-specific PE diagnostic strategy is needed before incorporating this tool in clinical practice.

REFERENCES

1. Sato R, Hasegawa D, Nishida K, Takahashi K, Schleicher M, Chaisson N. Prevalence of pulmonary embolism in patients with acute exacerbations of COPD: A systematic review and meta-analysis. The American Journal of Emergency Medicine. 2021;50:606-17.

2. Wang J, Ding YM. Prevalence and risk factors of pulmonary embolism in acute exacerbation of chronic obstructive pulmonary disease and its impact on outcomes: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci. 2021;25(6):2604-16.

3. Fu X, Zhong Y, Xu W, Ju J, Yu M, Ge M, et al. The prevalence and clinical features of pulmonary embolism in patients with AE-COPD: A meta-analysis and systematic review. PLoS One. 2021;16(9):e0256480.

4. Han W, Wang M, Xie Y, Ruan H, Zhao H, Li J. Prevalence of Pulmonary Embolism and Deep Venous Thromboembolism in Patients With Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. Frontiers in cardiovascular medicine. 2022;9:732855.

5. Hasegawa K, Tsugawa Y, Tsai CL, Brown DF, Camargo CA, Jr. Frequent utilization of the emergency department for acute exacerbation of chronic obstructive pulmonary disease. Respir Res. 2014;15(1):40.

6. Germini F, Veronese G, Marcucci M, Coen D, Ardemagni D, Montano N, et al. COPD exacerbations in the emergency department: Epidemiology and related costs. A retrospective cohort multicentre study from the Italian Society of Emergency Medicine (SIMEU). European journal of internal medicine. 2018;51:74-9.

7. Liew CQ, Hsu SH, Ko CH, Chou EH, Herrala J, Lu TC, et al. Acute exacerbation of chronic obstructive pulmonary disease in United States emergency departments, 2010-2018. BMC Pulm Med. 2023;23(1):217.

8. Couturaud F, Bertoletti L, Pastre J, Roy PM, Le Mao R, Gagnadoux F, et al. Prevalence of Pulmonary Embolism Among Patients With COPD Hospitalized With Acutely Worsening Respiratory Symptoms. JAMA. 2021;325(1):59-68.

9. Jiménez D, Agustí A, Tabernero E, Jara-Palomares L, Hernando A, Ruiz-Artacho P, et al. Effect of a Pulmonary Embolism Diagnostic Strategy on Clinical Outcomes in Patients Hospitalized for COPD Exacerbation: A Randomized Clinical Trial. JAMA. 2021;326(13):1277-85.

10. Kline JA, Mitchell AM, Kabrhel C, Richman PB, Courtney DM. Clinical criteria to prevent unnecessary diagnostic testing in emergency department patients with suspected pulmonary embolism. J Thromb Haemost. 2004;2(8):1247-55.

11. Celli BR, Fabbri LM, Aaron SD, Agusti A, Brook RD, Criner GJ, et al. Differential Diagnosis of Suspected Chronic Obstructive Pulmonary Disease Exacerbations in the Acute Care Setting Best Practice. American Journal of Respiratory and Critical Care Medicine. 2023;207(9):1134-44.

12. Rambaud G, Mai V, Motreff C, Sanchez O, Roy PM, Auffret Y, et al. Pulmonary embolism diagnostic strategies in patients with COPD exacerbation: Post-hoc analysis of the PEP trial. Thrombosis Research. 2023;231:58-64.

13. Righini M, Van Es J, Den Exter PL, Roy PM, Verschuren F, Ghuysen A, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. JAMA. 2014;311(11):1117-24.

14. van der Hulle T, Cheung WY, Kooij S, Beenen LFM, van Bemmel T, van Es J, et al. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. Lancet. 2017;390(10091):289-97.

15. Kearon C, de Wit K, Parpia S, Schulman S, Afilalo M, Hirsch A, et al. Diagnosis of Pulmonary Embolism with d-Dimer Adjusted to Clinical Probability. New England Journal of Medicine. 2019;381(22):2125-34.

16. Roy P-M, Friou E, Germeau B, Douillet D, Kline JA, Righini M, et al. Derivation and Validation of a 4-Level Clinical Pretest Probability Score for Suspected Pulmonary Embolism to Safely Decrease Imaging Testing. JAMA Cardiology. 2021;6(6):669-77.

17. Collins GS, Moons KGM, Dhiman P, Riley RD, Beam AL, Van Calster B, et al. TRIPOD+AI statement: updated guidance for reporting clinical prediction models that use regression or machine learning methods. BMJ. 2024;385:e078378.

18. Le Gal G, Righini M, Sanchez O, Roy PM, Baba-Ahmed M, Perrier A, et al. A positive compression ultrasonography of the lower limb veins is highly predictive of pulmonary embolism on computed tomography in suspected patients. Thrombosis and Haemostasis. 2006;95(6):963-6.

19. Steyerberg EW. Clinical Prediction Models: Springer Cham; 2019. XXXIII, 558 p.

20. Le Gal G, Righini M, Roy PM, Sanchez O, Aujesky D, Bounameaux H, et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Ann Intern Med. 2006;144(3):165-71.

21. Wells PS, Anderson DR, Rodger M, Stiell I, Dreyer JF, Barnes D, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. Ann Intern Med. 2001;135(2):98-107.

22. Alba AC, Agoritsas T, Walsh M, Hanna S, Iorio A, Devereaux PJ, et al. Discrimination and Calibration of Clinical Prediction Models: Users' Guides to the Medical Literature. JAMA. 2017;318(14):1377-84.

23. Kearon C, de Wit K, Parpia S, Schulman S, Afilalo M, Hirsch A, et al. Diagnosis of Pulmonary Embolism with d-Dimer Adjusted to Clinical Probability. New England Journal of Medicine. 2019;381(22):2125-34.

24. Anzueto A. Impact of exacerbations on COPD. European Respiratory Review. 2010;19(116):113-8.

25. Mai Vicky PM, Mulpuru Sunita, Thiruganasambandamoorthy Venkatesh, Code Catherine, Le Gal Grégoire. Prevalence of Pulmonary Embolism in Patients with Chronic Obstructive Pulmonary Disease Exacerbation in North America – A Single Center Experience. .

Table 1. Baseline characteristics of the patients

Characteristics	Derivation cohort (n=734)	Validation cohort (n=369)
Age, years (mean ± SD)	68.1 ± 10.8	70.3 ± 9.8
Female – n/N (%)	271/734 (36.9)	86 (23.3)
Body mass index, kg/m^2 (mean ± SD)	25.7 ± 6.7 [n=729]	NA
%FEV1 (mean ± SD)	52.7 ± 23.6 [n=670]	46.2 ± 18.1
GOLD stage - n (%)		
1	85 (13.9)	31 (8.4)
2	223 (36.4)	113 (30.6)
3	228 (37.3)	169 (45.8)
4	76 (12.4)	56 (15.2)
	[n=612]	
Tobacco use – n/N (%)		
Current smoker	262/730 (35.9)	118 (32.0)
Ex-smoker	413/730 (56.6)	245 (66.4)
Number of exacerbations in the last year - (median, IQR)	2.0 (0-3.0) [n=662]	1.0 (0-2.0)
Prolonged immobilization - n (%)	131/733 (17.9)	67 (18.2)
Familial history – n/N (%)	66/690 (9.6)	4 (1.1)
Cancer in the past 2 years – n/N (%)	58/732 (7.9)	12 (3.3)
Previous VTE – n/N (%)	54/733 (7.4)	10 (2.7)
Surgery – n/N (%)	23/732 (3.1)	67 (18.2)
Trauma – n/N (%)	15/734 (2.0)	NA
PE suspected – n/N (%)	294/734 (40.1)	0 (0.0)

DVT: deep venous thrombosis; FEV1: forced expiratory volume in 1 second; GOLD: Global Initiative for Obstructive Lung Disease; NA: not applicable; PE: pulmonary embolism; SD: standard deviation; VTE: venous thromboembolism;

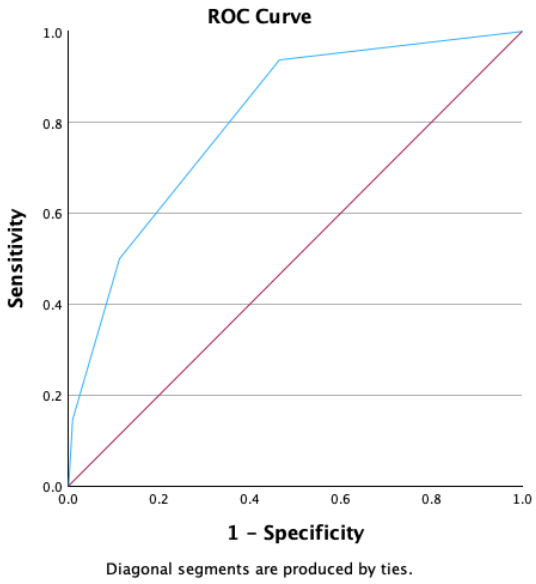
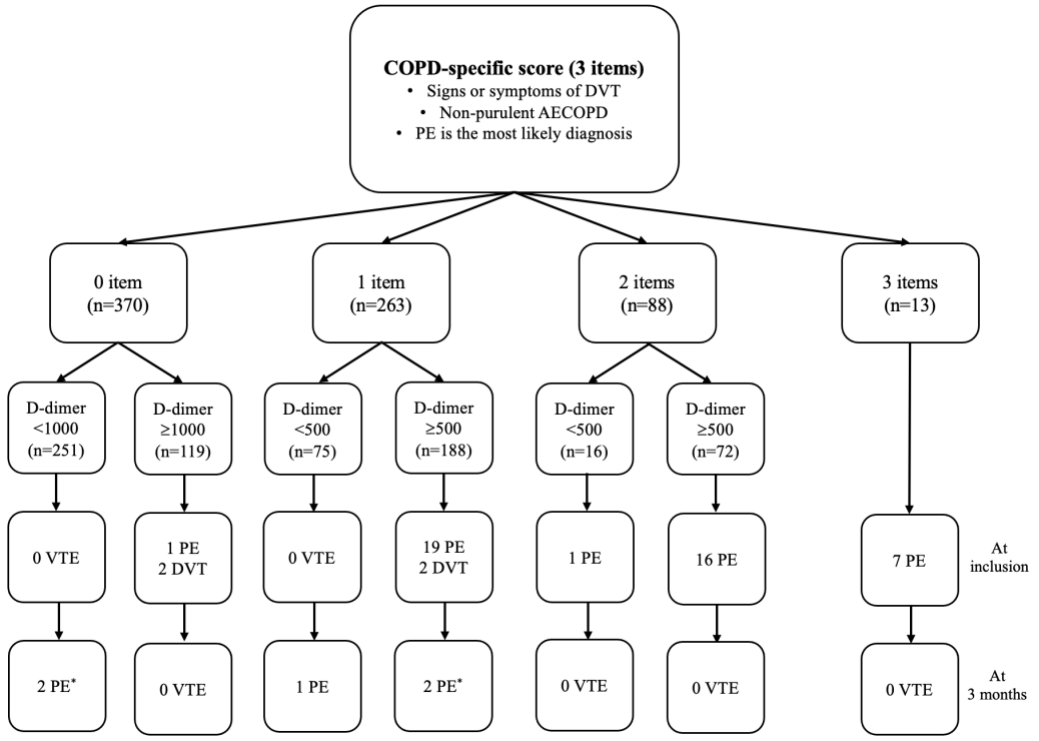


Figure 1. Receiving operating characteristic (ROC) curve of the COPD-specific score computed in the derivation cohort (area under the curve: 0.81; 95%CI 0.75-0.87)

A.



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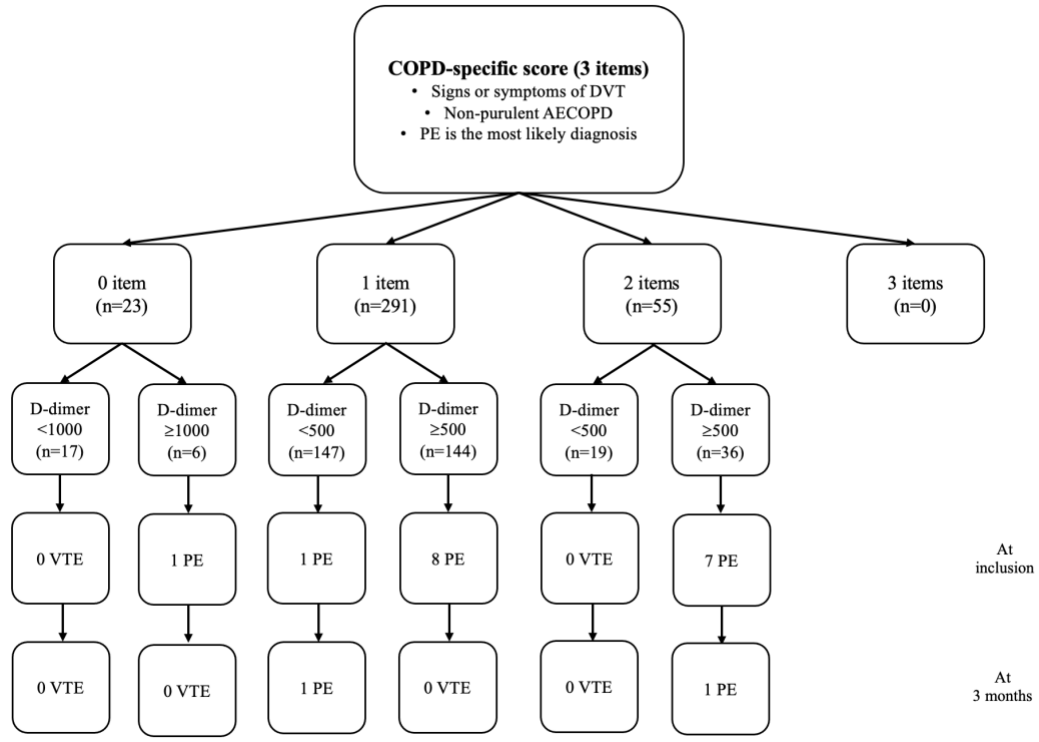
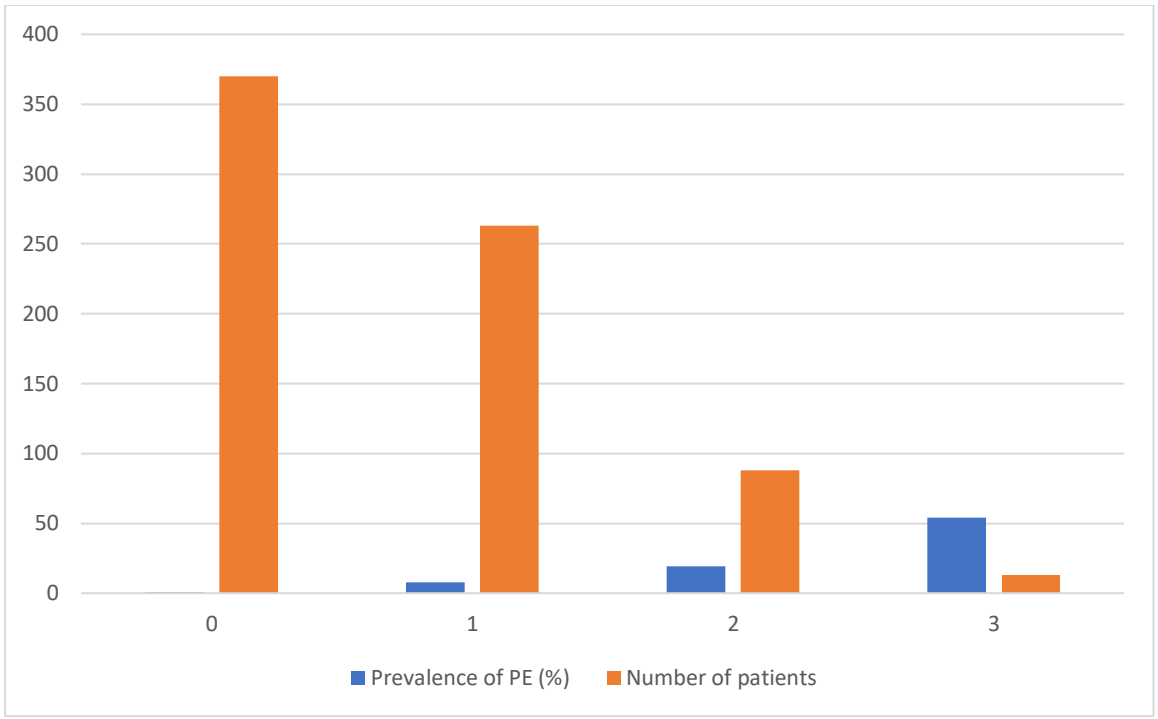


Figure 2. COPD-specific PE diagnostic strategy computed in the derivation cohort (A) and in the validation cohort (B).

*Deaths probably due to PE (1 in the 0 item group and 2 in the 1 item group). COPD: chronic obstructive pulmonary disease; PE: pulmonary embolism.

A.



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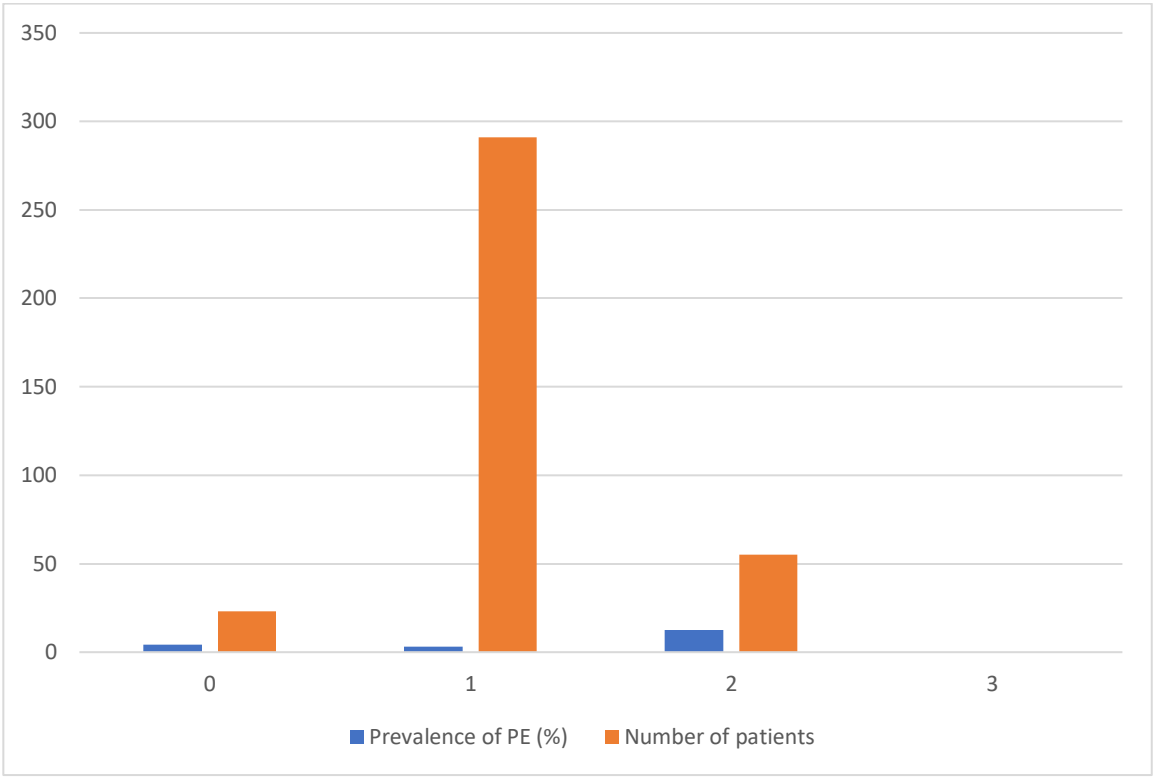

Figure 3. Number of patients and prevalence of pulmonary embolism per clinical pre-test probability groups for the chronic obstructive pulmonary disease-specific score in the derivation cohort (A) and in the validation cohort (B)

CHAPTER 7: Manuscript 6 - The feasibility and challenges of prospectively evaluating the prevalence of pulmonary embolism in patients with chronic obstructive pulmonary disease exacerbation

7.1 Preface of the manuscript 6

This last project of my thesis allowed me to explore a new study design: a pilot study. It also allowed me to gain experience in order to have more tools in conducting a prospective cohort study in the future after the PhD. This pilot study evaluated the feasibility and challenges in assessing the prevalence of PE in patients hospitalized with AECOPD. I worked on the literature review, study conception, data collection, data analysis, interpretation of the data and manuscript drafting. Co-authors helped with the supervision and revision of the manuscript.

I aim in submitting the manuscript in a peer-reviewed journal by fall 2025.

7.2 Manuscript 6

The feasibility and challenges of prospectively evaluating the prevalence of pulmonary embolism in patients with chronic obstructive pulmonary disease exacerbation

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Abstract: 266 words
Manuscript: 2070 words

ABSTRACT

Introduction: Data on the prevalence of pulmonary embolism (PE) in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) in North America is lacking. The aim of this study is to describe the feasibility of the prospective collection of data to explore the diagnosis and prediction of PE in patients admitted for AECOPD in Canada, and its associated challenges.

Methods: This is a secondary analysis of a pilot prospective cohort study assessing the diagnosis of AECOPD among hospitalized patients. Items of the Wells PE and revised Geneva scores were prospectively collected. All patients underwent D-dimer testing within 24 hours of admission. All patients were followed for 3 months. Feasibility outcomes were the ability to collect prospective data collection necessary to evaluate the prevalence of PE including D-dimer level measurements and 3-month follow-up. The study was considered feasible if ≥90% of the patients had prospective data collected to assess the prevalence of PE, ≥80% of the patients had D-dimer levels measured, and ≥80% of the patients had a 3-month follow-up. Challenges to the identification and collection of the data were also assessed.

Results: Twenty patients were included in the pilot. All 20 patients (100.0%) had prospective data collection to assess the prevalence of PE. D-dimer level was available for 18 (90.0%) patients and 3-month follow-up evaluation was performed in 16 (80.0%) patients. Challenges included recruitment of patients, adequate pre-test probability assessment and consistent PE diagnostic strategy use. No PE was diagnosed during the study period.

Conclusion: This study highlights the feasibility and challenges in evaluating the prevalence of PE in patients admitted for AECOPD in Canada.

INTRODUCTION

Patients with chronic obstructive pulmonary disease (COPD) experience acute exacerbations of COPD (AECOPD) which are characterized by worsening dyspnea and/or cough and sputum(1). It is estimated that AECOPD occurs at a rate of 0.5 to 3.5 exacerbations/patient/year(2) and AECOPD become more frequent as the severity of COPD progresses(3). AECOPD is marked by an increased inflammatory state which increases the risk of developing pulmonary embolism (PE)(4). Moreover, in addition to increasing morbidity, PE in the presence of AECOPD increases the risk of mortality by five-fold compared to patients without PE(5).

The burden of PE in patients with AECOPD, as either inpatients or outpatients, is not well defined. The existing literature describes variable prevalence of PE in patients with AECOPD, ranging from 0.3% to 36.1%(5-8). The majority of studies evaluating the prevalence of PE in patients with AECOPD are cross-sectional or prospective cohort studies. The cross-sectional study design allows evaluation of the prevalence of PE in a time-efficient manner and with lower cost, whereas a prospective cohort study design allows more accurate measurement of the outcome and the evaluation of the incidence of PE during follow-up, which can capture a PE that would have been missed at initial assessment. Moreover, prevalence of PE in patients with AECOPD seems to vary by geography (8). Recent prospective studies conducted in Europe and Asia showed a prevalence of PE of 5.9%(9) and 16.8%(10), respectively. To our knowledge, no prospective study evaluated the prevalence of PE in patients with AECOPD in North America in the era of computed tomography pulmonary angiogram (CTPA). In a recent retrospective study, (11) the prevalence of PE was found to be much lower at 1.1%, which suggests the possibility of missed PE.

Before initiating a large resource intensive prospective cohort study, the aim of this study was to describe the feasibility and challenges, if any, of prospective clinical data collection to explore diagnosis and prediction of PE in patients hospitalized with AECOPD in Canada.

METHODS

Study design

This is a secondary analysis of a pilot prospective observational study whose primary aim was to assess the diagnosis of AECOPD among hospitalized patients at the Ottawa Hospital. Details of this study are published elsewhere (REF). We used this pilot patient cohort to determine the feasibility and challenges of assessing the prevalence of PE among hospitalized patients with AECOPD at a North American Center.

Study participants

We included adult patients with AECOPD, as diagnosed by the admitted physician, and assessed them within 24 hours of their hospitalization to seek informed consent to participate in research. We did not approach patients who required non-invasive ventilation, or were admitted to the intensive care unit. Patients were also excluded if they had decreased level of consciousness or severe cognitive impairment. These patients were excluded since they would not have been able to give informed consent.

Study procedure and data collection

Standardized collection forms were developed and used to collect data. At inclusion, information on the items of the Wells PE score(12) and the revised Geneva score(13) were prospectively

collected except for the immobilization component of the item "surgery or immobilization ≥ 3 days" of the Wells PE score that was missing. Patients were managed by their admitting physician independent of the clinical pre-test probability assessment with the Wells PE and revised Geneva scores(12, 13). All patients underwent serum D-dimer testing. If D-dimer level was ≥ age-adjusted threshold the decision to perform chest imaging to rule out PE was left to the admitting physician's discretion. Age-adjusted D-dimer was considered positive if 1) D-dimer level ≥500mcg/L in patients <50 years old or if 2) D-dimer level ≥(age*10) in patients ≥50 years old(14). A 3-month follow-up questionnaire was completed by phone and included information on suspicion or diagnosis of venous thromboembolism (VTE), diagnostic modality used, treatment initiated if VTE was diagnosed, re-hospitalization and death (**Appendix**).

Outcomes

Feasibility outcomes included the ability to prospectively collect data necessary to evaluate the prevalence of PE, D-dimer level measurement and follow-up. The study was to be considered feasible if ≥90% of the patients had prospective data collected to assess the prevalence of PE, ≥80% of the patients had D-dimer level measured, and ≥80% of the patients had their 3-month follow-up visit completed. Challenges were defined as difficulties encountered during the study that made it challenging to assess adequately the prevalence of PE in this population.

Statistical analysis

Baseline characteristics of the cohort are presented as means and standard deviations or median and interquartile ranges depending of their distribution. Proportion of patients in whom data was prospectively collected for prevalence of PE assessment was calculated as well as the proportion

of patients who had D-dimer level measured and 3-month follow-up evaluation, respectively. Also, proportion of patients categorized in each c-PTP group was calculated. PE diagnostic strategies using the Wells PE score and the revised Geneva score combined with D-dimer level (using either the age-adjusted cut-off or a fixed cut-off at 500mcg/L) were presented by using figures(12-14). Analyses were performed with SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Mac, Version 27.0. Armonk, NY: IBM Corp).

RESULTS

The pilot study was conducted from November 2022 to June 2023 at the Ottawa Hospital. Recruitment of all patients was performed from November 2022 to March 2023. No recruitment was done from mid-December to mid-January due to absence of a research coordinator. Twenty patients were included. The mean age was 74.7 ± 9.1 years and 50.0% of the patients were female. Mean FEV1 was 1.2 ± 0.5L. One patient had active malignancy and one patient had prior VTE (**Table 1**). Data on anticoagulation use was not collected. The prevalence of PE was 0.0% (95%CI 0.0%-16.8%).

Feasibility

All 20 patients (100.0%) had prospective data collection to assess the prevalence of PE. D-dimer level was available for 18 (90.0%) patients. For one patient, the D-dimer level was evaluated with blood drawn 9 days before the day of inclusion, so it was excluded from the analysis and for another patient, the D-dimer level result was never received. The 3-month follow-up evaluation was performed in 16 (80.0%) patients. One patient was lost to follow-up, one patient did not want to answer the follow-up questions, and 2 deaths occurred.

Clinical pre-test probability assessment, D-dimer testing, imaging and follow-up

According to the Wells PE score, 16 (80.0%) patients had low c-PTP, 4 (20.0%) patients had moderate c-PTP and 0 patient had high c-PTP (**Figure 1**). According to the revised Geneva score, 2 (10.0%) patients had low c-PTP, 17 (85.0%) patients had intermediate c-PTP and 1 (5.0%) had high c-PTP (**Figure 2**). Mean D-dimer was 1351.4 ± 1164.8mcg/L. When age-adjusted D-dimer cut-off was used, 7 patients (38.9%) had negative D-dimer and 11 patients (61.1%) had positive D-dimer (**Figure 1A** and **Figure 2A**). When fixed D-dimer cut-off was used, 6 patients had D-dimer <500 mcg/L and 12 patients had D-dimer ≥500 mcg/L (**Figure 1B** and **Figure 2B**). Chest imaging by computed tomography was performed in 10 patients (9 with intravenous contrast and 1 without intravenous contrast). During the 3-month follow-up, one suspected VTE occurred, but no VTE was diagnosed.

Challenges

A few challenges were encountered during this study. First, the recruitment of patients hospitalized with AECOPD was challenging since it is an older and sicker population and they were thus less often willing to participate in the study. Second, adequate pre-test probability assessment with existing clinical decision rules (Wells PE and revised Geneva scores) was also challenging. Initially, some patients had an overestimation of their risk of having PE with more points attributed to items related to signs or symptoms of DVT when assessed by someone not experienced with VTE. This issue was corrected by doing some teaching to the research coordinator who was using the risk scores. Third, investigations for PE were not consistent and a structured PE diagnostic strategy was not systematically used.

DISCUSSION

This pre-planned secondary analysis of the AECOPD pilot study demonstrated the feasibility of performing a prospective cohort study to evaluate the diagnosis and prediction of PE in patients admitted for AECOPD in Canada. This study also highlights the challenges in using this study design for the evaluation of this outcome in this specific population, such as recruitment of patients, adequate pre-test probability assessment and consistent PE diagnostic strategy use.

To evaluate the prevalence of PE in patients with AECOPD, retrospective cohort studies are usually cost and time efficient, but it may not be the most optimal study design to assess this outcome since results are subject to inaccuracy with detection bias related to inconsistent investigations and misclassification of the diagnosis of AECOPD. Indeed, even though in this prospective pilot study, all patients had an admitting diagnosis of AECOPD at inclusion, only 12/20 (60.0%) patients had a diagnosis of AECOPD confirmed by the adjudication committee (REF). Cross-sectional study design allows evaluation of the prevalence of PE at initial assessment in this population while being easy to conduct and less costly. Although more costly and requiring more resources and time, a prospective cohort study has the advantage of evaluating the prevalence of PE at initial assessment, potentially using a standardized algorithm, but also the incidence of PE during follow-up. In PE diagnostic management studies, the 3-month follow-up is used to assess the incidence of VTE among those considered being negative for PE, as a surrogate for the rate of PE missed by the diagnostic strategy at presentation (15). However, in patients with COPD, some of these venous thromboembolic events might not be related to a missed VTE, but rather to

actual *de novo* episodes, related to patients' acute medical illness, hospital admission and comorbidities.

We also note important challenges. The recruitment of patients was challenging since patients hospitalized for AECOPD are usually sicker than the general population and have more comorbidities. Moreover, pre-test probability assessment could have been inaccurate when done by someone not working in the VTE area. Minimal training could thus be required prior using the Wells PE and revised Geneva scores. Systematically using a PE diagnostic strategy for all patients would allow consistency in the evaluation of patients and in the detection of the outcome. This study shows that chest imaging was not performed according to PE diagnostic strategies, but rather based on the physician's impression which is not surprising for patients with AECOPD since no specific diagnostic algorithm has been specifically derived and validated for this population. Without consistent diagnostic strategy, detection bias may occur since the clinical threshold in deciding to perform CTPA or V/Q scan varies from a physician to another. Moreover, if we rely on validated PE diagnostic strategies, such as the Wells PE(12) or revised Geneva scores(13), we acknowledge that some patients would have benefited from radiological imaging testing to rule out PE and others had imaging testing but would not have needed it. Therefore, those who were overtested were exposed to the down sides of CTPA such as cost, radiation, possible contrast-induced allergy and incidental findings, whereas those who were undertested might had a PE that was missed which can be fatal when not treated. It is to be noted that systematically applying a PE diagnostic strategy to all patients presenting with AECOPD could lead to over-testing if the prevalence of PE is low. Given the frequent AECOPD episodes in this population, over-testing

may be problematic which brings up another issue as to know which patients should be targeted to conduct the PE workup.

We acknowledge limitations. First, due to the study design, no systematic PE diagnostic strategy was applied which makes it challenging to evaluate the feasibility of a future diagnostic management study. Second, there is presence of misclassification with only 12 (60.0%) patients who had a confirmed diagnosis of AECOPD by the adjudication committee (REF). This study also has strengths. It allows reflection on the feasibility and challenges in conducting a prospective cohort study evaluating the prevalence of PE in patients with AECOPD in Canada. This study brings us one step closer in conducting a larger project being a multicenter prospective cohort study evaluating this issue in this special population which will be the first one to be conducted in North America in the era of CTPA.

CONCLUSION

This study highlights the feasibility and challenges in evaluating the prevalence of PE in patients admitted for AECOPD in Canada. A larger prospective cohort study could thus be conducted by integrating the strengths of the study and by improving the recruitment of patients, pre-test probability assessment and consistent PE diagnostic strategy use.

BIBLIOGRAPHY

1. Celli BR, Fabbri LM, Aaron SD, Agusti A, Brook R, Criner GJ, et al. An Updated Definition and Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbations: The Rome Proposal. Am J Respir Crit Care Med. 2021;204(11):1251-8.

2. Seemungal TAR, Hurst JR, Wedzicha JA. Exacerbation rate, health status and mortality in COPD--a review of potential interventions. Int J Chron Obstruct Pulmon Dis. 2009;4:203-23.

3. Miravitlles M, Guerrero T, Mayordomo C, Sánchez-Agudo L, Nicolau F, Segú JL. Factors associated with increased risk of exacerbation and hospital admission in a cohort of ambulatory COPD patients: a multiple logistic regression analysis. The EOLO Study Group. Respiration. 2000;67(5):495-501.

4. Konstantinides SV, Meyer G. The 2019 ESC Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism. Eur Heart J. 2019;40(42):3453-5.

5. Sato R, Hasegawa D, Nishida K, Takahashi K, Schleicher M, Chaisson N. Prevalence of pulmonary embolism in patients with acute exacerbations of COPD: A systematic review and meta-analysis. The American Journal of Emergency Medicine. 2021;50:606-17.

6. Wang J, Ding YM. Prevalence and risk factors of pulmonary embolism in acute exacerbation of chronic obstructive pulmonary disease and its impact on outcomes: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci. 2021;25(6):2604-16.

7. Fu X, Zhong Y, Xu W, Ju J, Yu M, Ge M, et al. The prevalence and clinical features of pulmonary embolism in patients with AE-COPD: A meta-analysis and systematic review. PLoS One. 2021;16(9):e0256480.

8. Han W, Wang M, Xie Y, Ruan H, Zhao H, Li J. Prevalence of Pulmonary Embolism and Deep Venous Thromboembolism in Patients With Acute Exacerbation of Chronic Obstructive

Pulmonary Disease: A Systematic Review and Meta-Analysis. Frontiers in cardiovascular medicine. 2022;9:732855.

9. Couturaud F, Bertoletti L, Pastre J, Roy PM, Le Mao R, Gagnadoux F, et al. Prevalence of Pulmonary Embolism Among Patients With COPD Hospitalized With Acutely Worsening Respiratory Symptoms. JAMA. 2021;325(1):59-68.

10. Liu X, Jiao X, Gong X, Nie Q, Li Y, Zhen G, et al. Prevalence, Risk Factor and Clinical Characteristics of Venous Thrombus Embolism in Patients with Acute Exacerbation of COPD: A Prospective Multicenter Study. Int J Chron Obstruct Pulmon Dis. 2023;18:907-17.

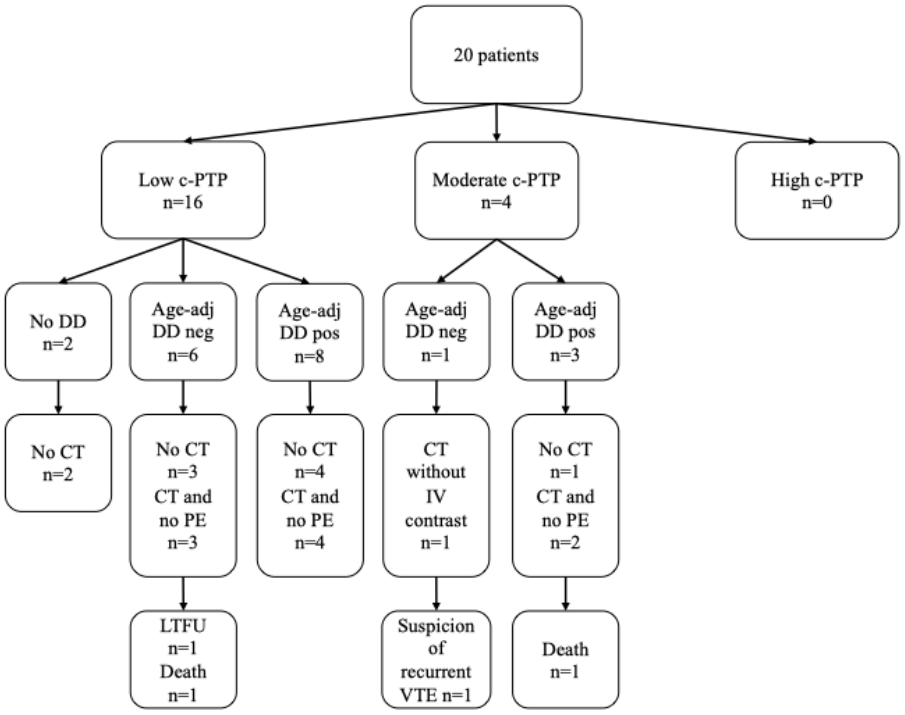
11. Mai Vicky PM, Mulpuru Sunita, Thiruganasambandamoorthy Venkatesh, Code Catherine, Le Gal Grégoire. Prevalence of Pulmonary Embolism in Patients with Chronic Obstructive Pulmonary Disease Exacerbation in North America – A Single Center Experience. .

12. Wells PS, Anderson DR, Rodger M, Stiell I, Dreyer JF, Barnes D, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. Ann Intern Med. 2001;135(2):98-107.

13. Le Gal G, Righini M, Roy PM, Sanchez O, Aujesky D, Bounameaux H, et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Ann Intern Med. 2006;144(3):165-71.

14. Righini M, Van Es J, Den Exter PL, Roy PM, Verschuren F, Ghuysen A, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. JAMA. 2014;311(11):1117-24.

15. Dronkers CEA, van der Hulle T, Le Gal G, Kyrle PA, Huisman MV, Cannegieter SC, et al. Towards a tailored diagnostic standard for future diagnostic studies in pulmonary embolism: communication from the SSC of the ISTH. J Thromb Haemost. 2017;15(5):1040-3.



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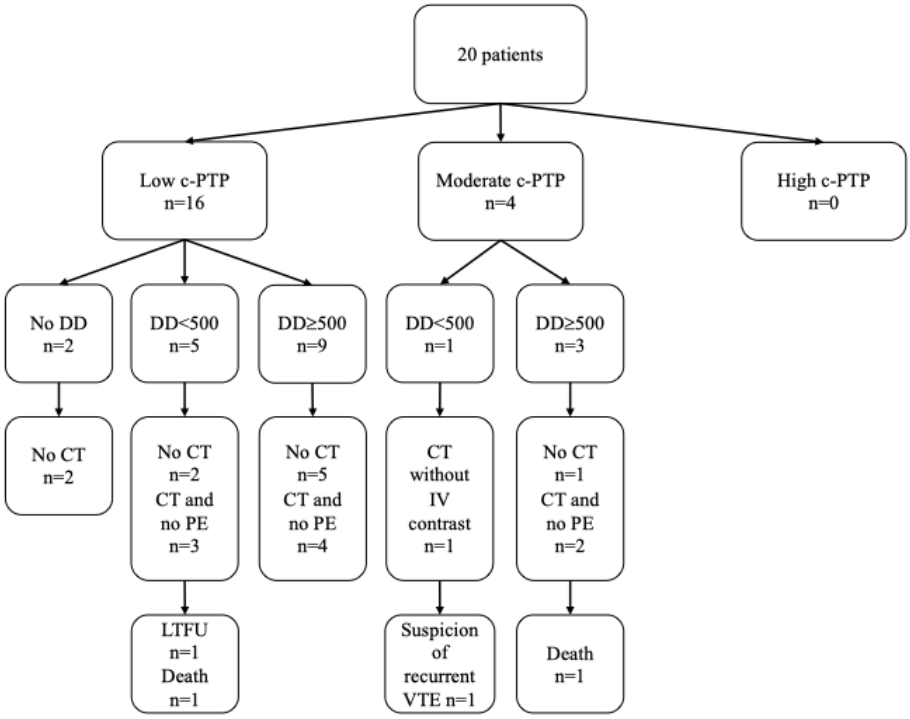
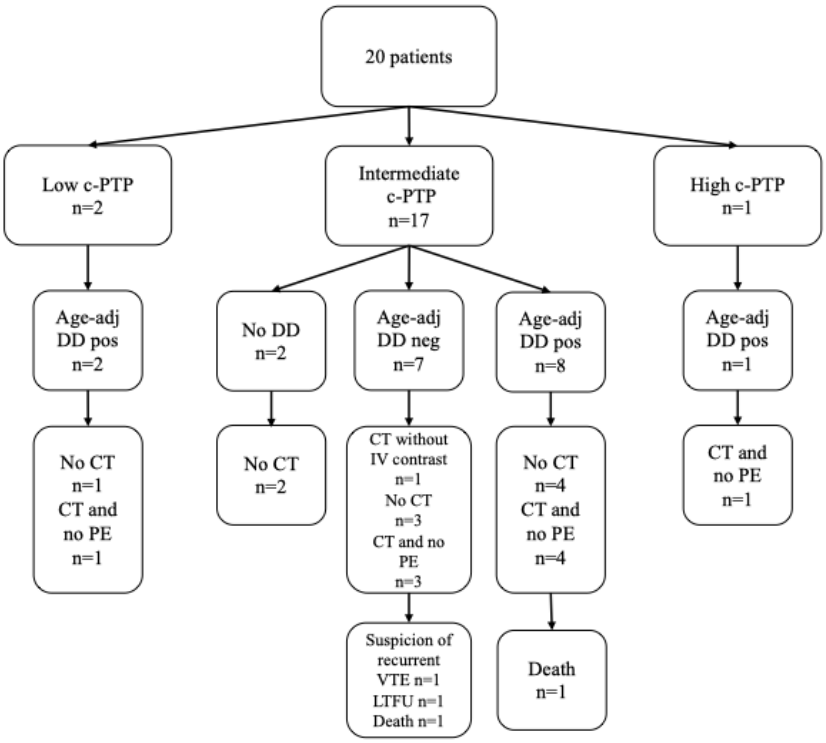
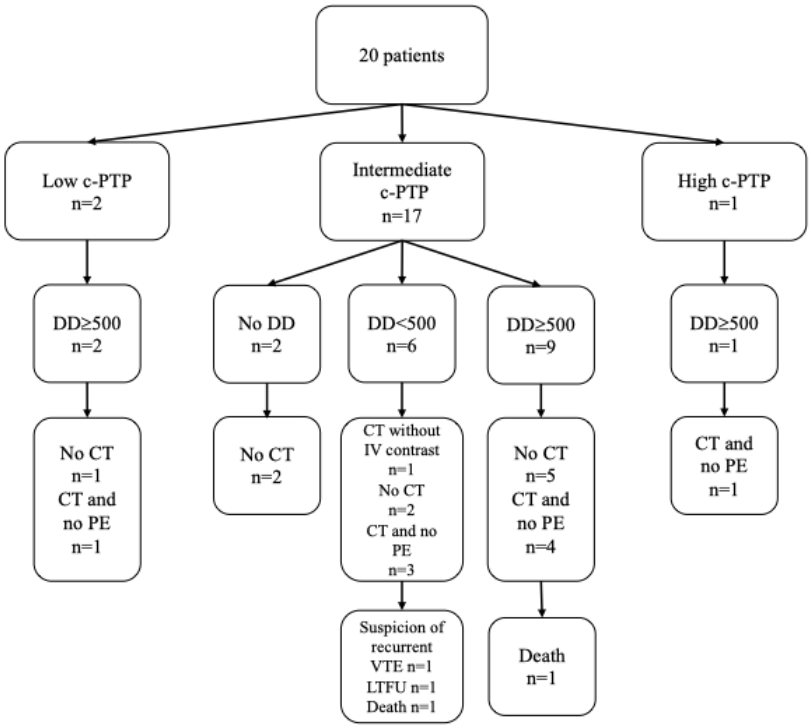


B.

Figure 1. Diagnostic algorithm using the Wells pulmonary embolism score combined with age-adjusted D-dimer (A) and fixed D-dimer cut-off (B).



A.



B.

Figure 2. Diagnostic algorithm using the revised Geneva score combined with age-adjusted D-dimer (A) and fixed D-dimer cut-off (B).

CHAPTER 8: DISCUSSION

8.1 Lessons learned during the PhD

During the first year of the PhD program, I completed mandatory epidemiology and professional skills courses. I also successfully completed the comprehensive examination (written and oral). These requirements allowed me to improve my knowledge in epidemiology and acquire a solid basis in the field by mastering important core concepts in epidemiology. The various projects conducted as part of my thesis were done by applying all the knowledge learned in the program.

This journey in the PhD program allowed me to develop skills that will help me throughout my future career in research. I developed writing skills such as writing a protocol, developing a research proposal and submitting a research proposal for funding by using a convincing language. I wrote and submitted the protocol of project 6 for the CanVECTOR Research Start-up Award and received funding ($2,500). I also wrote and submitted a research proposal for the Dragons' Den Competition of the International Network of VENous Thromboembolism Clinical Research Networks (INVENT). Moreover, I applied to the Canadian Institutes of Health Research (CIHR) Research Excellence, Diversity, and Independence Early Career Transition Award which was a large application that included a complete research proposal and a mentoring plan with 6 diversified international mentors. I also developed knowledge translation skills by presenting oral presentations, poster presentations and participating at a podcast of Thrombosis Canada, a national organization with a main interest in thrombosis. I learned to identify knowledge gaps in the literature. Indeed, I added a research project to my thesis, the systematic review with meta-analysis aiming in evaluating the association between PE and the type of AECOPD, since this knowledge gap was discovered throughout my work on the topic. Furthermore, the peer-review process in research is an important aspect to ensure robustness of data published in the literature. I improved my peer-review skills by reviewing manuscripts submitted to peer-reviewed journals and abstracts submitted to national and international conferences. I received feedback from my co-supervisor, Dr. Le Gal, to improve this skillset.

Ultimately, writing this thesis and conducting the research projects allowed me to identify, explore, critique, and master the literature of PE in patients with AECOPD.

8.2 Summary of the research projects included in the thesis

The findings from the 6 research projects helped answer to the general objective of my research program which was to determine the optimal management of patients with suspicion of PE among patients with AECOPD. Each study provided important information to improve knowledge on this topic.

Project 1 informed more clearly on the epidemiology of PE in patients with AECOPD by providing data from a Canadian center which was an element that was lacking in the literature. Also, it is one of the largest published cohorts evaluating the prevalence of PE in patients with AECOPD. This study showed that the prevalence of PE was low, but there is potential underestimation since no systematic diagnostic algorithm was used and thus, very few patients had chest imaging.

Projects 2 and 3 evaluated current available PE diagnostic algorithms in patients with chronic lung disease and COPD, respectively, and showed concordant results. Standard PE diagnostic strategies (revised Geneva and Wells PE score combined with D-dimer at a fixed cut-off of 500 mcg/L) were safe, but a high proportion of patients would need imaging to rule out PE. On the other hand, CTPA-sparing diagnostic strategies reduced the need for imaging, but at a cost of an increased in the diagnostic failure rate, higher than normally accepted. These studies confirmed that PE diagnostic strategies for patients with AECOPD could be optimized since no PE diagnostic algorithm seemed ideal.

Third, project 4 showed an association between PE and the type of AECOPD. PE was more frequently associated with non-purulent or unknown purulence status AECOPD than purulent AECOPD. This information is clinically relevant for physicians since it may help evaluate more accurately the probability of a patient in having a PE when they present with symptoms compatible with AECOPD.

Since prior projects showed that current available PE diagnostic strategies were not optimal for patients with AECOPD, either too many patients would need chest imaging to rule out PE or either the diagnostic failure rate was too high, there was a need to develop a PE diagnostic algorithm specifically for patients with AECOPD (Project 4). Project 5 is a core element of my thesis since

it reports on the derivation and a validation attempt of a PE diagnostic strategy specifically for patients with AECOPD. The PE diagnostic strategy is simple and includes elements specifically related to this population with chronic respiratory disease. This study brings us one step closer in improving PE diagnostic management in this special population. It is also the first PE diagnostic strategy developed specifically for patients with AECOPD. These data are novel and have the potential to be practice changing, if these results are confirmed in a prospective validation study.

Finally, Project 6 demonstrated the feasibility and challenges in conducting a prospective study evaluating the prevalence of PE in patients with AECOPD. Such findings will help me in the planned development of a larger project in the future.

8.3 Networking

To conduct research projects, collaboration is crucial. Among others, it facilitates recruitment of patients for prospective studies, it helps generalize the results and it allows data sharing. Facilitated by my supervisors, I got the opportunity to start building a network with researchers in the field of thrombosis across the globe. Indeed, for Project 2, I collaborated with researchers from the Netherlands and Japan and for Projects 3, 4 and 5, I collaborated with researchers from France and Spain. Moreover, for all 6 Projects, I created multidisciplinary relationships by working with internists, respirologists, hematologists, emergency department physicians, nuclear medicine physicians and epidemiologists. The various points of view of each collaborator according to their type of practice reinforces the work of each project. Moreover, this important networking will facilitate collaborations for future projects.

8.4 Strengths and limitations

This thesis has strengths. First, my thesis includes 6 projects of various study designs which allowed me to apply the wide breadth of course and workshop learnings. Second, results of each project bring new data in the literature on the topic of PE and AECOPD. Third, all 6 projects, collectively, help answer my overall general thesis objective.

I acknowledge that my thesis has limitations. The definition of AECOPD is poorly defined and validated in the literature which makes it challenging to target adequately the studied population.

Also, there is significant heterogeneity on the initial physician diagnostic assessment when evaluating a patient with COPD presenting with acute breathlessness. This influences the population studied and consequently, it affects the diagnostic algorithm performance. Moreover, the definition of purulent AECOPD is not adequately defined in the literature which makes it challenging to incorporate in studies. Unfortunately, I was not able to find a cohort of patients with AECOPD that was entirely representative of the derivation cohort to validate the PE diagnostic strategy that was derived in Project 5. Thus, the PE diagnostic strategy derived specifically for patients with AECOPD was validated in a cohort of patients in whom data were collected prospectively, but the patients admitted for AECOPD did not have PE as the most likely diagnosis. Without a prospective validation, this new tool cannot yet be used in clinical practice.

8.5 Next steps

Although this thesis brings significant data in the literature on the topic, more research is needed. Since CTPA is frequently used as the diagnostic modality in patients with AECOPD, I am planning to conduct a study aiming to evaluate the accuracy of CTPA in this population. Moreover, to close the loop of projects conducted as part of my thesis, I plan in conducting a prospective study aiming to validate the PE diagnostic strategy specifically derived for patients with AECOPD. This step is needed prior integrating this new tool in clinical practice. If the tool validates, it would certainly be practice changing as it will improve PE diagnostic management in patients with AECOPD. Thus, less patients would need imaging to rule out PE and the safety of this algorithm would have been proven.

8.6 Conclusion

My thesis included projects that helped better understand the burden of PE in patients with AECOPD and the performance of available PE diagnostic algorithms in this population. Moreover, this work proposed a new prediction tool for PE specifically for patients with AECOPD. My thesis work brings us one step closer in improving PE diagnostic management in patients with AECOPD and consequently improve clinical care of this special population.

CHAPTER 9: REFERENCES

1. Kearon C. Natural History of Venous Thromboembolism. Circulation. 2003;107(23_suppl_1):I-22-I-30.

2. Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol. 2015;12(8):464-74.

3. Kearon C. Epidemiology of venous thromboembolism. Seminars in vascular medicine. 2001;1(1):7-26.

4. Wendelboe AM, Raskob GE. Global Burden of Thrombosis. Circulation Research. 2016;118(9):1340-7.

5. Kumar DR, Hanlin E, Glurich I, Mazza JJ, Yale SH. Virchow's contribution to the understanding of thrombosis and cellular biology. Clin Med Res. 2010;8(3-4):168-72.

6. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing G-J, Harjola V-P, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). 2019:1901647.

7. Piazza G, Goldhaber SZ. Acute Pulmonary Embolism. Circulation. 2006;114(2):e28-e32.

8. Thomson D, Kourounis G, Trenear R, Messow C-M, Hrobar P, Mackay A, et al. ECG in suspected pulmonary embolism. Postgraduate Medical Journal. 2019;95(1119):12-7.

9. Krishnan AS, Barrett T. Westermark Sign in Pulmonary Embolism. New England Journal of Medicine. 2012;366(11):e16.

10. Sreenivasan S, Bennett S, Parfitt VJ. Images in cardiovascular medicine. Westermark's and Palla's signs in acute pulmonary embolism. Circulation. 2007 Feb 27;115(8):e211.

11. McGrath BM, Groom AG. Hampton's Hump. New England Journal of Medicine. 2013;368(23):2219-.

12. Ortel TL, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood advances. 2020;4(19):4693-738.

13. Wells PS, Anderson DR, Rodger M, Stiell I, Dreyer JF, Barnes D, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. Ann Intern Med. 2001;135(2):98-107.

14. Le Gal G, Righini M, Roy PM, Sanchez O, Aujesky D, Bounameaux H, et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Ann Intern Med. 2006;144(3):165-71.

15. van Belle A, Büller HR, Huisman MV, Huisman PM, Kaasjager K, Kamphuisen PW, et al. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. Jama. 2006;295(2):172-9.

16. Wauthier L, Favresse J, Hardy M, Douxfils J, Le Gal G, Roy PM, et al. D-dimer testing: A narrative review. Adv Clin Chem. 2023;114:151-223.

17. Carrier M, Righini M, Djurabi RK, Huisman MV, Perrier A, Wells PS, et al. VIDAS D-dimer in combination with clinical pre-test probability to rule out pulmonary embolism. A systematic review of management outcome studies. Thromb Haemost. 2009;101(5):886-92.

18. Carrier M, Wells PS, Rodger MA. Excluding pulmonary embolism at the bedside with low pre-test probability and D-dimer: safety and clinical utility of 4 methods to assign pre-test probability. Thrombosis Research. 2006;117(4):469-74.

19. Klok FA, Kruisman E, Spaan J, Nijkeuter M, Righini M, Aujesky D, et al. Comparison of the revised Geneva score with the Wells rule for assessing clinical probability of pulmonary embolism. J Thromb Haemost. 2008;6(1):40-4.

20. Righini M, Van Es J, Den Exter PL, Roy PM, Verschuren F, Ghuysen A, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. JAMA. 2014;311(11):1117-24.

21. van der Hulle T, Cheung WY, Kooij S, Beenen LFM, van Bemmel T, van Es J, et al. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. Lancet. 2017;390(10091):289-97.

22. Kearon C, de Wit K, Parpia S, Schulman S, Afilalo M, Hirsch A, et al. Diagnosis of Pulmonary Embolism with d-Dimer Adjusted to Clinical Probability. New England Journal of Medicine. 2019;381(22):2125-34.

23. Roy PM, Moumneh T, Penaloza A, Schmidt J, Charpentier S, Joly LM, et al. Diagnostic Strategy for Suspected Pulmonary Embolism in Emergency Departments Based on the 4-Level Pulmonary Embolism Clinical Probability Score: Study Protocol of SPEED&PEPS Trial. Diagnostics. 2022;12(12) (no pagination).

24. Wittram C, Maher MM, Yoo AJ, Kalra MK, Shepard J-AO, McLoud TC. CT Angiography of Pulmonary Embolism: Diagnostic Criteria and Causes of Misdiagnosis. RadioGraphics. 2004;24(5):1219-38.

25. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). Jama. 1990;263(20):2753-9.

26. Sostman HD, Stein PD, Gottschalk A, Matta F, Hull R, Goodman L. Acute pulmonary embolism: sensitivity and specificity of ventilation-perfusion scintigraphy in PIOPED II study. Radiology. 2008;246(3):941-6.

27. Bajc M, Schümichen C, Grüning T, Lindqvist A, Le Roux P-Y, Alatri A, et al. EANM guideline for ventilation/perfusion single-photon emission computed tomography (SPECT) for diagnosis of pulmonary embolism and beyond. European Journal of Nuclear Medicine and Molecular Imaging. 2019;46(12):2429-51.

28. Boers E, Barrett M, Su JG, Benjafield AV, Sinha S, Kaye L, et al. Global Burden of Chronic Obstructive Pulmonary Disease Through 2050. JAMA Network Open. 2023;6(12):e2346598-e.

29. WHO. Chronic obstructive pulmonary disease (COPD) 2023 [Available from: https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd).

30. GOLD 2024 report 2024 [Available from: https://goldcopd.org/2024-gold-report/.]

31. Celli BR, Wedzicha JA. Update on Clinical Aspects of Chronic Obstructive Pulmonary Disease. N Engl J Med. 2019;381(13):1257-66.

32. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26(5):948-68.

33. Seemungal TAR, Hurst JR, Wedzicha JA. Exacerbation rate, health status and mortality in COPD--a review of potential interventions. Int J Chron Obstruct Pulmon Dis. 2009;4:203-23.

34. Anzueto A. Impact of exacerbations on COPD. European Respiratory Review. 2010;19(116):113-8.

35. Celli BR, Fabbri LM, Aaron SD, Agusti A, Brook RD, Criner GJ, et al. Differential Diagnosis of Suspected Chronic Obstructive Pulmonary Disease Exacerbations in the Acute Care

Setting Best Practice. American Journal of Respiratory and Critical Care Medicine. 2023;207(9):1134-44.

36. Sapey E, Stockley RA. COPD exacerbations . 2: aetiology. Thorax. 2006;61(3):250-8.

37. Sato R, Hasegawa D, Nishida K, Takahashi K, Schleicher M, Chaisson N. Prevalence of pulmonary embolism in patients with acute exacerbations of COPD: A systematic review and meta-analysis. The American Journal of Emergency Medicine. 2021;50:606-17.

38. Fu X, Zhong Y, Xu W, Ju J, Yu M, Ge M, et al. The prevalence and clinical features of pulmonary embolism in patients with AE-COPD: A meta-analysis and systematic review. PLoS One. 2021;16(9):e0256480.

39. Wang J, Ding YM. Prevalence and risk factors of pulmonary embolism in acute exacerbation of chronic obstructive pulmonary disease and its impact on outcomes: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci. 2021;25(6):2604-16.

40. Han W, Wang M, Xie Y, Ruan H, Zhao H, Li J. Prevalence of Pulmonary Embolism and Deep Venous Thromboembolism in Patients With Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. Frontiers in cardiovascular medicine. 2022;9:732855.

41. Couturaud F, Bertoletti L, Pastre J, Roy PM, Le Mao R, Gagnadoux F, et al. Prevalence of Pulmonary Embolism Among Patients With COPD Hospitalized With Acutely Worsening Respiratory Symptoms. JAMA. 2021;325(1):59-68.

42. Sadeghi S, Ardestani ME, Raofi E, Jalaie Esfandabadi A. Diagnostic value of d-dimer in detecting pulmonary embolism in patients with acute copd exacerbation. Tanaffos. 2020;19(4):371-9.

43. Kline JA, Mitchell AM, Kabrhel C, Richman PB, Courtney DM. Clinical criteria to prevent unnecessary diagnostic testing in emergency department patients with suspected pulmonary embolism. J Thromb Haemost. 2004;2(8):1247-55.

44. Jiménez D, Agustí A, Tabernero E, Jara-Palomares L, Hernando A, Ruiz-Artacho P, et al. Effect of a Pulmonary Embolism Diagnostic Strategy on Clinical Outcomes in Patients Hospitalized for COPD Exacerbation: A Randomized Clinical Trial. JAMA. 2021;326(13):1277-85.

APPENDIX A – Manuscript 1

Prevalence of diagnosed pulmonary embolism in patients with chronic obstructive pulmonary disease exacerbation presenting at the emergency department of a large North American academic hospital center

Running head: Pulmonary embolism in patients with chronic obstructive pulmonary disease exacerbation

Appendix

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Table S1. Baseline characteristics of the patients based on whether patients had or had not imaging to rule out PE

Characteristics	Patients who had imaging to rule out PE (n=184*)	Patients who did not have imaging to rule out PE (n=974)
Age (mean ± SD)	72.3 ± 10.2	69.4 ± 11.5
Female – n (%)	100 (54.3)	520 (53.4)
Weight (kg) (mean ± SD)	73.2 ± 22.0[1]	71.0 ± 23.6[2]
Body mass index (kg/m^2) (mean ± SD)	26.4 ± 7.7[3]	25.5 ± 8.1[4]
Tobacco use – n (%)		
Current	84 (45.7)	542 (55.6)
Prior	94 (51.1)	339 (34.8)
Never	3 (1.6)	42 (4.3)
Unknown	3 (1.6)	51 (5.2)
Exacerbations in the last year – n (%)		
0	117 (63.6)	623 (64.0)
1	36 (19.6)	173 (17.8)
2	22 (12.0)	93 (9.5)
3	5 (2.7)	38 (3.9)
4	3 (1.6)	14 (1.4)
≥ 5	0 (0.0)	32 (3.3)
Unknown	1 (0.5)	1 (0)
Antiplatelets – n (%)	55 (29.9)	258 (26.5)
Cancer – n (%)		
Active	45 (24.5)	98 (10.1)
Prior	29 (15.8)	84 (8.6)
Prior venous thromboembolic event – n (%)	9 (4.9)	28 (2.9)
FEV1 - liters (mean ± SD)	1.25 ± 0.63[5]	1.41 ± 0.61[6]
%FEV1 (mean ± SD)	50 ± 19[7]	55 ± 19[8]
GOLD stage – n (%)		
1	6/101 (5.9)	40/429 (9.3)
2	45/101 (44.6)	213/429 (49.7)
3	34/101 (33.7)	131/429 (30.5)
4	16/101 (15.8)	45/429 (10.5)
Purulent COPD exacerbation – n (%)	52 (28.3)	338 (34.7)
Hospitalization after the visit at the emergency department – n (%)	120 (65.2)	344 (35.3)

COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; FEV1/FVC: forced expiratory volume in 1 second / forced vital capacity;

[*]One patient had a computed tomography pulmonary angiogram and a ventilation/perfusion scan; [1]90 participants; [2]232 participants; [3]86 participants; [4]213 participants; [5]98 participants; [6]410 participants; [7]101 participants; [8]429 participants;

APPENDIX B – Manuscript 2

Safety and Efficiency of Diagnostic Strategies for Ruling Out Pulmonary Embolism in Patients with Chronic Lung Disease: An Individual-Patient Data Meta-analysis

Supplemental file

Authors

Table S1. Wells and revised Geneva scores with D-dimer testing

Wells PE		**Revised Geneva**	
Criteria	**Points**	**Criteria**	**Points**
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	+3	Age > 65 years old	+1
An alternative diagnosis is less likely than PE	+3	Previous DVT or PE	+3
Heart rate greater than 100	+1.5	Surgery (under general anesthesia) or fracture (of the lower limbs) within 1 month	+2
Immobilization or surgery in the previous four weeks	+1.5	Active malignant condition (solid or hematologic malignant condition, currently active or considered cured < 1 year)	+2
Previous DVT/PE	+1.5	Unilateral lower-limb pain	+3
Hemoptysis	+1	Hemoptysis	+2
Malignancy (on treatment, treated in the last six months or palliative)	+1	Heart rate 75-94 beats/minute ≥95 beats/minute	 +3 +5
		Pain on lower-limb deep venous system palpation and unilateral edema	+4
Clinical pre-test probability *3-level* Low Moderate High *2-level* Unlikely Likely	 <2 2-6 >6 ≤4 >4	***Clinical pre-test probability*** Low Intermediate High	 0-3 4-10 ≥11
Fixed D-dimer cut-off: used for patients with non-high clinical pre-test probability < 500 mcg/L: PE ruled out ≥ 500 mcg/L: chest imaging needed			
Age-adjusted D-dimer cut-off: used for patients with non-high clinical pre-test probability (Age-adjusted D-dimer was considered positive if D-dimer level ≥500mcg/L in patients <50 years old or if D-dimer level ≥(age*10) in patients ≥50 years old) < age-adjusted: PE ruled out			

≥ age-adjusted: chest imaging needed

Table S2. YEARS algorithm

3 YEARS items
Clinical signs of deep vein thrombosis
Hemoptysis
Pulmonary embolism the most likely diagnosis
D-dimer cut-offs
0 YEARS item
< 1000 mcg/L: PE ruled out
≥ 1000 mcg/L: chest imaging needed
≥ 1 YEARS item
< 500 mcg/L: PE ruled out
≥ 500 mcg/L: chest imaging needed

Table S3. PEGeD algorithm

Wells PE		Revised Geneva	
Criteria	**Points**	**Criteria**	**Points**
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	+3	Age > 65 years old	+1
An alternative diagnosis is less likely than PE	+3	Previous DVT or PE	+3
Heart rate greater than 100	+1.5	Surgery (under general anesthesia) or fracture (of the lower limbs) within 1 month	+2
Immobilization or surgery in the previous four weeks	+1.5	Active malignant condition (solid or hematologic malignant condition, currently active or considered cured < 1 year)	+2
Previous DVT/PE	+1.5	Unilateral lower-limb pain	+3
Hemoptysis	+1	Hemoptysis	+2
Malignancy (on treatment, treated in the last six months or palliative)	+1	Heart rate 75-94 beats/minute ≥95 beats/minute	 +3 +5
		Pain on lower-limb deep venous system palpation and unilateral edema	+4
Clinical pre-test probability Low Moderate High	 0-4.0 4.5-6.0 ≥ 6.5	***Clinical pre-test probability*** Low Intermediate High	 0-5 6-10 ≥11
D-dimer cut-offs: used for patients with non-high clinical pre-test probability *Low clinical pre-test probability* < 1000 mcg/L: PE ruled out ≥ 1000 mcg/L: chest imaging needed *Moderate/intermediate pre-test probability* < 500 mcg/L: PE ruled out ≥ 500 mcg/L: chest imaging needed			

Table S4. Diagnostic yield of D-dimer

	Overall cohort % (95%CI)	**Absence of chronic lung disease % (95CI)**	**Presence of chronic lung disease % (95%CI)**
Fixed D-dimer cut-off			
Prevalence of VTE in patients with negative D-dimer	0.7 (0.5-1.0)	0.7 (0.5-1.0)	1.1 (0.5-2.6)
Prevalence of VTE in patients with positive D-dimer	29.7 (28.8-30.6)	31.4 (30.4-32.4)	19.6 (17.7-21.6)
Age-adjusted D-dimer cut-off			
Prevalence of VTE in patients with negative D-dimer	1.3 (1.0-1.6)	1.2 (1.0-1.5)	1.6 (1.0-2.7)
Prevalence of VTE in patients with positive D-dimer	32.6 (31.6-33.6)	34.1 (33.0-35.2)	22.9 (20.7-25.4)

VTE: venous thromboembolism; CI: confidence interval

Figure S1. Risk of bias assessment using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) tool for the 12 included studies

APPENDIX C – Manuscript 3

APPENDIX

e-Table 1. Performance of the standard diagnostic strategies (revised Geneva and Wells PE scores combined with fixed D-dimer cut-off)

Diagnostic strategies		PE at admission n/N (% [95% CI])	Isolated DVT at admission n/N (% [95% CI])	VTE (DVT and/or PE) at admission n/N (% [95% CI])	PE case fatality rate at admission n/N (%)	PE at 3 months n/N (% [95% CI])	Overall mortality at 3 months n/N (%)	PE case fatality at 3 months n/N (%)
Revised Geneva[1]								
Low risk	**D-dimer < 500 ng/mL**	0/52 (0.0% [0.0 - 6.8])	0/52 (0.0% [0.0 - 6.8])	0/52 (0.0% [0.0 - 6.8])	-	1/52 (1.9% [0.3 - 10.2])	0/52 (0.0%)	0/1 (0.0%)
	D-dimer ≥ 500 ng/mL	4/86 (4.7% [1.8 - 11.4])	1/86 (1.2% [0.2 - 6.3]) (proximal:1)	5/86 (5.8% [2.5 - 12.9])	1/4 (25.0%)	1/78 (1.3% [0.2 - 6.9])	6/85 (7.1%)	1/1 (100%)
	D-dimer not done	1/1 (100.0% [20.7 - 100.0])	0/1 (0.0% [0.0 - 79.4])	1/1 (100.0% [20.7 - 100.0])	0/1 (0.0%)	-	0/1 (0.0%)	-
	Total	5/139 (3.6% [1.6 - 8.2])	1/139 (0.7% [0.1 - 4.0]) (proximal:1)	6/139 (4.3% [2.0 - 9.1])	1/5 (20.0%)	2/130 (1.5% [0.4 - 5.4])	6/139 (4.3%)	1/2 (50.0%)
Intermediate risk	**D-dimer < 500 ng/mL**	0/160 (0.0% [0.0 - 2.3])	0/160 (0.0% [0.0 - 2.3])	0/160 (0.0% [0.0 - 2.3])	-	1/160 (0.6% [0.1 - 3.5])	6/160 (3.8%)	0/1 (0.0%)
	D-dimer ≥ 500 ng/mL	32/414 (7.7% [5.5 - 10.7])	7/414 (1.7% [0.8 - 3.4]) (proximal:3; distal:4)	39/414 (9.4% [7.0 - 12.6])	1/32 (3.1%)	2/363 (0.6% [0.2 - 2.0])	36/413 (8.7%)	2/2 (100%)
	D-dimer not done	2/10 (20.0% [5.7 - 51.0])	0/10 (0.0% [0.0 - 27.8])	2/10 (20.0% [5.7 - 51.0])	0/2 (0.0%)	0/7 (0.0% [0.0 - 35.4])	0/10 (0.0%)	-
	Total	34/584 (5.8% [4.2 - 8.0])	7/584 (1.2% [0.6 - 2.5]) (proximal:3; distal:4)	41/584 (7.0% [5.2 - 9.4])	1/34 (2.9%)	3/530 (0.6% [0.2 - 1.7])	42/584 (7.2%)	2/3 (66.7%)
High risk	**Total**	5/17 (29.4% [13.3 - 53.1])	2/17 (11.8% [3.3 - 34.3]) (distal:2)	7/17 (41.2% [21.6 – 64.0])	0/5 (0.0%)	0/10 (0.0% [0.0 - 27.8])	2/17 (11.8%)	-
Wells PE[2]								
Low risk	**D-dimer < 500 ng/mL**	0/163 (0.0% [0.0 - 2.3])	0/163 (0.0% [0.0 - 2.3])	0/163 (0.0% [0.0 - 2.3])	-	1/163 (0.6% [0.1 - 3.4])	3/163 (1.8%)	0/1 (0.0%)
	D-dimer ≥ 500 ng/mL	17/312 (5.5% [3.4 - 8.6])	5/312 (1.6% [0.7 - 3.7]) (proximal:3; distal:2)	22/312 (7.1% [4.7 - 10.4])	1/17 (5.9%)	3/283 (1.1% [0.4 - 3.1])	20/310 (6.5%)	3/3 (100.0%)
	D-dimer not done	1/5 (20.0% [3.6 - 62.5])	0/5 (0.0% [0.0 - 43.5])	1/5 (20.0% [3.6 - 62.5])	0/1 (0.0%)	0/3 (0.0% [0.0 - 56.2])	0/5 (0.0%)	-
	Total	18/480 (3.8% [2.4 - 5.9])	5/480 (1.0% [0.4 - 2.6]) (proximal:3; distal:2)	23/480 (4.8% [3.2 - 7.1])	1/18 (5.6%)	4/449 (0.9% [0.4 - 2.3])	23/478 (4.8%)	3/4 (75.0%)
Moderate risk	**D-dimer < 500 ng/mL**	0/49	0/49	0/49	-	1/49	3/49	0/1

		(0.0% [0.0 - 7.3])	(0.0% [0.0 - 7.3])	(0.0% [0.0 - 7.3])		(2.0% [0.4 - 10.7])	(6.1%)	(0.0%)
	D-dimer ≥ 500 ng/mL	17/187 (9.1% [5.8 – 14.1])	3/187 (1.6% [0.5 - 4.6]) (proximal:1; distal:2)	20/187 (10.7% [7.0 – 16.0])	1/17 (5.9%)	0/159 (0.0% [0.0 - 2.4])	19/187 (10.2%)	-
	D-dimer not done	2/5 (40.0% [11.8 - 76.9])	0/5 (0.0% [0.0 - 43.5])	2/5 (40.0% [11.8 - 76.9])	0/2 (0.0%)	0/3 (0.0% [0.0 - 56.2])	0/5 (0.0%)	-
	Total	19/241 (7.9% [5.1 – 12.0])	3/241 (1.2% [0.4 - 3.6]) (proximal:1; distal:2)	22/241 (9.1% [6.1 - 13.4])	1/19 (5.3%)	1/211 (0.5% [0.1 - 2.6])	22/241 (9.1%)	0/1 (0.0%)
High risk	**Total**	7/19 (36.8% [19.2 – 59.0])	2/19 (10.5% [2.9 – 31.4]) (distal:2)	9/19 (47.4% [27.3 – 68.3])	0/7 (0.0%)	0/10 (0.0% [0.0 – 27.8])	5/19 (26.3%)	-

CI: confidence interval; DVT: deep venous thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism

e-Table 2. Standard diagnostic strategies

Revised Geneva[1]		**Wells PE[3]**	
Criteria	**Points**	**Criteria**	**Points**
Age > 65 years old	+1	Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	+3
Previous DVT or PE	+3	An alternative diagnosis is less likely than PE	+3
Surgery (under general anesthesia) or fracture (of the lower limbs) within 1 month	+2	Heart rate greater than 100	+1.5
Active malignant condition (solid or hematologic malignant condition, currently active or considered cured < 1 year)	+2	Immobilization or surgery in the previous four weeks	+1.5
Unilateral lower-limb pain	+3	Previous DVT/PE	+1.5
Hemoptysis	+2	Hemoptysis	+1
Heart rate 75-94 beats/minute ≥95 beats/minute	 +3 +5	Malignancy (on treatment, treated in the last six months or palliative)	+1

Pain on lower-limb deep venous system palpation and unilateral edema	+4		
Clinical pre-test probability		***Clinical pre-test probability***	
Low	0-3	Low	< 2
Intermediate	4-10	Moderate	2-6
High	≥11	High	> 6
Fixed D-dimer cut-off used in patients with low and intermediate/moderate clinical pre-test probability < 500 ng/mL: PE ruled out ≥ 500 ng/mL: chest imaging needed			

DVT: deep venous thrombosis; PE: pulmonary embolism

e-Table 3. Computed tomography pulmonary angiogram sparing diagnostic strategies (ADJUST-PE, YEARS, PEGeD, 4PEPS)

<table>
<tr><th colspan="2">ADJUST-PE[4]</th><th>YEARS[5]</th><th colspan="2">PEGeD[6]</th><th colspan="2">4PEPS[7]</th></tr>
<tr><td colspan="2">Based on the revised Geneva score*</td><td>YEARS items</td><td colspan="2">Based on the Wells PE score</td><td>Criteria</td><td>Points</td></tr>
<tr><td>Clinical pre-test probability
Low
Intermediate
High</td><td>Points

0-3
4-10
≥ 11</td><td>Clinical signs or symptoms of DVT</td><td>Clinical pre-test probability
Low
Moderate
High</td><td>Points

0-4.0
4.5-6.0
≥ 6.5</td><td>Age
< 50 years old
50-64 years old</td><td>
-2
-1</td></tr>
<tr><td colspan="2">Based on the Wells PE score</td><td>Hemoptysis</td><td colspan="2" rowspan="5">Diagnostic algorithm
Low clinical pre-test probability
D-dimer < 1000 ng/mL: PE ruled out
D-dimer ≥ 1000 ng/mL: chest imaging needed

Moderate clinical pre-test probability
D-dimer < 500 ng/mL: PE ruled out
D-dimer ≥ 500 ng/mL: chest imaging needed

High clinical pre-test probability
Chest imaging needed</td><td>Chronic respiratory disease</td><td>-1</td></tr>
<tr><td>Clinical pre-test probability
Unlikely
Likely</td><td>Points

≤ 4
> 4</td><td>PE is the most likely diagnosis</td><td>Heart rate < 80 beats per minute</td><td>-1</td></tr>
<tr><td colspan="2" rowspan="4">Age-adjusted D-dimer cut-off used in patients with low, intermediate and unlikely clinical pre-test probability.
In patients 50 years or older, D-dimer cut-off is < 10 multiplied by the patient's age.
< age-adjusted D-dimer cut-off: PE ruled out
≥ age-adjusted D-dimer cut-off: chest imaging needed</td><td rowspan="4">Diagnostic algorithm
0 YEARS item and D-dimer < 1000 ng/mL: PE rule out
0 YEARS item and D-dimer ≥ 1000 ng/mL: chest imaging needed
≥ 1 YEARS item and D-dimer < 500 ng/mL: PE ruled out
≥ 1 YEARS item and D-dimer ≥ 500 ng/mL: chest imaging needed</td><td>Chest pain and acute dyspnea</td><td>+1</td></tr>
<tr><td>Male</td><td>+2</td></tr>
<tr><td>Hormonal estrogenic treatment</td><td>+2</td></tr>
<tr><td>Personal history of VTE</td><td>+2</td></tr>
<tr><td>Syncope</td><td>+2</td></tr>
<tr><td>Immobility withing the last 4 weeks</td><td>+2</td></tr>
<tr><td>Pulse oxygen saturation < 95%</td><td>+3</td></tr>
<tr><td>Calf pain and/or unilateral limb edema</td><td>+3</td></tr>
</table>

In patients < 50 years old, fixed D-dimer cut-off is used (500 ng/mL) < 500 ng/mL: PE ruled out ≥ 500 ng/mL: chest imaging needed			PE is the most likely diagnosis	+5
			Clinical pre-test probability Very low Low Moderate High	 < 0 0-5 6-12 ≥ 13
			Diagnostic algorithm *Very low clinical pre-test probability* PE ruled out *Low clinical pre-test probability* D-dimer < 1000 ng/mL: PE ruled out D-dimer ≥ 1000 ng/mL: chest imaging needed *Moderate clinical pre-test probability* D-dimer < age-adjusted cut-off: PE ruled out D-dimer ≥ age-adjusted cut-off: chest imaging needed High clinical pre-test probability Chest imaging needed	

**Revised Geneva score used instead of the simplified revised Geneva score; DVT: deep venous thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism;*

e-Table 4. Comparison of the number of computed tomography pulmonary angiograms needed and the failure rate of pulmonary embolism and venous thromboembolism depending on the diagnostic strategies used

Diagnostic strategies	Number of CTPA needed n/N (% [95% CI])	Relative difference in CTPA compared to standard diagnostic strategy*	Diagnostic failure rate of PE at admission amongst patients who would not have had CTPA n/N (% [95% CI])	Diagnostic failure rate of PE at 3 months amongst patients who would not have had CTPA n/N (% [95% CI])	Diagnostic failure rate of PE during the entire study period amongst patients who would not have had CTPA n/N (% [95% CI])	Estimated diagnostic failure rate of PE during the entire study period in the entire cohort n/N (% [95% CI])	Diagnostic failure rate of VTE at admission amongst patients who would not have had CTPA n/N (% [95% CI])	Diagnostic failure rate of VTE at 3 months amongst patients who would not have had CTPA n/N (% [95% CI])	Diagnostic failure rate of VTE during the entire study period amongst patients who would not have had CTPA n/N (% [95% CI])	Estimated diagnostic failure rate of VTE during the entire study period in the entire cohort n/N (% [95% CI])
Revised Geneva + fixed D-dimer cut-off [1]	517/729 (70.9% [67.5-74.1])	NA	0/212 (0.0% [0.0-1.8])	2/212 (0.9% [0.3-3.4])	2/212 (0.9% [0.3-3.4])	5/670 (0.7% [0.3-1.7])	0/212 (0.0% [0.0-1.8])	2/212 (0.9% [0.3-3.4])	2/212 (0.9% [0.3-3.4])	5/670 (0.7% [0.3-1.7])
Wells PE + fixed D-dimer cut-off [2]	518/730 (71.0% [67.6-74.1])	+0.1%	0/212 (0.0% [0.0-1.8])	2/212 (0.9% [0.3-3.4])	2/212 (0.9% [0.3-3.4])	5/670 (0.7% [0.3-1.7])	0/212 (0.0% [0.0-1.8])	2/212 (0.9% [0.3-3.4])	2/212 (0.9% [0.3-3.4])	5/670 (0.7% [0.3-1.7])
ADJUST-PE (revised Geneva)[4]	407/729 (55.8% [52.2-59.4])	-15.1%	1/322 (0.3% [0.1-1.7])	3/317 (1.0% [0.3-2.8])	4/322 (1.2% [0.5-3.2])	6/671 (0.9% [0.4-1.9])	4/322 (1.2% [0.5-3.2])	3/317 (1.0% [0.3-2.8])	7/322 (2.2% [1.1-4.4])	9/674 (1.3% [0.7-2.5])
ADJUST-PE (Wells PE)[4]	446/734 (60.8% [57.2-64.2])	-10.1%	1/288 (0.4% [0.1-1.9])	2/283 (0.7% [0.2-2.5])	3/288 (1.0% [0.4-3.0])	6/671 (0.9% [0.4-1.9])	4/288 (1.4% [0.5-3.5])	2/283 (0.7% [0.2-2.5])	6/288 (2.1% [1.0-4.5])	9/674 (1.3% [0.7-2.5])
YEARS[5]	332/725 (45.8% [42.2-49.4])	-25.1%	3/393 (0.8% [0.3-2.2])	4/383 (1.0% [0.4-2.7])	7/393 (1.8% [0.9-3.6])	8/673 (1.2% [0.6-2.3])	5/393 (1.3% [0.5-2.9])	4/383 (1.0% [0.4-2.7])	9/393 (2.3% [1.2-4.3])	10/675 (1.5% [0.8-2.7])
PEGeD[6]	308/730 (42.2% [38.7-45.8])	-28.7%	4/422 (1.0% [0.4-2.4])	4/410 (1.0% [0.4-2.5])	8/422 (1.9% [1.0-3.7])	9/674 (1.3% [0.7-2.5])	7/422 (1.7% [0.8-3.4])	4/410 (1.0% [0.4-2.5])	11/422 (2.6% [1.5-4.6])	12/677 (1.8% [1.0-3.1])
4PEPS[7]	280/728 (38.5% [35.0-42.1])	-32.4%	5/448 (1.1% [0.5-2.6])	4/431 (0.9% [0.4-2.4])	9/448 (2.0% [1.1-3.8])	10/675 (1.5% [0.8-2.7])	9/448 (2.0% [1.1-3.8])	4/431 (0.9% [0.4-2.4])	13/448 (2.9% [1.7-4.9])	14/679 (2.1% [1.2-3.4])

CI: confidence interval; CTPA: computed tomography pulmonary angiogram; NA: not applicable; PE: pulmonary embolism; VTE: venous thromboembolism;

**Revised Geneva score with fixed D-dimer cut-off was considered the standard diagnostic strategy.*

e-Table 5. Performance of computed tomography pulmonary angiogram sparing diagnostic strategies (ADJUST-PE, YEARS, PEGeD and 4PEPS)

Diagnostic strategies		PE at admission n/N (% [95% CI])	Isolated DVT at admission n/N (% [95% CI])	VTE (DVT and/or PE) at admission n/N (% [95% CI])	PE case fatality rate at admission n/N (%)	PE at 3 months n/N (% [95% CI])	Overall mortality at 3 months n/N (%)	PE case fatality rate at 3 months n/N (%)
ADJUST-PE (revised Geneva)[4]								
Non-high risk	**D-dimer < 500 ng/mL**	0/212 (0.0% [0.0 - 1.8])	0/212 (0.0% [0.0 - 1.8])	0/212 (0.0% [0.0 - 1.8])	-	2/212 (0.9% [0.3 - 0.9])	6/212 (2.8%)	0/2 (0.0%)
	D-dimer ≥ 500 and < age-adjusted cut-off	1/110 (0.9% [0.2 - 5.0])	3/110 (2.7% [0.9 - 7.7]) (proximal:1; distal:2)	4/110 (3.6% [1.4 - 9.0])	0/1 (0.0%)	1/105 (1.0% [0.2 - 5.2])	4/108 (3.7%)	1/1 (100.0%)
	D-dimer ≥ age-adjusted cut-off	35/390 (9.0% [6.5 - 12.2])	5/390 (1.3% [0.6 - 3.0]) (proximal:3; distal:2)	40/390 (10.3% [7.6 - 13.7])	2/35 (5.7%)	2/336 (0.6% [0.2 - 2.2])	38/390 (9.7%)	2/2 (100.0%)
	D-dimer not done	3/11 (27.2% [9.7 - 56.6])	0/11 (0.0% [0.0 - 25.9])	3/11 (27.2% [9.7 - 56.6])	0/3 (0.0%)	0/7 (0.0% [0.0 - 35.4])	0/11 (0.0%)	-
	Total	39/723 (5.4% [4.0 - 7.3])	8/723 (1.1% [0.6 - 2.2]) (proximal:4; distal:4)	47/723 (6.5% [4.9 - 8.5])	2/39 (5.1%)	5/660 (0.8% [0.3 - 1.8])	48/721 (6.7%)	3/5 (60.0%)
High risk	**Total**	5/17 (29.4% [13.3 - 53.1])	2/17 (11.8% [3.3 - 34.3]) (distal:2)	7/17 (41.2% [21.6 - 66.6])	0/5 (0.0%)	0/10 (0.0% [0 - 27.8])	2/17 (11.8%)	-
ADJUST-PE (Wells PE)[4]								
Unlikely PE	**D-dimer < 500 ng/mL**	0/190 (0.0% [0.0 - 2.0])	0/190 (0.0% [0.0 - 2.0])	0/190 (0.0% [0.0 - 2.0])	-	1/190 (0.5% [0.1 - 2.9])	4/190 (2.1%)	0/1 (0.0%)
	D-dimer ≥ 500 and < age-adjusted cut-off	1/98 (1.0% [0.2 - 5.6])	3/98 (3.1% [1.1 - 8.6]) (proximal:1; distal:2)	4/98 (4.1% [1.6 - 10.0])	0/1 (0.0%)	1/93 (1.1% [0.2 - 5.9])	3/97 (3.1%)	1/1 (100.0%)
	D-dimer ≥ age-adjusted cut-off	24/320 (7.5% [5.1 - 10.9])	4/320 (1.3% [0.5 - 3.2]) (proximal:3; distal:1)	28/320 (8.8% [6.1 - 12.4])	2/24 (8.3%)	2/282 (0.7% [0.2 - 2.6])	29/319 (9.1%)	2/2 (100.0%)
	D-dimer not done	2/6 (33.3% [9.7 - 70.0])	0/6 (0.0% [0.0 - 39.0])	2/6 (33.3% [9.7 - 70.0])	0/2 (0.0%)	0/3 (0.0% [0.0 - 56.2])	0/6 (0.0%)	-
	Total	27/614 (4.4% [3.0 - 6.3])	7/614 (1.1% [0.6 - 2.3]) (proximal:4; distal:3)	34/614 (5.5% [4.0 - 7.6])	2/27 (7.4%)	4/568 (0.7% [0.3 - 1.8])	36/512 (7.0%)	3/4 (75.0%)
Likely PE	**Total**	17/126 (13.5% [8.6 - 20.5])	3/126 (2.4% [0.8 - 6.8]) (distal:3)	20/126 (15.9% [10.5 - 23.3])	0/17 (0.0%)	1/102 (1.0% [0.2 - 5.4])	14/126 (11.1%)	0/1 (0.0%)
YEARS[5]								
0 YEARS items	**D-dimer < 1000 ng/mL**	3/353 (0.9% [0.3 - 2.7])	2/353 (0.6% [0.2 - 2.1]) (distal:2)	5/353 (1.4% [0.6 - 3.3])	0/3 (0.0%)	3/343 (0.9% [0.3 - 2.5])	10/351 (2.8%)	2/3 (66.7%)
	D-dimer ≥ 1000 ng/mL	16/166 (9.6% [6.0 - 15.1])	3/166 (1.8% [0.6 - 5.2]) (proximal:3)	19/166 (11.5% [7.5 - 17.2])	1/16 (6.5%)	1/143 (0.7% [0.1 - 3.9])	18/166 (10.8%)	1/1 (100.0%)
	D-dimer not done	1/5	0/5	1/5	0/1	0/3	0/5	-

		(20.0% [3.6 - 62.5])	(0.0% [0.0 - 43.5])	(20.0% [3.6 - 62.5])	(0.0%)	(0.0% [0.0 - 56.2])	(0.0%)	
	Total	20/524 (3.8% [2.5 - 5.8])	5/524 (1.0% [0.4 - 2.2]) (proximal:3; distal:2)	25/524 (4.8% [3.3 - 7.0])	1/20 (5.0%)	4/489 (0.8% [0.3 - 2.1])	28/522 (5.4%)	3/4 (75.0%)
≥1 YEARS items	**D-dimer < 500 ng/mL**	0/40 (0.0% [0 - 8.8])	0/40 (0.0% [0.0 - 8.8])	0/40 (0.0% [0.0 - 8.8])	-	1/40 (2.5% [0.4 - 12.9])	3/40 (7.5%)	0/1 (0.0%)
	D-dimer ≥ 500 ng/mL	19/166 (11.5% [7.5 - 17.2])	4/166 (2.4% [0.9 - 6.0]) (proximal:1; distal:3)	23/166 (13.9% [9.4 - 19.9])	1/19 (5.3%)	0/137 (0.0% [0.0 - 2.7])	18/166 (10.8%)	-
	D-dimer not done	5/10 (50% [23.7 - 76.3])	1/10 (10% [1.8 - 40.4]) (distal:1)	6/10 (60% [31.2 - 83.2])	0/5 (0.0%)	0/4 (0.0% [0.0 - 49.0])	1/10 (10.0%)	-
	Total	24/216 (11.1% [7.6 - 16.0])	5/216 (2.3% [1.0 - 5.3]) (proximal:1; distal:4)	29/216 (13.4% [9.5 - 18.6])	1/24 (4.2%)	1/181 (0.6% [0.1 - 3.1])	22/216 (10.2%)	0/1 (0.0%)
PEGeD[6]								
Low risk	**D-dimer < 1000 ng/mL**	4/400 (1.0% [0.4 - 2.6])	3/400 (0.8% [0.3 - 2.2]) (proximal:1; distal:2)	7/400 (1.8% [0.9 - 3.6])	0/4 (0.0%)	3/388 (0.8% [0.3 - 2.2])	13/398 (3.3%)	2/3 (66.7%)
	D-dimer ≥ 1000 ng/mL	21/208 (10.1% [6.7 – 15.0])	4/208 (1.9% [0.8 – 4.8]) (proximal:3; distal:1)	25/208 (12.0% [8.3 – 17.1])	2/21 (9.5%)	1/177 (0.6% [0.1 – 3.1])	23/208 (11.1%)	1/1 (100.0%)
	D-dimer not done	2/6 (33% [9.7 – 70.0])	0/6 (0.0% [0.0 – 39.0])	2/6 (33% [9.7 – 70.0])	0/2 (0.0%)	0/3 (0.0% [0.0 – 56.2])	0/6 (0.0%)	-
	Total	27/614 (4.4% [3.0 - 6.3])	7/614 (1.1% [0.6 - 2.3]) (proximal:4; distal:3)	34/614 (5.5% [4.0 - 7.6])	2/27 (7.4%)	4/568 (0.7% [0.3 - 1.8])	36/612 (5.9%)	3/4 (75.0%)
Moderate risk	**D-dimer < 500 ng/mL**	0/22 (0.0% [0.0 – 14.9])	0/22 (0.0% [0 – 14.9])	0/22 (0.0% [0 – 14.9])	-	1/22 (4.6% [0.8 – 22.0])	2/22 (9.1%)	0/1 (0.0%)
	D-dimer ≥ 500 ng/mL	9/81 (11.1% [6.0 – 19.8])	1/81 (1.2% [0.2 – 6.7]) (distal:1)	10/81 (12.4% [6.9 – 21.3])	0/9 (0.0%)	0/67 (0.0% [0 – 5.4])	7/81 (8.6%)	-
	D-dimer not done	1/4 (25% [4.6 – 70.0])	0/4 (0.0% [0.0 – 49.0])	1/4 (25% [4.6 – 70.0])	0/1 (0.0%)	0/3 (0.0% [0.0 – 56.2])	0/4 (0.0%)	-
	Total	10/107 (9.4% [5.2 - 16.4])	1/107 (0.9% [0.2 - 5.1]) (distal:1)	11/107 (10.3% [5.8 - 17.5])	0/10 (0.0%)	1/92 (1.1% [0.2 - 5.9])	9/107 (8.4%)	0/1 (0.0%)
High risk	**Total**	7/19 (36.8% [19.2 - 59.0])	2/19 (10.5% [2.9 - 31.4]) (distal:2)	9/19 (47.4% [27.3 - 68.3])	0/7 (0.0%)	0/10 (0.0%)	5/19 (26.3%)	-
4PEPS[7]								
Very low risk	**Total**	2/83 (2.4% [0.7 - 8.4])	0/83 (0% [0 - 4.4])	2/83 (2.4% [0.7 - 8.4])	0/2 (0.0%)	2/80 (2.5% [0.7 - 8.7])	5/83 (6.0%)	1/2 (50.0%)
Low risk	**D-dimer < 1000 ng/mL**	3/315 (1.0% [0.3 - 2.8])	2/315 (0.6% [0.2 - 2.3]) (distal:2)	5/315 (1.6% [0.7 - 3.7])	0/3 (0.0%)	1/303 (0.3% [0.1 - 1.9])	12/313 (3.8%)	1/1 (100.0%)
	D-dimer ≥ 1000 ng/mL	17/156 (10.9% [6.9 - 16.8])	4/156 (2.6% [1.0 - 6.4]) (proximal:3; distal:1)	21/156 (13.5% [9.0 - 19.7])	1/17 (5.9%)	1/131 (0.8% [0.1 - 4.2])	13/156 (8.3%)	1/1 (100.0%)

	D-dimer not done	1/6 (16.7% [3.0 - 56.4])	0/6 (0.0% [0.0 - 39.0])	1/6 (16.7% [3.0 - 56.4])	0/1 (0.0%)	0/4 (0.0% [0.0 - 49.0])	0/6 (0.0%)	-
	Total	21/477 (4.4% [2.9 - 6.6])	6/477 (1.3% [0.6 - 2.7]) (proximal:3; distal:3)	27/477 (5.7% [3.9 - 8.1])	1/21 (4.8%)	2/438 (0.5% [0.1 - 1.7])	25/475 (5.3%)	2/2 (100.0%)
Moderate risk	**D-dimer < age-adjusted**	0/50 (0.0% [0 - 7.1])	2/50 (4.0% [1.1 - 13.5]) (proximal:1; distal:1)	2/50 (4.0% [1.1 - 13.5])	-	1/48 (2.1% [0.4 - 10.9])	3/50 (6.0%)	0/1 (0.0%)
	D-dimer ≥ age-adjusted cut-off	17/119 (14.3% [9.1 - 21.7])	1/119 (0.8% [0.2 - 4.6]) (distal:1)	18/119 (15.1% [9.8 - 22.7])	1/17 (5.9%)	0/98 (0.0% [0.0 - 3.8])	16/119 (13.5%)	-
	D-dimer not done	3/6 (50.0% [18.8 - 81.2])	0/6 (0% [0 - 39.0])	3/6 (50.0% [18.8 - 81.2])	0/3 (0.0%)	0/3 (0.0% [0.0 - 56.2])	0/6 (0.0%)	-
	Total	20/175 (11.4% [7.5 - 17.0])	3/175 (1.7% [0.6 - 4.9]) (proximal:1; distal:2)	23/175 (13.1% [8.9 - 19.0])	1/20 (5.0%)	1/149 (0.7% [0.1 - 3.7])	19/175 (10.9%)	0/1 (0.0%)
High risk	**Total**	1/5 (20.0% [3.6 - 62.5])	1/5 (20.0% [3.6 - 62.5]) (distal:1)	2/5 (40.0% [11.8 - 76.9])	0/5 (0.0%)	0/3 (0.0% [0.0 - 56.2])	1/5 (20.0%)	-

CI: confidence interval; DVT: deep venous thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism

e-Table 6. Subgroup analysis based on the suspicion of pulmonary embolism for the safety (diagnostic failure rate of venous thromboembolism) and efficacy (number of computed tomography pulmonary angiogram needed) outcomes of various diagnostic strategies

Diagnostic strategies	Estimated diagnostic failure rate of VTE during the entire study period in the entire cohort n/N (% [95% CI])	Number of CTPA needed n/N (% [95% CI])
Revised Geneva + fixed D-dimer cut-off[1]		
PE suspected	2/257 (0.8 [0.2-2.8])	216/291 (74.2 [68.9-78.9])
PE not suspected	3/413 (0.7 [0.3-2.1])	301/438 (68.7 [64.2-72.9])
Wells PE + fixed D-dimer cut-off[2]		
PE suspected	2/257 (0.8 [0.2-2.8])	217/292 (74.3 [69.0-79.0])
PE not suspected	3/413 (0.7 [0.3-2.1])	301/438 (68.7 [64.2-72.9])
ADJUST-PE (revised Geneva)[4]		
PE suspected	4/259 (1.5 [0.6-3.9])	178/291 (61.2 [55.5-66.6])
PE not suspected	5/415 (1.2 [0.5-2.8])	229/438 (52.3 [47.6-56.9])
ADJUST-PE (Wells PE)[4]		
PE suspected	4/259 (1.5 [0.6-3.9])	209/295 (70.9 [65.4-75.7])
PE not suspected	5/415 (1.2 [0.5-2.8])	237/439 (54.0 [49.3-58.6])
YEARS[5]		
PE suspected	4/259 (1.5 [0.6-3.9])	172/287 (59.9 [54.2-65.4])
PE not suspected	6/416 (1.4 [0.7-3.1])	160/438 (36.5 [32.2-41.1])
PEGeD[6]		
PE suspected	5/260 (1.9 [0.8-4.4])	155/292 (53.1 [47.4-58.7])
PE not suspected	7/417 (1.7 [0.8-3.4])	153/438 (34.9 [30.6-39.5])
4PEPS[7]		
PE suspected	6/261 (2.3 [1.1-4.9])	148/290 (51.0 [45.3-56.7])

PE not suspected	8/418 (1.9 [1.0-3.7])	132/438 (30.1 [26.0-34.6])

CI: confidence interval; CTPA: computed tomography pulmonary angiogram; PE: pulmonary embolism; VTE: venous thromboembolism;

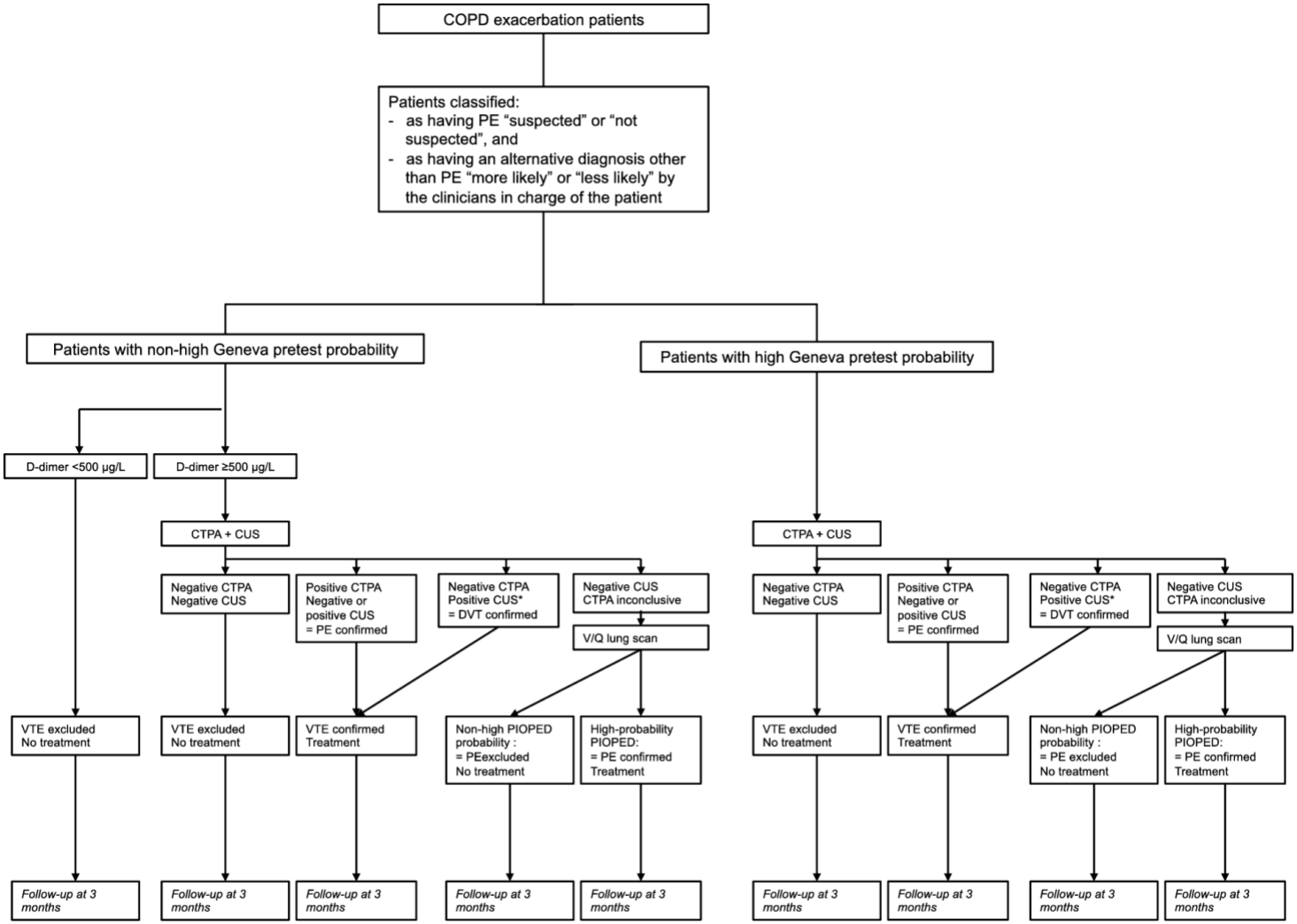
e-Table 7. Proportion of patients and prevalence of venous thromboembolism in each risk group based on each diagnostic strategies computed in the PEP cohort compared to the princeps studies

Diagnostic strategies	Risk groups	Proportion of patients (%)		Prevalence of VTE during the entire study period (%)	
		PEP cohort[8]	Princeps studies	PEP cohort[8]	Princeps studies
Revised Geneva[1]	Low	19	31-37	6	8-9*
	Intermediate	79	57-62	8	28-29*
	High	2	6-8	41	72-74*
	Total	100	100	8	23-26*
Wells PE[2]	Low	65	40	6	2-4*
	Moderate	33	52-53	10	19-21*
	High	2	7-8	50	50-67*
	Total	100	100	8	15-17*
ADJUST-PE (revised Geneva)[4]**	Non-high	98	87	7	NA
	High	2	13	41	NA
	Total	100	100	8	19
ADJUST-PE (Wells PE)[4]	Non-high	83	87	6	NA
	High	17	13	17	NA
	Total	100	100	8	19
YEARS[5]	0 YEARS item and D-dimer < 1000 ng/mL	49	38	2	0
	0 YEARS item and D-dimer ≥ 1000 ng/mL	23	12	12	14
	1 YEARS item and D-dimer < 500 ng/mL	6	10	3	1
	1 YEARS item and D-dimer ≥ 500 ng/mL	23	40	14	29
	Total	100	100	8	14
PEGeD[6]	Low and D-dimer < 1000 ng/mL	55	64	3	0
	Low and D-dimer ≥ 1000 ng/mL	28	23	13	19
	Moderate and D-dimer < 500 ng/mL	3	2	5	0

	Moderate and D-dimer ≥ 500 ng/mL	11	9	12	24
	High	3	2	47	40
	Total	100	100	8	7
4PEPS[7]	Very low	11	8-26	5	1-3*
	Low	64	49-58	6	6-10*
	Moderate	24	19-39	14	28-34*
	High	1	1-4	40	65-75*
	Total	100	100	8	11-21*

**In these princeps studies, only pulmonary embolism was collected, there was no information on isolated deep vein thrombosis;*
***Simplified revised Geneva score used in the princeps study; NA; not applicable; VTE: venous thromboembolism;*

e-Figure 1. Pulmonary embolism diagnostic algorithm from the PEP trial[8]



Bibliography

[1] G. Le Gal, M. Righini, P.M. Roy, O. Sanchez, D. Aujesky, H. Bounameaux, A. Perrier, Prediction of pulmonary embolism in the emergency department: the revised Geneva score, Ann Intern Med 144(3) (2006) 165-71.

[2] P.S. Wells, D.R. Anderson, M. Rodger, J.S. Ginsberg, C. Kearon, M. Gent, A.G. Turpie, J. Bormanis, J. Weitz, M. Chamberlain, D. Bowie, D. Barnes, J. Hirsh, Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer, Thromb Haemost 83(3) (2000) 416-20.

[3] P.S. Wells, D.R. Anderson, M. Rodger, I. Stiell, J.F. Dreyer, D. Barnes, M. Forgie, G. Kovacs, J. Ward, M.J. Kovacs, Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer, Ann Intern Med 135(2) (2001) 98-107.

[4] M. Righini, J. Van Es, P.L. Den Exter, P.M. Roy, F. Verschuren, A. Ghuysen, O.T. Rutschmann, O. Sanchez, M. Jaffrelot, A. Trinh-Duc, C. Le Gall, F. Moustafa, A. Principe, A.A. Van Houten, M. Ten Wolde, R.A. Douma, G. Hazelaar, P.M. Erkens, K.W. Van Kralingen, M.J. Grootenboers, M.F. Durian, Y.W. Cheung, G. Meyer, H. Bounameaux, M.V. Huisman, P.W. Kamphuisen, G. Le Gal, Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study, JAMA 311(11) (2014) 1117-24.

[5] T. van der Hulle, W.Y. Cheung, S. Kooij, L.F.M. Beenen, T. van Bemmel, J. van Es, L.M. Faber, G.M. Hazelaar, C. Heringhaus, H. Hofstee, M.M.C. Hovens, K.A.H. Kaasjager, R.C.J. van Klink, M. Kruip, R.F. Loeffen, A.T.A. Mairuhu, S. Middeldorp, M. Nijkeuter, L.M. van der Pol, S. Schol-Gelok, M. Ten Wolde, F.A. Klok, M.V. Huisman, Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study, Lancet 390(10091) (2017) 289-297.

[6] C. Kearon, K. de Wit, S. Parpia, S. Schulman, M. Afilalo, A. Hirsch, F.A. Spencer, S. Sharma, F. D'Aragon, J.-F. Deshaies, G. Le Gal, A. Lazo-Langner, C. Wu, L. Rudd-Scott, S.M. Bates, J.A. Julian, Diagnosis of Pulmonary Embolism with d-Dimer Adjusted to Clinical Probability, New England Journal of Medicine 381(22) (2019) 2125-2134.

[7] P.-M. Roy, E. Friou, B. Germeau, D. Douillet, J.A. Kline, M. Righini, G. Le Gal, T. Moumneh, A. Penaloza, Derivation and Validation of a 4-Level Clinical Pretest Probability Score for Suspected Pulmonary Embolism to Safely Decrease Imaging Testing, JAMA Cardiology 6(6) (2021) 669-677.

[8] F. Couturaud, L. Bertoletti, J. Pastre, P.M. Roy, R. Le Mao, F. Gagnadoux, N. Paleiron, J. Schmidt, O. Sanchez, E. De Magalhaes, M. Kamara, C. Hoffmann, L. Bressollette, M. Nonent, C. Tromeur, P.Y. Salaun, S. Barillot, F. Gatineau, P. Mismetti, P. Girard, K. Lacut, C.A. Lemarié, G. Meyer, C. Leroyer, Prevalence of Pulmonary Embolism Among Patients With COPD Hospitalized With Acutely Worsening Respiratory Symptoms, JAMA 325(1) (2021) 59-68.

APPENDIX D – Manuscript 4

Chronic obstructive pulmonary disease exacerbation purulence status and its association with pulmonary embolism: a systematic review with meta-analysis

Supplemental file

Vicky Mai[1], Laura Girardi[1,2], Kerstin de Wit[3], Lana A. Castellucci[1], Shawn Aaron[4], Francis Couturaud[5], Dean Fergusson[6], Grégoire Le Gal[1]

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APPENDIX 1 – Search strategies

Search strategy MEDLINE

1. “Chronic obstructive pulmonary disease”.ab,kw,ti.
2. Pulmonary disease, Chronic obstructive/
3. “Chronic obstructive lung disease”.ab,kw,ti.
4. “Chronic obstructive airway disease”.ab,kw,ti.
5. “Chronic airflow obstruction”.ab,kw,ti.
6. COPD.ab,kw,ti.
7. “Chronic bronchitis”.ab,kw,ti.
8. Bronchitis, Chronic/
9. “Pulmonary emphysema”.ab,kw,ti.
10. Pulmonary emphysema/
11. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12. “Venous thrombos*”.ab,kw,ti.
13. Venous thrombosis/
14. “Vein thrombosis”.ab,kw,ti.
15. “Vein thromboembolism”.ab,kw,ti.
16. “Pulmonary embolism”.ab,kw,ti.
17. Pulmonary embolism/
18. “Pulmonary embolisms”.ab,kw,ti.
19. “Pulmonary thromboembolism”.ab,kw,ti.
20. “Lung embolism”.ab,kw,ti.
21. “Lung embolisms”.ab,kw,ti.

22. “Lung thromboembolism”.ab,kw,ti.
23. “Venous thromboembolism”.ab,kw,ti.
24. Venous thromboembolism/
25. #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24

#11 AND #25

Search strategy Embase

1. “Chronic obstructive pulmonary disease”.ab,ti,kw
2. “Chronic obstructive pulmonary disease”/
3. “Chronic obstructive lung disease”.ab,ti,kw
4. “Chronic obstructive airway disease”.ab,ti,kw
5. “Chronic airflow obstruction”.ab,ti,kw
6. COPD.ab,ti,kw
7. “Chronic bronchitis”.ab,ti,kw
8. “Chronic bronchitis”/
9. “Pulmonary emphysema”.ab,ti,kw
10. “Pulmonary emphysema”/
11. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12. “Venous Thrombos*”.ti,ab,kw
13. “Venous thromboembolism”.ti,ab,kw
14. “Vein Thrombos*”.ti,ab,kw
15. “Vein thromboembolism”.ti,ab,kw
16. “Vein thrombosis”/

17. “Pulmonary embolism”.ti,ab,kw
18. “Pulmonary embolisms”.ti,ab,kw
19. “Pulmonary thromboembolism”.ti,ab,kw
20. “Lung embolism”.ti,ab,kw
21. “Lung embolisms”.ti,ab,kw
22. “Lung thromboembolism”.ti,ab,kw
23. “Lung embolism”/
24. #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23

#11 AND #24

Search strategy CENTRAL

1. “Chronic obstructive pulmonary disease”.ab,kw,ti.
2. Pulmonary disease, Chronic obstructive/
3. “Chronic obstructive lung disease”.ab,kw,ti.
4. “Chronic obstructive airway disease”.ab,kw,ti.
5. “Chronic airflow obstruction”.ab,kw,ti.
6. COPD.ab,kw,ti.
7. “Chronic bronchitis”.ab,kw,ti.
8. Bronchitis, Chronic/
9. “Pulmonary emphysema”.ab,kw,ti.
10. Pulmonary emphysema/
11. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12. “Venous thrombos*”.ab,kw,ti.

13. Venous thrombosis/

14. “Vein thrombosis”.ab,kw,ti.

15. “Vein thromboembolism”.ab,kw,ti.

16. “Pulmonary embolism”.ab,kw,ti.

17. Pulmonary embolism/

18. “Pulmonary embolisms”.ab,kw,ti.

19. “Pulmonary thromboembolism”.ab,kw,ti.

20. “Lung embolism”.ab,kw,ti.

21. “Lung embolisms”.ab,kw,ti.

22. “Lung thromboembolism”.ab,kw,ti.

23. “Venous thromboembolism”.ab,kw,ti.

24. Venous thromboembolism/

25. #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24

#11 AND #25

Table S1. Acute exacerbation of chronic obstructive pulmonary disease purulence status definition per study

Studies	Definition of purulent AECOPD
Studies including patients with purulent AECOPD and non-purulent/unknown etiology AECOPD	
Bahloul 2015	Tracheobronchial infection (possible)
Choi 2013	Purulent sputum (definitive) Symptoms of respiratory infection (possible)
Couturaud 2021	Bronchial infection and pneumonia (possible)
Dentali 2020	Purulent sputum (definitive)
Hassen 2019	Purulent sputum (definitive)
Jiménez 2021	Yellow or green sputum, as reported by the patient (definitive)
Li 2016	Yellow sputum (definitive)
Mai 2023	Purulent sputum (definitive)
Meitei 2021	Consolidation on CTPA (possible)

AECOPD: acute exacerbation of chronic obstructive pulmonary disease; CTPA: computed tomography pulmonary angiogram

Table S2. Risk of bias assessment of each included study using the ROBINS-E tool

Study name	Domain 1: Risk of bias due to confounding	Domain 2: Bias arising from measurement of the exposure	Domain 3: Bias in selection of participants into the study	Domain 4: Bias due to post-exposure interventions	Domain 5: Bias due to missing data	Domain 6: Bias in measurement of the outcome	Domain 7: Bias in selection of the reported result	Overall bias
Bahloul 2015	Some concerns	High	High	High	High	Some concerns	Low	High
Choi 2013	Some concerns	Low	Some concerns	Low	Low	Some concerns	Low	Some concerns
Couturaud 2021	Some concerns	Low	Some concerns	Low	Low	Low	Low	Some concerns
Dentali 2020	Some concerns	Some concerns	Some concerns	High	High	Some concerns	Low	High
Hassen 2019	Some concerns	Low	High	Low	High	Some concerns	Low	High
Jimenez 2021	Low (except for concerns for uncontrolled confounding)	Low	Some concerns	Low	Low	Low	Low	Some concerns
Li 2016	High	High	Low	Some concerns	Very high	High	Some concerns	Very high
Mai 2023	Some concerns	Some concerns	Some concerns	High	Some concerns	Some concerns	Low	High
Meitei 2021	Some concerns	Very high	High	High	Some concerns	Some concerns	Low	Very high
Andrejak 2012	High	Low	High	Low	High	Some concerns	Some concerns	High
Chaudhary 2021	Some concerns	Low	Some concerns	Low	High	Low	Low	High

Jindal 2020	Some concerns	Low	Some concerns	Low	High	Low	Low	High
Tillie-Leblond 2006	Some concerns	Low	High	Low	High	Low	Low	High
Wang 2013	Some concerns	Low	High	Low	High	Low	Low	High

Table S3. Subgroup analyses for the pooled proportions of pulmonary embolism according to AECOPD purulent status

Subgroup analyses	Number of studies (n)	Number of patients (n)	PE % (95%CI)	I^2 (%)
Purulent AECOPD - Study design				
Randomized controlled trial	1	24	5.8 (0.2-18.3)	*
Prospective cohort studies	4	612	8.2 (0.6-23.1)	91.9
Retrospective cohort studies	4	932	7.5 (0.7-20.3)	96.9
Non-purulent/unknown etiology AECOPD – Study design				
Randomized controlled trial	1	346	4.8 (2.8-7.2)	*
Prospective cohort studies	8	1,110	16.9 (11.5-23.1)	84.5
Cross-sectional study	1	110	18.5 (11.8-26.2)	*
Retrospective cohort studies	4	1,922	8.9 (1.7-21.2)	98.0
Purulent AECOPD – Systematic search of PE with imaging regardless of the clinical probability or clinical suspicion				
Yes	1	56	2.6 (0.1-8.2)	*
No	8	1,568	8.2 (2.5-16.6)	95.4
Non-purulent/unknown etiology AECOPD – Systematic search of PE with imaging regardless of the clinical probability or clinical suspicion				
Yes	5	662	19.6 (12.5-27.9)	83.4
No	9	2,826	10.4 (5.3-17.1)	95.9
Purulent AECOPD – Localization of PE				
Subsegmental and more proximal	3	515	10.9 (0.0-39.7)	90.7
Segmental and more proximal	3	531	4.0 (0.3-19.3)	95.6
Unknown	3	522	10.7 (8.2-13.5)	0.0
Non-purulent/unknown etiology AECOPD – Localization of PE				
Subsegmental and more proximal	5	1,048	12.5 (6.4-20.3)	91.4
Segmental and more proximal	4	971	10.0 (0.9-27.5)	96.0
Unknown	5	1,469	17.0 (9.9-25.5)	92.2

AECOPD: acute exacerbation of chronic obstructive pulmonary disease; PE: pulmonary embolism; *I^2 could not be evaluated;

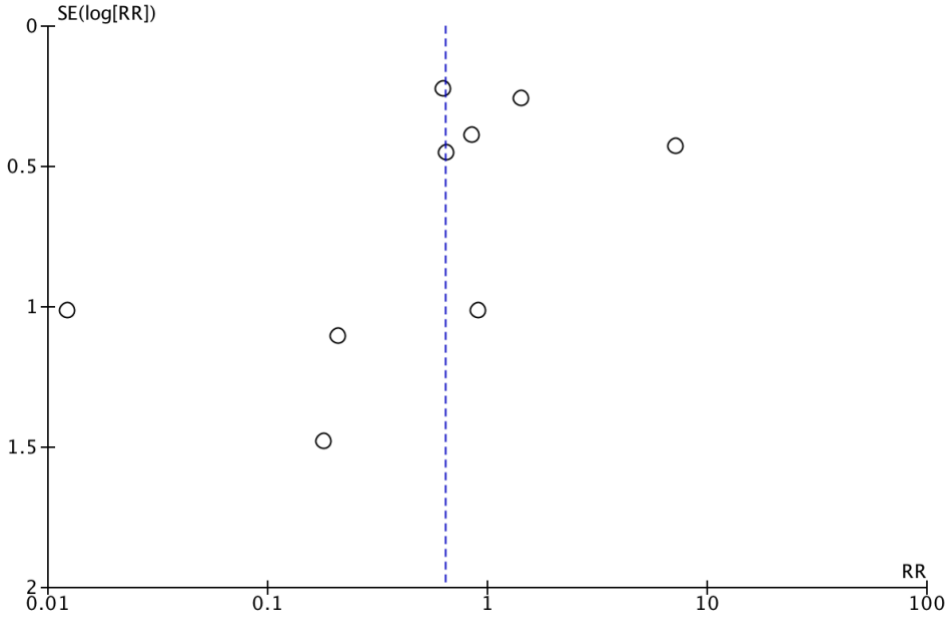
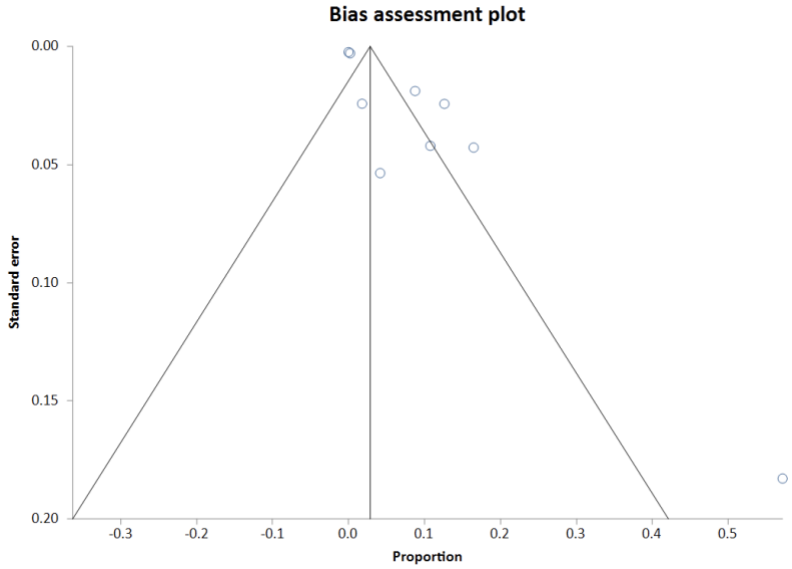
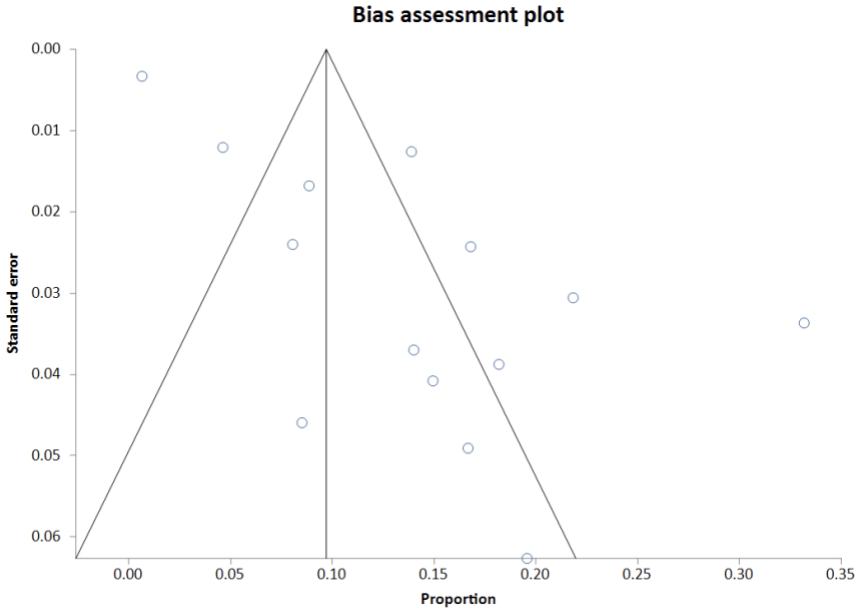


Figure S1. Funnel plot for the analysis evaluating the relative risk of pulmonary embolism and acute exacerbation of chronic obstructive pulmonary disease purulence status



A.



B.

Figure S2. Funnel plot for the analysis of pooled proportions of pulmonary embolism for A) studies including patients with purulent acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and B) studies including patients with non-purulent/unknown etiology AECOPD

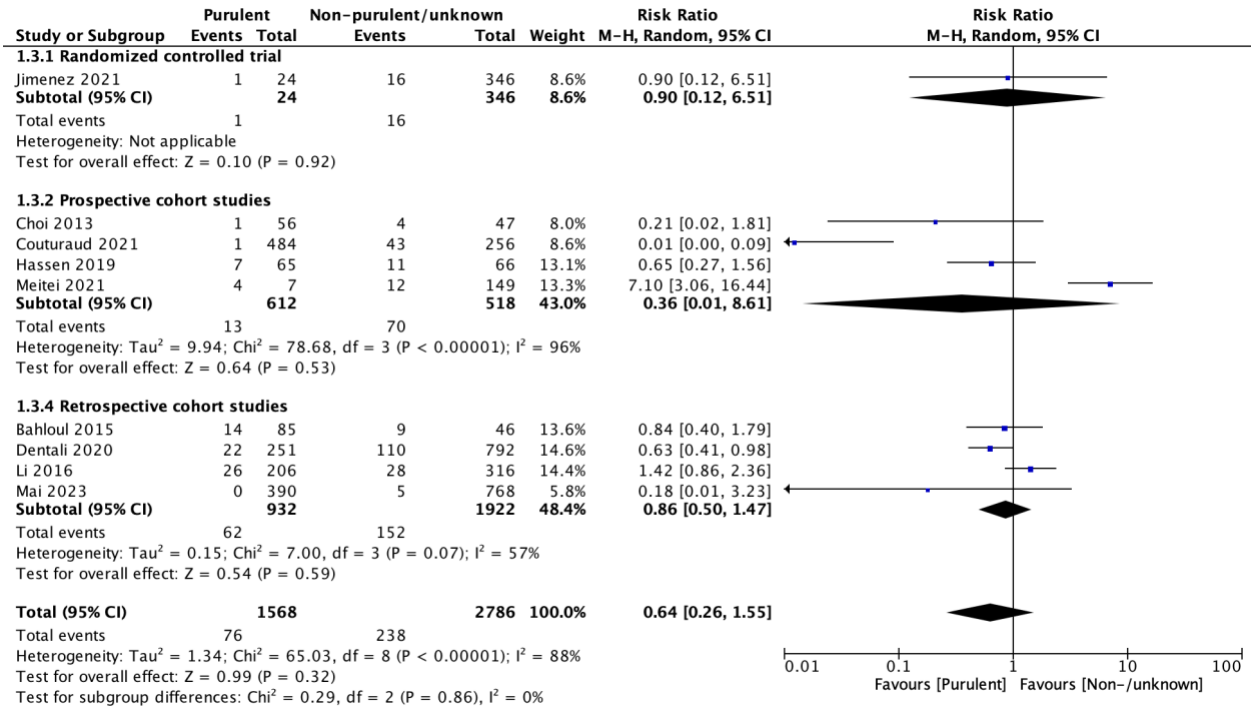


Figure S3. Forest plot and relative risk for the association between the risk of pulmonary embolism and the acute exacerbation of chronic obstructive pulmonary disease purulence status based on the study design

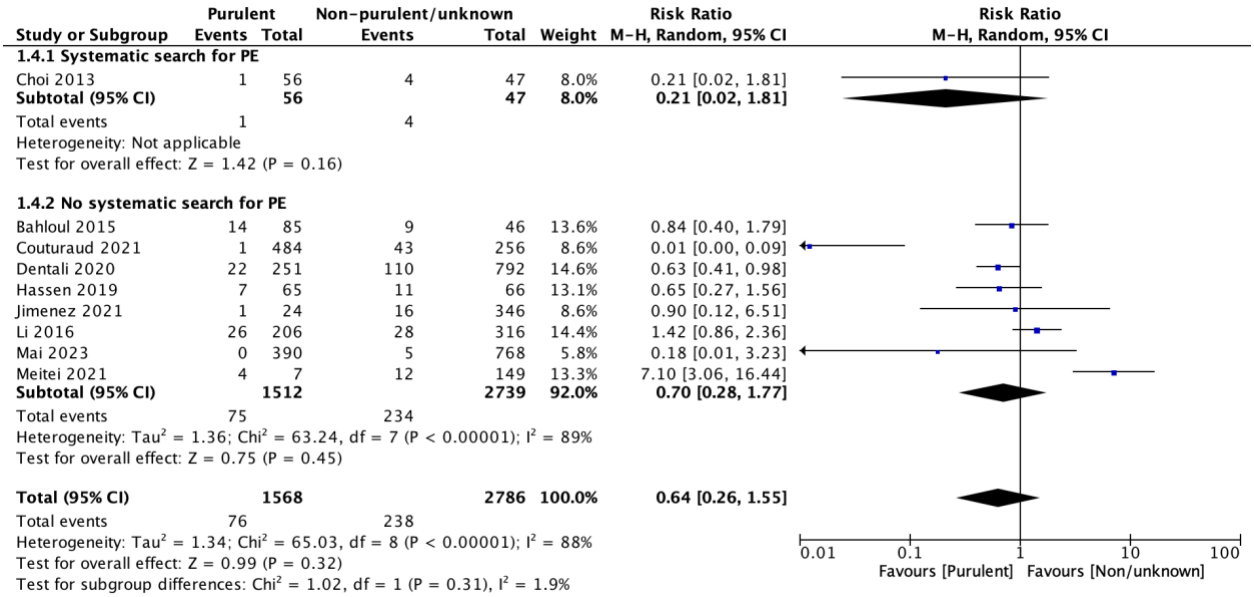


Figure S4. Forest plot and relative risk for the association between the risk of pulmonary embolism and the acute exacerbation of chronic obstructive pulmonary disease purulence status based on the systematic search of PE or no systematic search of PE with imaging regardless of the clinical probability or clinical suspicion

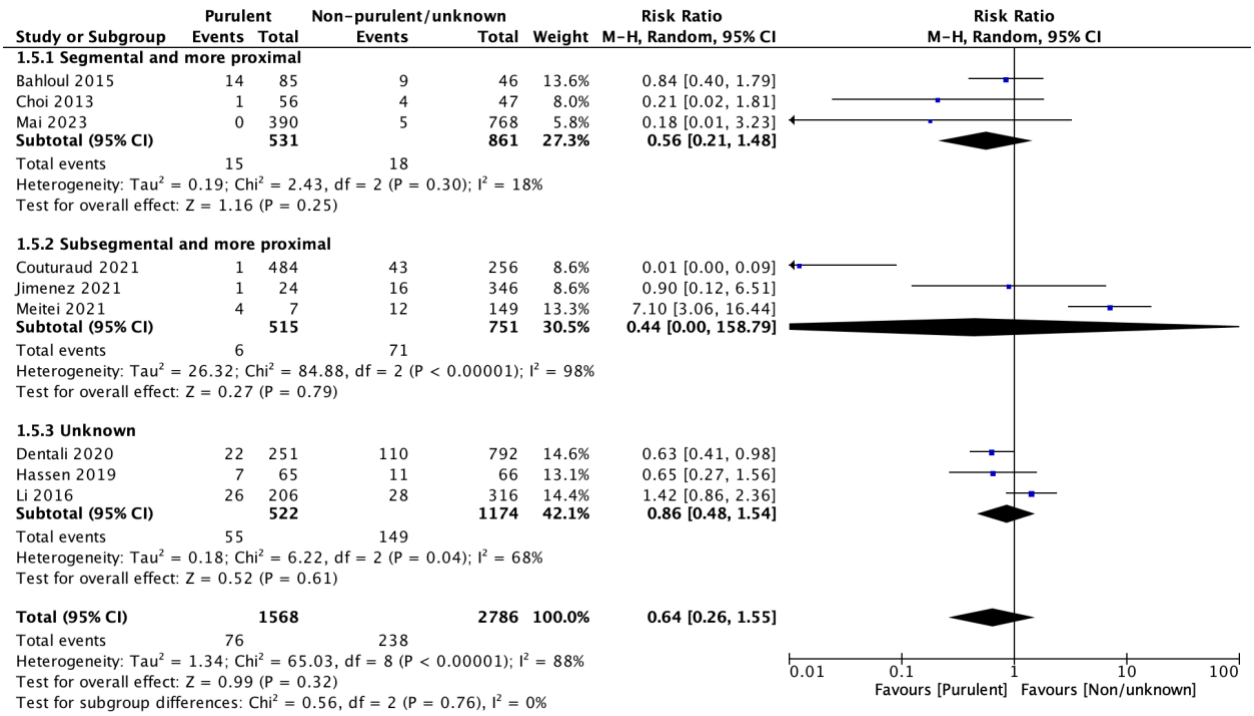


Figure S5. Forest plot and relative risk for the association between the risk of pulmonary embolism and the acute exacerbation of chronic obstructive pulmonary disease purulence status based on the localization of PE

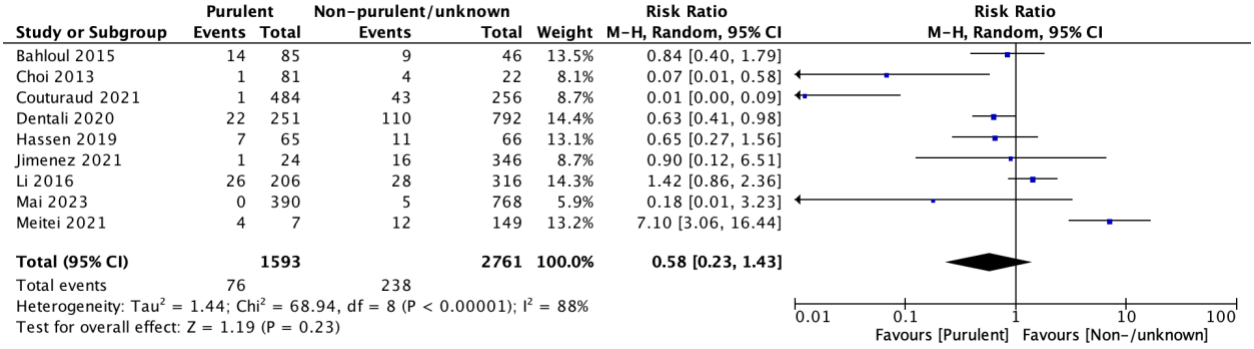


Figure S6. Forest plot and relative risk for the association between the risk of pulmonary embolism and the acute exacerbation of chronic obstructive pulmonary disease (AECOPD) purulence status based on the definition of purulent AECOPD (possible purulent AECOPD definition used primarily)

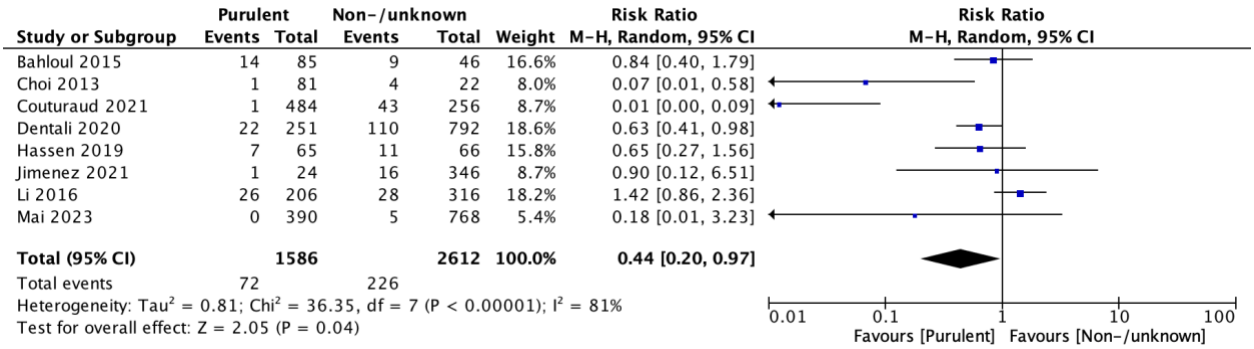


Figure S7. Forest plot and relative risk for the association between the risk of pulmonary embolism and the acute exacerbation of chronic obstructive pulmonary disease (AECOPD) purulence status based on the definition of purulent AECOPD (clinical purulent AECOPD definition and possible purulent AECOPD definition used primarily)

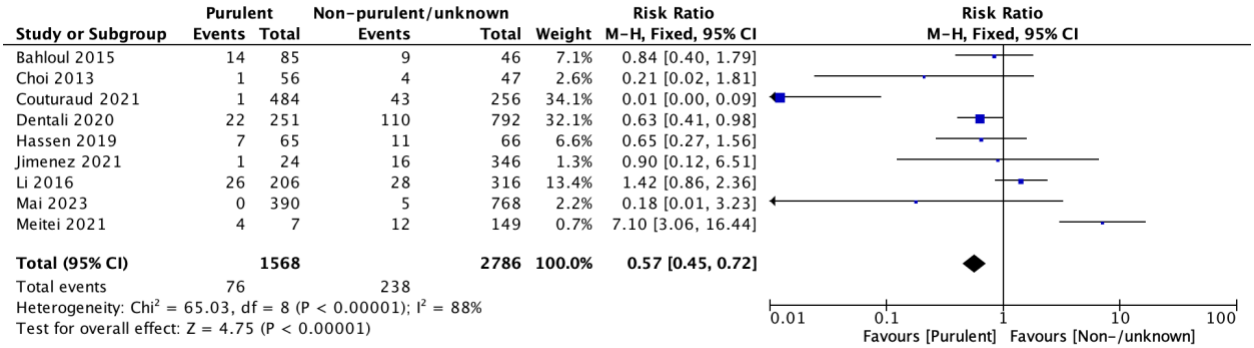


Figure S8. Forest plot and relative risk for the association between the risk of pulmonary embolism and the acute exacerbation of chronic obstructive pulmonary disease (AECOPD) purulence status using fixed-effects model

APPENDIX E – Published protocol related to manuscript 4

Chronic obstructive pulmonary disease exacerbation purulence status and its association with pulmonary embolism: protocol for a systematic review with meta-analysis

Vicky Mai[1], Laura Girardi[1,2], Kerstin de Wit[3], Lana A. Castellucci[1], Shawn Aaron[4], Francis Couturaud[5], Dean Fergusson[6], Grégoire Le Gal[1]

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E-mail: glegal@toh.ca

Abstract word count: 290
Manuscript word count: 1869

ABSTRACT

Introduction: Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) increases the risk of pulmonary embolism (PE). AECOPD and PE have similar symptoms which results in a high proportion of patients with AECOPD undergoing imaging to rule out PE. Finding predictors and explanatory factors of PE in AECOPD, such as purulence status, could help reduce the need for imaging. This systematic review with meta-analysis aims to evaluate if there is an association between purulence status in AECOPD and PE diagnosis.

Methods and analysis: MEDLINE, EMBASE and CENTRAL will be searched from database inception to April 2024. Randomized trials, cohort studies and cross-sectional studies on the prevalence of PE in patients with AECOPD will be included if the prevalence of PE based on the AECOPD purulence status is available. There will be no restriction on language. The primary outcome will be PE at the initial assessment and secondary outcomes will be all venous thromboembolism (deep venous thrombosis (DVT) and PE) and DVT, respectively, diagnosed at initial assessment. Relative risks (RR) with their 95% confidence interval (CI) will be calculated by using a Mantel-Haenszel random-effect model to compare the association between the risk of PE and the AECOPD purulence status (purulent vs non-purulent/unknown). Subgroup analyses will be performed based on the type of study, systematic search of PE vs no systematic search of PE and localization of PE. Risk of bias will be evaluated by the ROBINS-E tool, publication bias will be evaluated with the funnel plot. The manuscript will be drafted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.

Ethics and dissemination: This study does not require ethics approval. This work will be submitted for presentation in an international conference and for publication in a peer-reviewed journal.

PROSPERO registration number: CRD42023459429

Strengths and limitations of this study

- An experienced patient partner from the Canadian Venous Thromboembolism Research Network (CanVECTOR) patient partner platform was involved in the protocol elaboration.
- The AECOPD purulence status may not be homogenous across studies, which may make it more challenging to pool some data.
- Not all studies reported on the prevalence of PE according to the AECOPD purulence status and consequently, the data included in this systematic review may thus represent a limited proportion of all the data available on the prevalence of PE in patients with AECOPD.

INTRODUCTION

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) increases the risk of pulmonary embolism (PE)[1] due to increased systemic inflammation as well as in the airways[2]. Moreover, PE is associated with a 5-fold increased risk of mortality in patients with chronic obstructive pulmonary disease (COPD)[3]. Diagnosing PE in the context of AECOPD is challenging for several reasons. First, due to confounding symptoms of AECOPD and PE, it is unknown when PE should be suspected in patients with COPD. Second, even when PE is not suspected, or when another diagnosis is more likely, the prevalence of PE [i.e., 4.5% (PEP[4] and SLICE[5])] is not low enough to safely exclude PE on clinical grounds only. Clinical decision rules and D-dimers, when applied to patients with AECOPD and whether PE is suspected or not, have lower clinical utility in AECOPD, since > 65% of the patients would need imaging to rule out PE if standard diagnostic strategy were used[4]. In addition, negative effects are seen with computed tomography pulmonary angiogram (CTPA) such as cost, radiation exposure, contrast-induced nephropathy, and incidental findings. Furthermore, as the severity of the COPD progresses, AECOPD occurs more frequently[6] and it is expected that the need to rule out PE will become more frequent. Finding predictors and explanatory factors of PE in AECOPD, such as the purulence status, could help reduce the need for imaging. Clinically, it would make sense that if the AECOPD is explained by an infectious process, then the PE would be less likely and conversely, if the AECOPD is unexplained, it would make sense that PE would be more likely to be the explanation for the AECOPD. As a matter of fact, some studies showed a lower risk of PE or VTE in patients with purulent AECOPD[7-9].

Thus, the main aim of this systematic review with meta-analysis is to evaluate whether purulence status in AECOPD is associated with PE. We hypothesize that the risk of PE will be lower in purulent AECOPD compared to non-purulent or unknown purulent status AECOPD, since the

etiology of the exacerbation is unknown in up to 30% of the AECOPD[10] and PE could thus be an explanation in those cases. As a secondary aim, we would like to evaluate the association between AECOPD purulence status and the risk of venous thromboembolism (VTE) [deep venous thrombosis (DVT) of the lower extremity and PE] and the risk of DVT, respectively. We hypothesize that the risk of VTE and DVT, respectively, will be lower in patients with purulent AECOPD compared to non-purulent or unknown purulent status AECOPD.

STUDY OBJECTIVES

Primary objective

The primary objective is to evaluate the risk of PE in patients with purulent AECOPD compared to non-purulent or unknown purulent status AECOPD.

Secondary objective

The secondary objective is to evaluate the risk of VTE (including DVT of the lower extremity and PE) and the risk of DVT, respectively, in patients with purulent AECOPD compared to non-purulent or unknown purulent status AECOPD.

METHODS AND ANALYSIS

Eligibility criteria

Randomized trials, cohort studies (retrospective or prospective) and cross-sectional studies on the prevalence of PE in patients with AECOPD will be included if the prevalence of PE according to the AECOPD purulence status is available. AECOPD purulence status will be categorized as definitive purulent AECOPD (purulent AECOPD or purulent sputum), possible purulent AECOPD

(clinical and/or radiological evidence of tracheobronchial infection or pneumonia), non-purulent AECOPD or unknown purulence status AECOPD.

Information sources and search strategy

MEDLINE, EMBASE and CENTRAL will be searched from inception to April 2024. Conference abstracts from the American Thoracic Society, American College of Chest Physicians, European Respiratory Society, British Thoracic Society, American Society of Hematology, International Society on Thrombosis and Haemostasis will be hand searched from January 2000 to April 2024. There will be no restriction on language. The search strategy will be reviewed by a research librarian with expertise in knowledge synthesis and translation, and will be included in the supplemental file (**Appendix 1**).

Study records

Two reviewers (V.M. and L.G.) will independently screen all the titles and abstracts for potentially eligible studies. Full texts of potentially eligible studies will be obtained and screened by two reviewers independently. Both levels of screening will be conducted using Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Any disagreements will be resolved by further discussion or by consulting a third reviewer (G.L.G.). If the same cohort was published in multiple papers, the paper with the largest cohort providing the required information needed will be selected.

Data items

Two independent reviewers (V.M. and L.G.) will extract the data from included papers by using a standardized collection form. Collected data will include study characteristics (study ID, reference, study design), patients' characteristics [number of patients, age, sex, BMI, mean forced expiratory volume in 1 second (FEV1), Global Initiative for Chronic Obstructive Lung Disease (GOLD)

stage, prior personal or familial venous thromboembolic event, current tobacco use, active cancer (defined as current diagnosis of cancer, receiving treatment for cancer or not receiving treatment for cancer and not in complete response as per the International Society on Thrombosis and Haemostasis Common Data Elements), number of previous AECOPD in the last year, pre-test clinical probability, mean D-dimers level, VTE (PE and/or DVT), AECOPD purulence status], proportion of patients who had imaging to rule out VTE, whether or not all patients systematically had diagnostic imaging searching for PE (or VTE) was undertaken, localization of PE, clinical setting (inpatients vs outpatients) and use of independent adjudication. Study authors will be contacted if important information is missing.

Outcome measures

The primary outcome will be PE at the initial assessment. PE will include symptomatic PE involving subsegmental branches or more proximal arteries on CTPA, high probability on a planar ventilation/perfusion (V/Q) scan, at least one segmental mismatch or two subsegmental mismatches on a V/Q SPECT (EANM criteria)[11] and incidental PE found fortuitously on imaging and fatal PE. If the localization of the PE was not mentioned in the article, the study will still be included, and subgroup analyses will be performed. Secondary outcomes will include VTE (proximal DVT and/or PE), proximal DVT and distal DVT, respectively, at the initial assessment. DVT will include DVT of the lower extremity, either symptomatic or incidental. In case it was not mentioned if the DVT was proximal or distal, the study will still be included, and subgroup analyses will be performed. The initial assessment will be defined as the first 48 hours from hospital admission if the patient is admitted, as the first 48 hours from the initial medical evaluation if the patient is managed as an outpatient or as defined by individual studies.

Assessment of risk of bias in included studies

The risk of bias of included studies will be evaluated by two independent reviewers (V.M. and L.G.) by using the ROBINS-E tool[12]. Publication bias will be assessed by conducting and evaluating the funnel plot for the primary outcome. A symmetrical funnel plot indicates absence of publication bias.

Data synthesis

The prevalence of PE, VTE and DVT, respectively, at initial assessment will be calculated with its 95% confidence interval (CI) by using the binomial exact method[13] for each study. Data will be pooled using Review Manager version 5.3 (The Cochrane Collaboration, Oxford, England). Relative risks (RR) with their 95%CI will be calculated by using a Mantel-Haenszel random-effects model to compare the association between the risk of PE in patients with purulent AECOPD and the risk of PE in patients with non-purulent/unknown purulence status AECOPD. Events will be categorized in the definitive purulent AECOPD group if it was mentioned purulent AECOPD or the sputum was described as purulent. Events will be categorized in the possible purulent AECOPD group if there was clinical and/or radiological evidence of tracheobronchial infection or pneumonia. Similar analyses will be conducted to evaluate the association between the risk of VTE and the risk of DVT, respectively, and the AECOPD purulence status. Forest plots will be presented. If some studies cannot be pooled in the RR analysis evaluating the association between the risk of PE and the type of AECOPD, pooled proportions of PE of patients with purulent AECOPD and with non-purulent/unknown purulence status AECOPD, respectively, will be calculated using StatsDirect statistical software. I^2 will be calculated to evaluate heterogeneity and will be considered significant if I^2 is > 50%. Subgroup analyses will be performed based on the type of study (randomized trials vs prospective cohort studies vs retrospective cohort studies vs cross-sectional studies), systematic search of PE (or VTE) vs no systematic search of PE (or VTE)

and localization of PE (or DVT). Sensitivity analyses will be performed by including only studies at low risk of bias. The manuscript will be drafted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.

Patient and public involvement

An experienced patient partner from the Canadian Venous Thromboembolism Research Network (CanVECTOR) patient partner platform revised the protocol and approved the design and conduct of the study, as well as the outcome measures.

ETHICS AND DISSEMINATION

Since this is a systematic review with meta-analysis of published studies, ethics approval and patients' consent will not be required. We aim to submit this work for presentation at an international conference and for publication in a peer-reviewed journal.

DISCUSSION

This systematic review with meta-analysis aims at comparing the association between the risk of PE in patients with purulent AECOPD and the risk of PE in patients with non-purulent/unknown purulence status AECOPD. Finding predictors or explanatory factors for PE in patients with AECOPD, such as AECOPD purulence status, could help reduce the need for imaging. If the risk of PE is shown to be lower in patients with purulent AECOPD compared to non-purulent or unknown status AECOPD, this new information may help improve PE diagnostic algorithm in reducing the need for imaging in ruling out PE and thus, improve the care of patients with AECOPD. Moreover, if the prevalence of PE is shown to be very low in patients with purulent

AECOPD and being low enough to exclude PE without further investigations, this will certainly reduce the need for imaging in ruling out PE and subsequently, reduce the side effects of CTPA.

We acknowledge that this study may have some limitations and that we may face some challenges when conducting it. First, only a certain number of studies on the prevalence of PE in patients with AECOPD have reported the prevalence of PE based on the AECOPD purulence status. The data included in this systematic review may thus represent a limited proportion of all the data available on the prevalence of PE in patients with AECOPD. Second, the definition of the AECOPD purulence status may not be homogenous across studies which could make it more challenging to pool the data. Finally, although we will analyze all patients with AECOPD, there might be some heterogeneity within this population (e.g. patients admitted vs treated as an outpatient).

Improving PE diagnostic algorithm for patients with AECOPD is of high importance to reduce the burden of imaging since PE and AECOPD share similar symptoms, but also to minimize the proportion of missed PE. This systematic review with meta-analysis aims at evaluating if AECOPD purulence status could be a predictor of PE in order to improve the care of patients with COPD.

ACKNOWLEDGMENTS

We want to thank Danielle Morneault for her contribution to this protocol by revising the protocol and approving the design and conduct of the study.

CONTRIBUTORS

VM, FC and GLG conceived the idea and design of this systematic review. VM, LG, KdW, LC, SA, FC, DF and GLG developed the methodology for the protocol of this systematic review. The content of this manuscript was drafted by VM and GLG with input from all members of the authorship team. The manuscript was reviewed by LG, KdW, LC, SA, FC, DF and GLG for important intellectual content. All authors read and approved the final version of the manuscript.

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Medicine, University of Ottawa, and a Clinician-Scientist Award from the Heart and Stroke Foundation of Canada.

COMPETING INTERESTS

VM, LG, KdW, SA, FC and DF do not have conflicts of interest. LC's research institution has received honoraria from Bayer, BMS-Pfizer Alliance, The Academy for Continued Advancement in Healthcare Education, Amag Pharmaceutical, LEO Pharma, Sanofi, Valeo Pharma, and Servier. GLG is a co-investigator for a clinical trial from Pfizer and one from Bristol-Myers Squibb and GLG received honoraria from Pfizer, Sanofi and Aspen Pharma.

REFERENCES

1. Konstantinides SV, Meyer G. The 2019 ESC Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism. *Eur Heart J* 2019;40(42):3453-55. doi: 10.1093/eurheartj/ehz726 [published Online First: 2019/11/08]
2. Hurst JR, Perera WR, Wilkinson TM, et al. Systemic and upper and lower airway inflammation at exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006;173(1):71-8. doi: 10.1164/rccm.200505-704OC [published Online First: 2005/09/24]
3. Sato R, Hasegawa D, Nishida K, et al. Prevalence of pulmonary embolism in patients with acute exacerbations of COPD: A systematic review and meta-analysis. *The American Journal of Emergency Medicine* 2021;50:606-17. doi: https://doi.org/10.1016/j.ajem.2021.09.041
4. Couturaud F, Bertoletti L, Pastre J, et al. Prevalence of Pulmonary Embolism Among Patients With COPD Hospitalized With Acutely Worsening Respiratory Symptoms. *JAMA* 2021;325(1):59-68. doi: 10.1001/jama.2020.23567 [published Online First: 2021/01/06]
5. Jiménez D, Agustí A, Tabernero E, et al. Effect of a Pulmonary Embolism Diagnostic Strategy on Clinical Outcomes in Patients Hospitalized for COPD Exacerbation: A Randomized Clinical Trial. *JAMA* 2021;326(13):1277-85. doi: 10.1001/jama.2021.14846 [published Online First: 2021/10/06]
6. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to Exacerbation in Chronic Obstructive Pulmonary Disease. *New England Journal of Medicine* 2010;363(12):1128-38. doi: 10.1056/NEJMoa0909883
7. Choi KJ, Cha SI, Shin KM, et al. Prevalence and predictors of pulmonary embolism in Korean patients with exacerbation of chronic obstructive pulmonary disease. *Respiration* 2013;85(3):203-09.

8. Dentali F, Pomero F, Micco PD, et al. Prevalence and risk factors for pulmonary embolism in patients with suspected acute exacerbation of COPD: a multi-center study. *European journal of internal medicine* 2020;80:54-59. doi: 10.1016/j.ejim.2020.05.006 [published Online First: 2020/06/01]

9. Liu X, Jiao X, Gong X, et al. Prevalence, Risk Factor and Clinical Characteristics of Venous Thrombus Embolism in Patients with Acute Exacerbation of COPD: A Prospective Multicenter Study. *Int J Chron Obstruct Pulmon Dis* 2023;18:907-17. doi: 10.2147/copd.S410954 [published Online First: 2023/05/24]

10. Connors AF, Jr., Dawson NV, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). *Am J Respir Crit Care Med* 1996;154(4 Pt 1):959-67. doi: 10.1164/ajrccm.154.4.8887592 [published Online First: 1996/10/01]

11. Bajc M, Schümichen C, Grüning T, et al. EANM guideline for ventilation/perfusion single-photon emission computed tomography (SPECT) for diagnosis of pulmonary embolism and beyond. *European Journal of Nuclear Medicine and Molecular Imaging* 2019;46(12):2429-51. doi: 10.1007/s00259-019-04450-0

12. ROBINS-E Development Group (Higgins J MR, Rooney A, Taylor K, Thayer K, Silva R, Lemeris C, Akl A, Arroyave W, Bateson T, Berkman N, Demers P, Forastiere F, Glenn B, Hróbjartsson A, Kirrane E, LaKind J, Luben T, Lunn R, McAleenan A, McGuinness L, Meerpohl J, Mehta S, Nachman R, Obbagy J, O'Connor A, Radke E, Savović J, Schubauer-Berigan M, Schwingl P, Schunemann H, Shea B, Steenland K, Stewart T, Straif K, Tilling K, Verbeek V, Vermeulen R, Viswanathan M, Zahm S, Sterne J). Risk Of Bias In Non-

randomized Studies - of Exposure (ROBINS-E). 2022 [published Online First: Launch version, June 1, 2022]

13. Kohn MA SJ. Sample Size Calculators (website). UCSF CTSI. 2021

APPENDIX F – Manuscript 5

Derivation and validation of a COPD-specific pulmonary embolism diagnostic strategy for patients with COPD and acutely worsening respiratory symptoms

Supplemental file

Table S1. Univariate analyses

Variables	p-value	Missing values$^{\varphi}$ n, (%)
Dichotomous variables		
Sex*	**0.08**	0
Atrial fibrillation on EKG*	**<0.01**	66 (9.0)
Current or prior tobacco smoking*	0.48	4 (0.5)
Weaned tobacco smoking*	**0.08**	60 (8.2)
Cyanosis*	0.51	12 (1.6)
Neuropsychiatric problems*	0.78	4 (0.5)
Lower extremities edema*	0.18	7 (1.0)
Asterixis*	1.00	23 (3.1)
Accessories muscles use at inspiration*	0.65	20 (2.7)
Thoraco-abdominal swinging*	0.91	22 (3.0)
Paradoxical respiration*	0.77	11 (1.5)
Prior AECOPD*	0.45	72 (9.8)
Current antibiotic prior hospitalization*	0.32	NA
≥ 2 antibiotic treatments in the last month prior hospitalization*	0.38	1 (0.1)
COPD treatment*	0.99	0
COPD treatment: short-acting beta2-agonists*	0.12	76 (10.4)
COPD treatment: long-acting beta2-agonists*	0.34	76 (10.4)
COPD treatment: inhaled corticosteroid*	0.29	76 (10.4)
COPD treatment: long term oxygen therapy*	0.73	76 (10.4)
COPD treatment: macrolides*	0.98	76 (10.4)
COPD treatment: short-acting anticholinergic*	0.54	76 (10.4)
COPD treatment: long-acting anticholinergic*	0.28	76 (10.4)
COPD treatment: oral corticosteroid*	0.59	76 (10.4)
COPD treatment: non-invasive ventilation*	0.15	76 (10.4)
COPD treatment: others*	**0.05**	76 (10.4)
Medical immobilization ≥ 3 days in the last 3 months*	0.18	1 (0.1)
Traumatic orthopedic immobilization ≥ 3 days in the last 3 months*	0.30	0
Surgery in the last 3 months*	1.00	2 (0.3)
Travel in the last 3 months*	1.00	3 (0.4)
Varicose veins or venous insufficiency*	0.99	5 (0.7)
Prior VTE*	0.40	1 (0.1)
Heart failure*	0.42	0
Family history of VTE*	0.84	44 (6.0)
PE naturally suspected by the physician*	**<0.01**	0
Clinical signs of PE*	0.58	0
Clinical signs of PE: dyspnea*	0.73	9 (1.2)
Clinical signs of PE: thoracic basolateral pain*	**0.06**	9 (1.2)
Clinical signs of PE: malaise or loss of consciousness*	0.37	9 (1.2)

Clinical signs of PE: hemoptysis*	0.73	9 (1.2)
Clinical signs of PE: right heart failure*	**<0.01**	9 (1.2)
Clinical signs of PE: choc*	0.11	9 (1.2)
Clinical signs of PE: tachycardia*	0.54	9 (1.2)
Clinical signs of DVT	**<0.01**	0
Clinical signs of superficial vein thrombosis*	**0.08**	0
Alternative diagnosis less likely than PE*	**<0.01**	0
Current anticoagulation*	0.80	0
Cancer*	**0.02**	2 (0.3)
Type of AECOPD*	**<0.01**	0
Continuous variables		
Age*	0.05	0
Duration of COPD	0.24	8 (1.1)
Heart rate*	0.43	2 (0.3)
Systolic blood pressure*	0.43	5 (0.7)
Diastolic blood pressure*	0.66	5 (0.7)
Oxygen saturation*	0.32	1 (0.1)
Respiratory frequency*	0.72	232 (31.6)
Weight*	0.77	2 (0.3)
Height*	0.28	5 (0.7)
Body mass index	0.84	5 (0.7)
Glasgow score*	1.00	21 (2.9)
Number of AECOPD in the last 12 months requiring antibiotics/corticosteroids treatment*	0.92	72 (9.8)
D-dimer*	**<0.01**	14 (1.9)
Hemoglobin *	0.12	1 (0.1)
Platelet count*	0.63	4 (0.5)
Activated partial thromboplastin clotting time*	0.19	141 (19.2)
Prothrombin time*	**0.08**	120 (16.3)
Fibrinogen*	0.62	248 (33.8)
Protein C reactive*	0.85	319 (43.5)
Creatinine*	0.34	4 (0.5)
Troponins*	0.29	426 (58.0)
B-type natriuretic protein*	**0.01**	391 (53.3)
Arterial oxygen pressure*	0.31	101 (13.8)
Partial pressure of carbon dioxide*	0.11	101 (13.8)
pH*	**0.07**	103 (14.0)
Forced expiratory volume in the first second (liters)*	0.60	64 (8.7)
Forced vital capacity*	0.76	62 (8.4)

AECOPD: acute exacerbation of chronic obstructive pulmonary disease; COPD: chronic obstructive pulmonary disease; DVT: deep venous thrombosis; EKG: electrocardiogram; PE: pulmonary embolism; VTE: venous thromboembolism; ᵠAmong the 734 patients included in this post-hoc analysis; *Imputation performed for these variables;

Variables in the dataset not evaluated as a predictor in the univariate analysis (ambient air or oxygen needed*, antibiotic prior hospitalization*, medical immobilization ≥ 3 days in the last

month*, traumatic orthopedic immobilization ≥ 3 days in the last month*, surgery in the last month*, travel in the last month*, prior PE*, thrombophilia*, prior systemic disease*, clinical signs of DVT: spontaneous pain of a lower limb*, clinical signs of DVT: provoked pain of a lower limb*, clinical signs of DVT: edema of a lower limb*, clinical signs of DVT: hardened cord*, clinical signs of DVT: local signs of inflammation*, item of the Wells score (personal history of PE or DVT)*, item of the Wells score (surgery or immobilization in the last 4 weeks)*, item of the Wells score (active cancer)*, item of the Wells score (heart rate > 100 beats per minute)*, item of the Wells score (hemoptysis)*, item of the Wells score (signs of DVT)*, item of the Wells score (alternative diagnosis less likely than PE)*, item of the revised Geneva score (age > 65 years old)*, item of the revised Geneva score (prior history of PE or DVT)*, item of the revised Geneva score (surgery or immobilization)*, item of the revised Geneva score (active cancer)*, item of the revised Geneva score (hemoptysis)*, item of the revised Geneva score (spontaneous pain to the calf)*, item of the revised Geneva score (heart rate 75-94 beats per minute)*, item of the revised Geneva score (heart rate ≥ 95 beats per minute)*, item of the revised Geneva score (clinical signs of DVT)*; number of pack-years*, forced expiratory volume in the first second (%)*,

Table S2. Initial 4-item score

Items	Regression coefficients	Points
Presence of clinical signs of DVT	0.92	1.0
Alternative diagnosis less likely than PE	0.68	0.7
pH > 7.35	2.27	2.5
Purulent AECOPD*	-3.16	-3.4

AECOPD: acute exacerbation of chronic obstructive pulmonary disease; DVT: deep venous thrombosis; *Pneumonia included;

Table S3. COPD-specific score (3-item score)

Items	Regression coefficients
Presence of clinical signs of DVT	0.92
Alternative diagnosis less likely than PE	0.76
Purulent AECOPD*	-3.09

AECOPD: acute exacerbation of chronic obstructive pulmonary disease; DVT: deep venous thrombosis; *Pneumonia included;

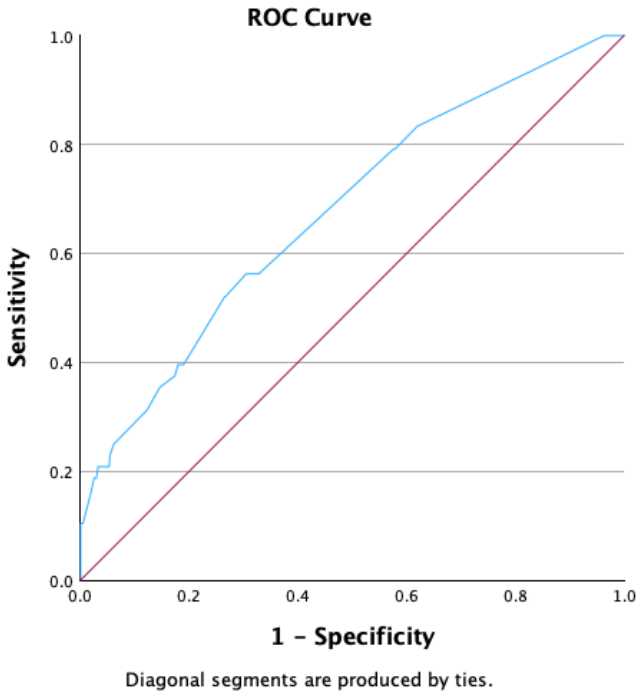


Figure S1. Receiving operating characteristic (ROC) curve for the items of the Wells pulmonary embolism score computed in the derivation cohort (area under the curve: 0.68; 95%CI 0.60-0.76).

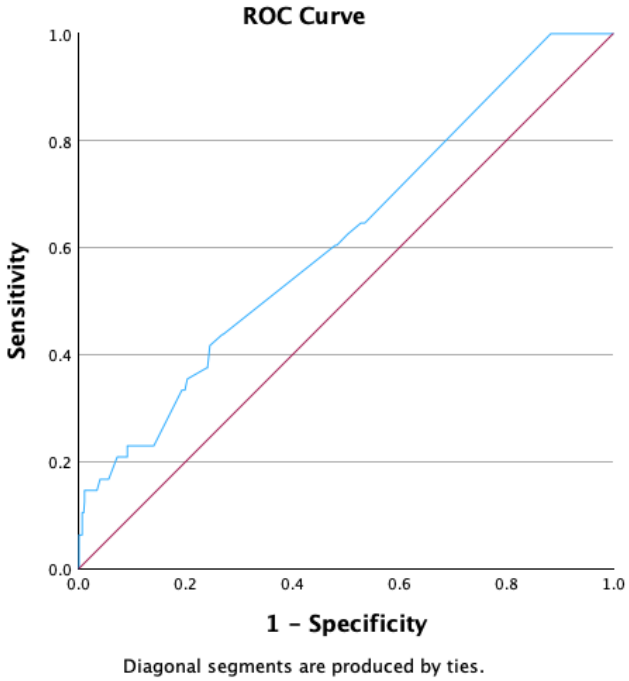


Figure S2. Receiving operating characteristic (ROC) curve for the items of the revised Geneva score computed in the derivation cohort (area under the curve: 0.62; 95%CI 0.54-0.70).

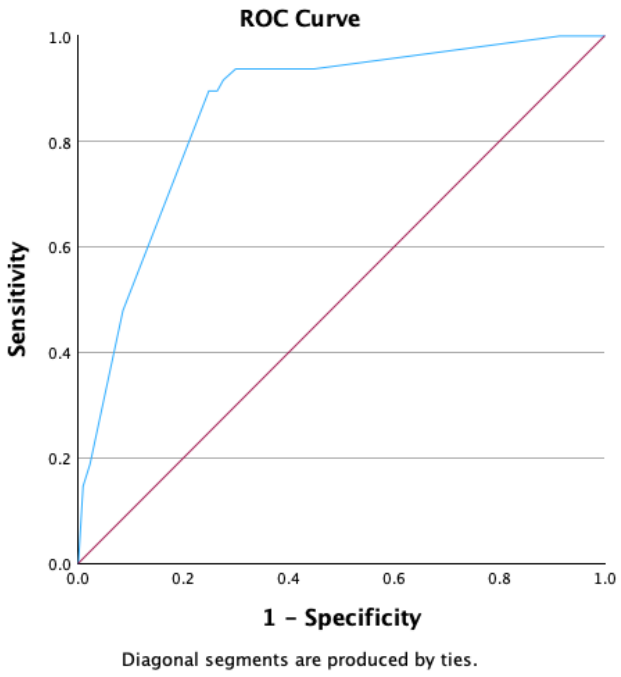


Figure S3. Receiving operating characteristic (ROC) curve of the initial 4-item score computed in the derivation cohort (area under the curve 0.86; 95%CI 0.81-0.91).

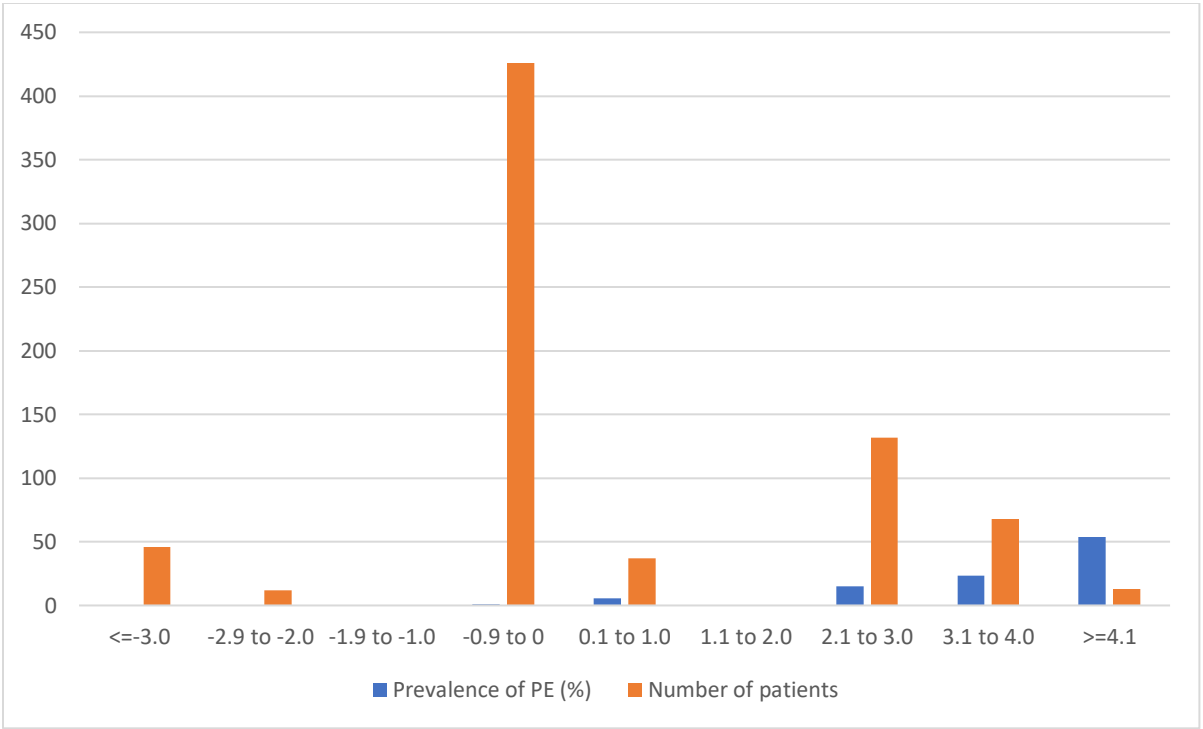


Figure S4. Number of patients and prevalence of pulmonary embolism per clinical pre-test probability groups for the initial 4-items score in the derivation cohort.

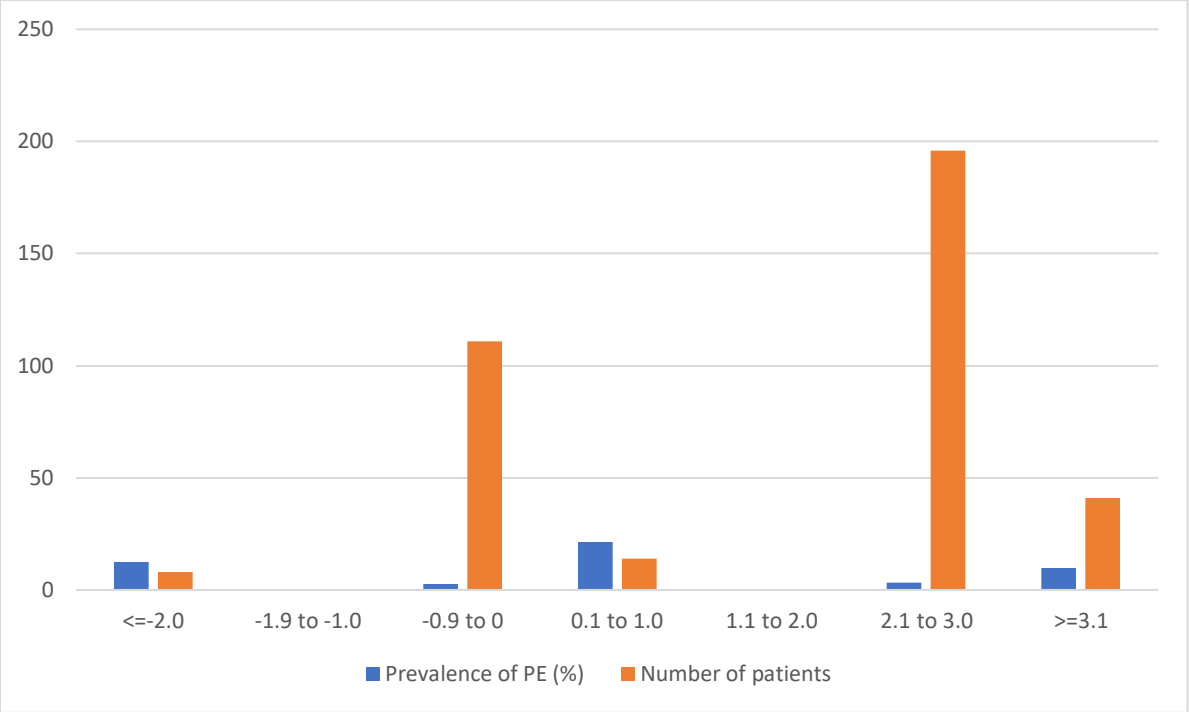
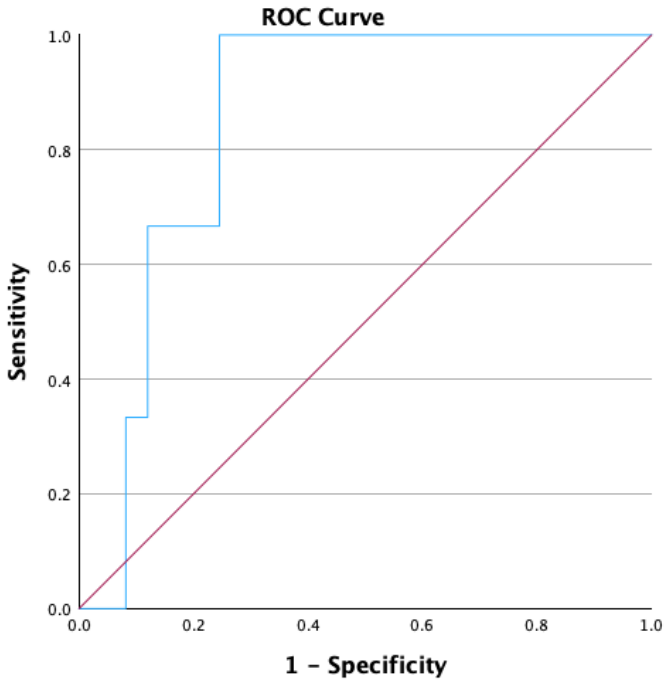
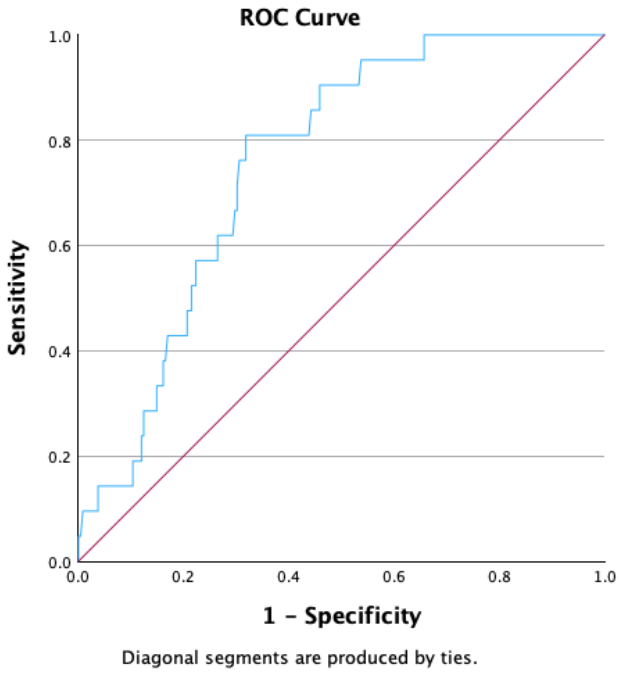


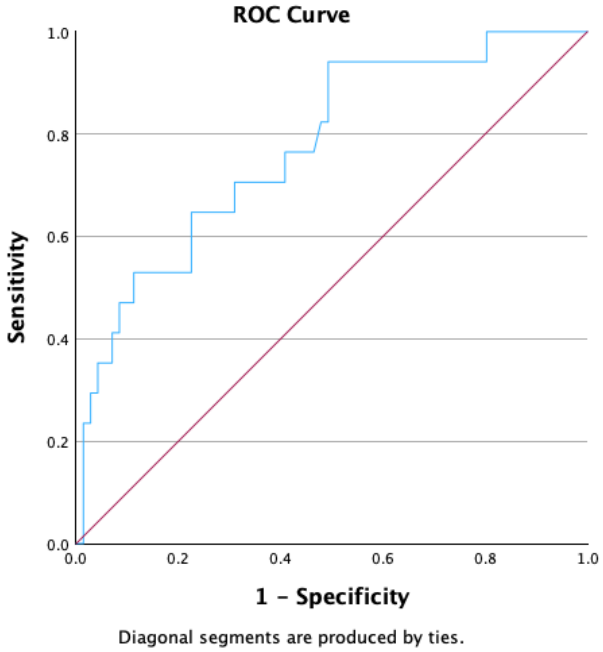
Figure S5. Number of patients and prevalence of pulmonary embolism per clinical pre-test probability groups for the initial 4-items score in the validation cohort.

A.





B.



C.

Figure S6. Receiving operating characteristic (ROC) curve evaluating D-dimer in predicting PE (or isolated proximal DVT) in the A) 0 item group, B) 1 item group and C) 2 items group. Sensitivity was 100% up to a D-dimer level of 1145 mcg/L, 536 mcg/L and 448 mcg/L in the 0, 1 and 2 items groups, respectively.

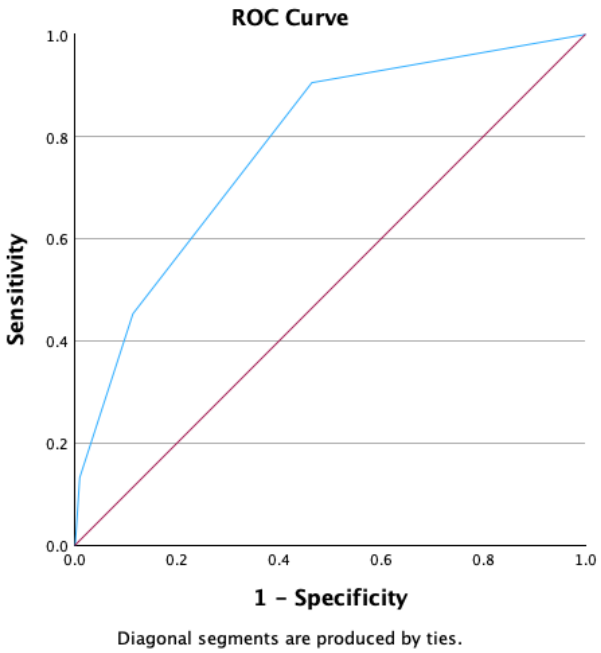


Figure S7. Sensitivity analysis evaluating the receiving operating characteristic (ROC) curve of the chronic obstructive pulmonary disease-specific score (3-item score) computed in the derivation cohort with the predicted outcomes being pulmonary embolism and proximal deep venous thrombosis diagnosed at admission and during the 3-month follow-up (area under the curve: 0.78; 95%CI 0.72-0.84).

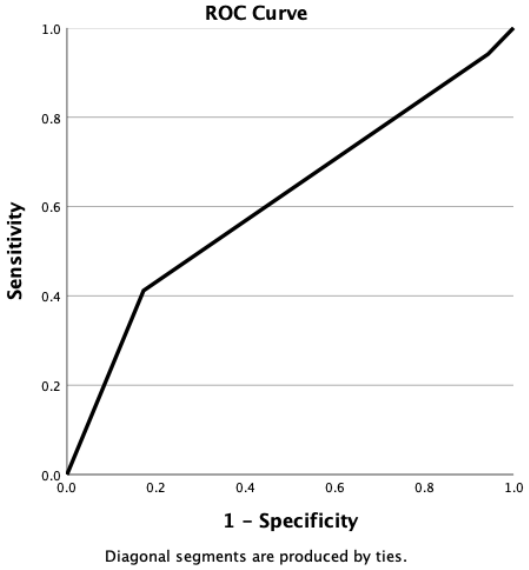


Figure S8. Sensitivity analysis evaluating the receiving operating characteristic (ROC) curve of the chronic obstructive pulmonary disease-specific score (3-item score) computed in the validation cohort with the predicted outcomes being pulmonary embolism and proximal deep venous thrombosis diagnosed at admission and during the 3-month follow-up (area under the curve: 0.61; 95%CI 0.46-0.77).