



Prevalence of Pulmonary Embolism in Acute Exacerbations of COPD* A Systematic Review and Metaanalysis

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Background: Nearly 30% of all exacerbations of COPD do not have a clear etiology. Although pulmonary embolism (PE) can exacerbate respiratory symptoms such as dyspnea and chest pain, and COPD patients are at a high risk for PE due to a variety of factors including limited mobility, inflammation, and comorbidities, the prevalence of PE during exacerbations is uncertain.

Methods: A systematic review of the literature was performed to determine the reported prevalence of PE in acute exacerbations of COPD in patients who did and did not require hospitalization. The literature search was performed using MEDLINE, CINAHL, and EMBASE, and complemented by hand searches of bibliographies. Only cross-sectional or prospective studies that used CT scanning or pulmonary angiography for PE diagnosis were included.

Results: Of the 2,407 articles identified, 5 met the inclusion criteria (sample size, 550 patients). Overall, the prevalence of PE was 19.9% (95% confidence interval [CI], 6.7 to 33.0%; $p = 0.014$). In hospitalized patients, the prevalence was higher at 24.7% (95% CI, 17.9 to 31.4%; $p = 0.001$) than those who were evaluated in the emergency department (3.3%). Presenting symptoms and signs were similar between patients who did and did not have PE.

Conclusions: One of four COPD patients who require hospitalization for an acute exacerbation may have PE. A diagnosis of PE should be considered in patients with exacerbation severe enough to warrant hospitalization, especially in those with an intermediate-to-high pretest probability of PE. (CHEST 2009; 135:786–793)

Key words: COPD; metaanalysis; prevalence; pulmonary embolism

Abbreviations: CI = confidence interval; DVT = deep venous thrombosis; PE = pulmonary embolism; RR = relative risk; \dot{V}/\dot{Q} = ventilation/perfusion; VTE = venous thromboembolism

COPD is a major health burden worldwide. It is the fourth-leading cause of mortality, accounting for > 3 million deaths annually; and by 2020, COPD

will be the third-leading cause of death, trailing only ischemic heart disease and stroke.¹ Most COPD-related deaths occur during periods of exacerbation.^{2,3} Previous studies² estimate that 50 to 70% of all COPD exacerbations are precipitated by an infectious process, while 10% are due to environmental pollution. Up to 30% of exacerbations are caused by an unknown etiology.² Exacerbations are charac-

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For editorial comment see page 592

terized by increase in cough and dyspnea. A study⁴ suggests that patients with COPD have approximately twice the risk of pulmonary embolism (PE) and other venous thromboembolic events (venous thromboembolism [VTE]) than those without COPD. Since thromboembolic events can lead to cough and dyspnea (just like infectious events), PE

may be another common cause of COPD exacerbations.⁵ However, dissimilar to infectious etiologies, which are effectively treated by antimicrobials and systemic corticosteroids, thromboembolic diseases require anticoagulant therapy and significant delays in treatment are associated with poor outcomes.⁶ Owing to multiple perfusion and ventilation abnormalities frequently observed in COPD lungs (even in the absence of VTE), noninvasive diagnosis of PE using imaging modalities was a significant challenge until quite recently. With the advent of contrast-enhanced (multidetector) CT, it is now possible to reliably diagnose PE in COPD subjects with minimal discomfort or risk to the patients. The primary purpose of this review was to determine the reported prevalence of PE in patients with COPD who required hospitalization for their disease.

MATERIALS AND METHODS

Data Searches and Study Selection

A comprehensive literature search for English and French articles was conducted using MEDLINE (1949–April 2008), CINAHL (1982–April 2008), and EMBASE (1980–April 2008). Search terms for VTE, which included “pulmonary embolism,” “PE,” “thromboembolism,” or “venous thromboembolism” were combined with those for COPD, which included “COPD,” “COPD exacerbation,” “emphysema,” and “bronchitis.” This process was complemented by hand searching of bibliographies of retrieved articles to find additional articles that may have been missed during the electronic search.

We limited our search to studies that met the following criteria: (1) estimated the prevalence of PE during exacerbations of COPD; (2) were either cross-sectional or prospective in design; (3) enrolled patients ≥ 18 years old, who did not have another obvious cause for the respiratory deterioration such as sepsis/bacteremia, malignancy, pneumothorax, or myocardial infarction; (4) enrolled patients with COPD diagnosed based on clinical symptoms and spirometry; and (5) employed either contrast-enhanced CT angiography or pulmonary angiography within 48 h of presentation to a health-care service facility. We excluded studies for the following: (1) retrospective design; (2) PE diagnosis strictly based on ventilation/perfusion (\dot{V}/\dot{Q}) scanning, autopsy, or occurrence of deep vein thrombosis (DVT); or (3) published only in abstract form.

Data Extraction

From the retrieved articles, data abstraction was performed, which included the following: study location; date, design, and setting (emergency department, inpatients, outpatients, or ICUs); number of centers involved; number of patients enrolled; mean age; sex; medical history (including malignancy, prior DVT or PE, thrombophilia, recent trauma, surgery, immobilization, paralysis, congestive heart failure, severity of COPD); medication use (especially birth control pills or hormone replacement therapy); pulmonary function test results; arterial blood gas levels; smoking history; use of domiciliary oxygen; family history of DVT or PE; clinical presentation on arrival to a health-care facility (including dyspnea, chest pain, hemoptysis, cough, syncope); physical exam-

ination (including heart rate, respiratory rate, temperature, BP, signs of right ventricular failure, edema of the lower limbs); chest radiographic findings; ECG findings; diagnostic tests for VTE (blood d-dimer levels, lower-leg ultrasound, \dot{V}/\dot{Q} scan, contrast-enhanced CT, or pulmonary angiography), prevalence of DVT and PE; follow-up after discharge; and mortality.

Statistical Analysis

Where possible the prevalence estimates for PE and DVT (collectively referred to as VTE) were combined using the sample size of each retrieved study as weights. *A priori*, we hypothesized that the prevalence of PE and DVT would be higher among patients who were hospitalized than those who were investigated as outpatients or in the emergency departments. We thus classified the studies into two categories: (1) studies that investigated patients who required hospitalization; and (2) studies that investigated patients in the emergency department or as an outpatient. The quality of the included studies were assessed using the Strengthening the Reporting of Observational Studies in Epidemiology⁷ guidelines; *t* tests (with two tails) were used to determine whether the (aggregated) prevalence estimates were $> 0\%$. All analyses were conducted using statistical software (SAS version 9.1; SAS Institute; Cary, NC).

RESULTS

Study Selection

A total of 2,407 articles were identified using the MEDLINE, CINAHL, and Embase search engines; 2,384 articles were excluded because they did not meet the inclusion criteria or were multiple articles from the same cohort. The remaining 23 articles were retrieved for detailed examination. Of these, 11 articles were excluded for the following reasons on further review: (1) they contained a significant selection bias for VTE; (2) they did not employ CT scanning or pulmonary angiography in their diagnostic workup for VTE; (3) they lacked objective diagnosis of COPD (using spirometry); or (4) they employed a retrospective study design. An additional six articles were excluded because they were not original articles, and one study was excluded because it did not contain any prevalence estimates of VTE. This left five articles for analysis. The selection process for this review is summarized in Figure 1.

Characteristics of the Included Studies

The clinical and study characteristics of the selected articles are summarized in Tables 1, 2. Of the five studies,^{8–12} four studies^{8,10–12} were published between 2000 and 2007, and one study⁹ was published in 1992. The total number of patients assessed in these studies was 550, with a range of 31 to 197 subjects per study. Mean age of the patients ranged from 56 to 71 years, and the percentage of male subjects was from 43 to 84%. The studies were conducted in various European countries and the

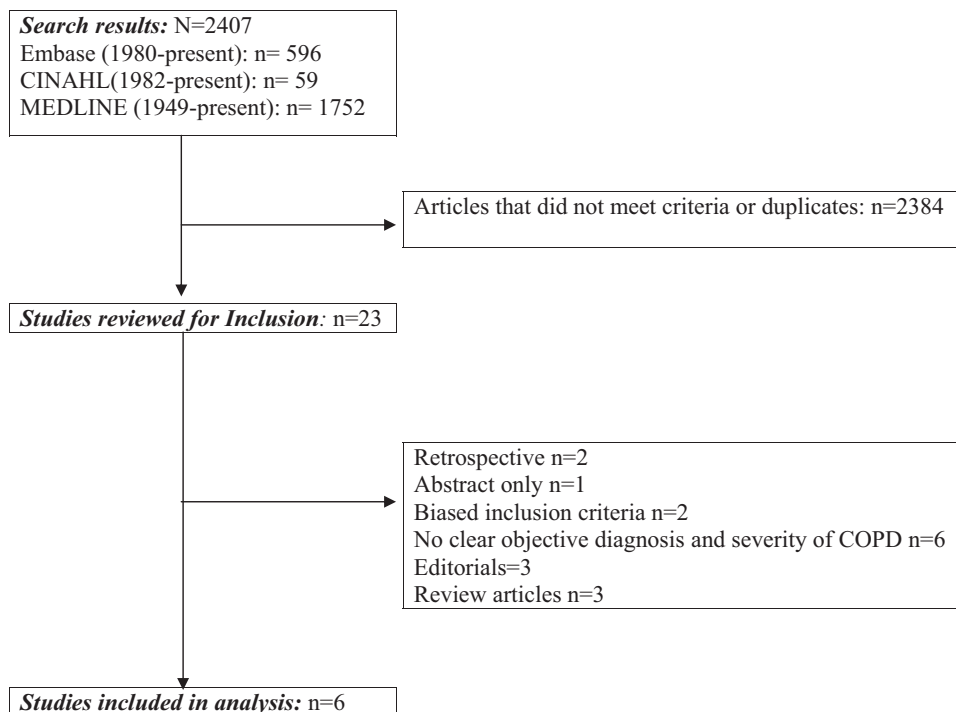


FIGURE 1. Flow diagram of study selection.

United States; two of the studies were conducted in France but at different institutions. The study by Rutschmann et al¹¹ was the only study that investigated the prevalence of PE in COPD patients presenting to the emergency department, while the remaining four studies evaluated patients who were hospitalized. The two studies^{8,9} also included patients presenting in the outpatient department with an exacerbation of COPD.

Prevalence of VTE During COPD Exacerbations

The prevalence estimates for VTE for each of the study are summarized in Table 1. Overall, the prevalence of PE in these studies was 19.9% (95% confidence interval [CI], 6.7 to 33.0%; $p = 0.014$). In a sensitivity analysis, we excluded the largest of the study (*ie*, Tillie-Leblond et al¹²) and found that the overall prevalence of PE was similar at 17.0% ($p = 0.072$), although no longer significant owing to a smaller sample size. In the four studies that included hospitalized COPD patients, the prevalence was higher at 24.7% (95% CI, 17.9 to 31.4%; $p = 0.001$). The one study¹¹ that included only patients in the emergency department had a lower prevalence of PE (3.3%) [Fig 2]. In the two studies that exclusively evaluated patients who were hospitalized for COPD exacerbation,^{10,12} the prevalence of PE was 25.5% (95% CI, 8.1 to 43.0%; $p = 0.034$).

In the two studies that included both inpatients and outpatients with a COPD exacerbation, the prevalence of PE was slightly lower at 23.6% (95% CI, – 39.7 to 86.9%; $p = 0.133$).^{8,9} In general, the prevalence of DVTs was lower than that of PE. The overall prevalence estimate of DVT was 12.4% (95% CI, – 2.2 to 27.1%; $p = 0.074$). The prevalence was higher in the group that evaluated hospitalized patients (prevalence estimate, 16.6%; 95% CI, 1.1 to 32.1%; $p = 0.044$).

Prevalence of Risk Factors for VTE

The prevalence of risk factors for VTE in each of the studies is summarized in Table 2. Three studies^{9,10,12} reported VTE risk factors in patients with and without PE. Tillie-Leblond et al¹² found that COPD patients with PE were more likely to have a history of VTE (relative risk [RR], 2.43; 95% CI, 1.49 to 3.49) or malignancy (RR, 1.82; 95% CI, 1.3 to 2.92) compared to COPD patients without PE. Overall, the prevalence of VTE risk factors was lower among patients who presented to an emergency department than those who required hospitalization. The prevalence of previous VTE, surgery, and cancer was 3%, 2%, and 5%, respectively, in the study by Rutschmann et al.¹¹ In contrast, it was 14%, 13%, and 10%, respectively, in the study by Hartmann et al.⁸

Table 1—Characteristics of Individual Studies Included in This Review

Study	Study Date	Country	Patients, No.	Setting	No. of Centers	Diagnostic Modality	PE, %	DVT, %	Important Issues	STROBE* Quality Score (Maximum Score Is 22) ⁷
Tillie-Leblond et al ¹²	April 1999 to December 2002	France	197	Inpatients	1	Lower-leg ultrasound**; spiral CT angiography**	25	12.69	High rate of malignancy (29%); criteria for PE diagnosis†; only included severe COPD exacerbation‡	22
Rutschmann et al ¹¹	February 2003 to December 2004	Switzerland	123	Emergency department	2	d-Dimer**; lower-leg ultrasound**; spiral CT angiography**	3.30	1.63	Criteria for PE diagnosis§; included moderate and severe COPD exacerbation	21
Mispelaere et al ¹⁰	May 1998 to April 1999	France	31	Inpatients	1	d-Dimer**; lower-leg ultrasound**; spiral CT angiography**; pulmonary angiography**	29	25.81	Excluded patients with negative d-dimer; patients with moderate-to-severe COPD exacerbation¶	20
Lesser et al ⁹	January 1985 to September 1986	United States	108	Inpatients and outpatients	6	V/Q scan**; pulmonary angiography**; autopsy (in one patient)	19	Not available	Patients with mild-to-severe COPD exacerbation#;	19
Hartmann et al ⁸	May 1997 to March 1998	Netherlands	91	Inpatients and outpatients	6	d-Dimer**; lower-leg ultrasound**; V/Q scan††; spiral CT angiography††; pulmonary angiography	29	21.98	Pulmonary function tests done only in 39.8% of patients Possibility of patients misclassified as COPD; severity of COPD not documented	21

*Strengthening the Reporting of Observational Studies in Epidemiology.⁷

†Six patients with PE based on positive DVT result but negative spiral CT chest result.

‡Severity of COPD exacerbation was defined as acute deterioration from a stable condition that required hospitalization. Severity according to American Thoracic Society criteria: grade 1: FEV₁ > 50% of predicted (66 patients; 41%); grade 2: FEV₁ from 35 to 50% of predicted (67 patients; 42%); grade 3: FEV₁ < 35% of predicted (27 patients; 17%).

§Excluded patients with blood d-dimer < 500 µg/L.

||Severity of COPD exacerbation based on Global Initiative for Chronic Obstructive Lung Disease: very severe, 35 patients (28%); severe, 61 patients (50%); moderate, 27 patients (22%).

¶Severity of COPD exacerbation reported as FEV₁ (mean FEV₁ was 33.9% (SD, 8.4%) in patients with PE, vs 40.9% (SD, 16.1%) in patients without PE.

#Severe COPD exacerbation was defined as FEV₁ < 50% (42% of patients), moderate as FEV₁ 50 to 64% (26% of patients), and mild as FEV₁ 65 to 80% (19% of patients).

**Investigation conducted on all enrolled patients.

††If perfusion defects are present, ventilation scintigraphy then spiral CT angiography regardless of results.

‡‡Pulmonary angiography if spiral CT result is negative.

Table 2—Clinical Characteristics and Risk Factors of VTE in Patients With Exacerbations of COPD With and Without PE

Study	Men, %	Mean Age, yr	Previous VTE, %		Surgery, %		Cancer, %		Immobility/Travel History, %		Statistically Significant Differences Between Patients With and Without PE
			With PE	Without PE	With PE	Without PE	With PE	Without PE	With PE	Without PE	
Tillie-Leblond et al ¹²	83.76	60.5	25	7.43	4	2.03	43	24.32	10	4.73	Previous VTE (RR, 2.43; 95% CI, 1.49–3.49); malignancy (RR, 1.82; 95% CI, 1.13–2.92); decrease in PaCO ₂ of at least 5 mm Hg (RR, 2.1)
Rutschmann et al ¹¹	68	71	3*		2*	5*	16*				Chest pain, syncope, absence of purulent sputum or cough; severe hypoxemia
Mispelaere et al ¹⁰	83.87	69.9	22.22†	18.18†	0†	0†	11.11†	9.09†	11.11	22.7†	Worse hypoxemia with a decrease in PaO ₂ of 21.8 mm Hg (SD 8.5) vs 8.9 mm Hg (SD 10.6)
Lesser et al ⁹	45	56.1	14†	6†	33†	24†	10†	14†	43†	41†	No difference in clinical, chest radiographic or arterial blood gas results between the two groups
Hartmann et al ⁸	43	65	14*		13*	10*					Not available

*Overall prevalence in COPD patients with and without PE.

†No statistical significance.

Clinical Presentation of COPD Patients Who Did and Did Not Have PE

Three studies^{9,11,12} compared symptoms on presentation in COPD patients with and without PE. Tillie-Leblond et al¹² and Lesser et al⁹ failed to find significant differences in the occurrence of dyspnea, chest pain, hemoptysis, cough, or palpitations between these two groups. However, Rutschmann et al¹¹ found that patients with PE were more likely to complain of chest pain, syncope, and less likely to report cough or purulent sputum. In that study,¹¹ approximately 28% of the patients presented with chest pain (42% in those with PE and 19% in those without PE [p = 0.008]). The chest pain was described as pleuritic (in 50% of the cases), oppressive (in 6% of the cases), reproduced by palpation (in 2% of the cases), and nonpleuritic (in 7% of the cases). The presence of cough was less frequent when PE was suspected (75% vs 93%, p = 0.009). Syncope was the presenting complaint in 6% of patients with PE, but none presented with syncope if they did not have PE (p = 0.051). In general, there were no significant differences in the physical examination findings between patients who did and did not have PE. Similarly, chest radiographic and ECG findings were similar between the two groups. The findings on arterial blood gas levels were discordant. Tillie-Leblond et al¹² noted a decrease in PaCO₂ of at least 5 mm Hg from baseline in patients with PE (RR, 2.10; 95% CI, 1.23 to 3.58). However, this was not shown in other studies.^{9,10} Similarly, severity of hypoxemia was shown to be a risk factor for PE in two studies^{10,11} but not in another study.¹²

Other Considerations

There were some important differences in other characteristics between the studies. For instance, in the study by Tillie-Leblond et al,¹² the rate of malignancy was 29%, while it was 5% in the study by Rutschmann et al,¹¹ 10% in the study by Hartmann et al,⁸ 10% in the study by Mispelaere et al,¹⁰ and 13% in the study by Lesser et al.⁹ There were also differences in the way PE was investigated between the studies. The case definition of PE in one study was a positive result on a contrast-enhanced CT angiogram or a positive finding on a lower-leg ultrasound.¹² In this study, the diagnosis of a PE was made in six patients who had a positive lower-limb ultrasound results but negative contrast-enhanced CT chest results. When these six patients are excluded, the rate of PE in this study decreased from 25 to 22%. Rutschmann et al¹¹ and Mispelaere et al,¹⁰ however, excluded patients with a negative d-dimer test result,

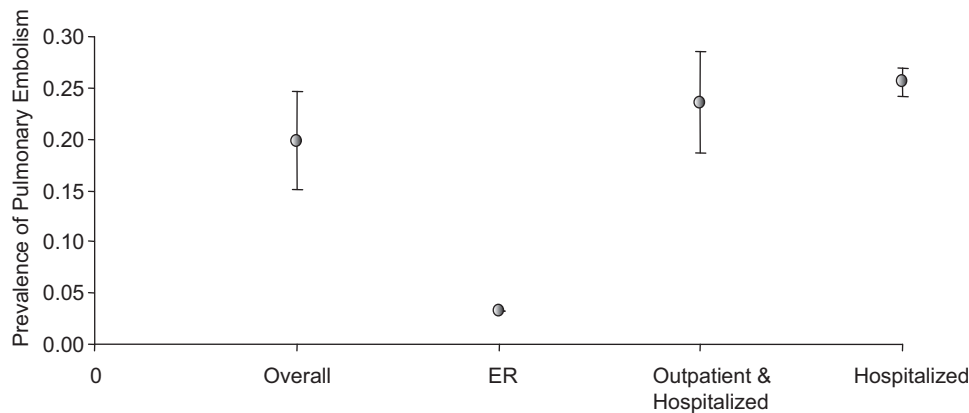


FIGURE 2. The prevalence of PE across different sites. The filled circles represent the mean, and the line bars represent SE; p value for overall = 0.014; p value for emergency department (ER) is not calculable because there was only one study; p value for studies that evaluated inpatients and outpatients = 0.133; p value for studies that evaluated only hospitalized patients = 0.034.

which may have led to an underdiagnosis of PE. Finally, the severity of the underlying COPD differed across the studies.

DISCUSSION

The most important finding of our study was the relatively high prevalence of PE among patients who required hospitalization for acute exacerbations of COPD. Overall, one of four COPD patients who were hospitalized and investigated for VTE had objective evidence for PE requiring anticoagulant therapy. While striking, these data should be interpreted cautiously owing to the heterogeneity in the design, the setting, and enrollment criteria among the included studies.

Because symptoms of PE may be nonspecific, clinical prediction rules are used to reduce the need for imaging. Of the studies that were assessed, only one study¹² applied a validated clinical prediction rule (*ie*, a Geneva score¹³) to determine the pretest probability of PE. It found that even patients in the low-risk category (a Geneva score ≤ 4) had a substantive prevalence of PE (approximately 9%), although the prevalence was lower compared to those in the intermediate-risk category (a score of 5 to 8; 38% prevalence) or high-risk category (a score ≥ 9 ; 46% prevalence). These data suggest that the Geneva risk scores may not be optimal in risk stratifying COPD patients for PE. Alternative instruments include the Wells criteria,¹⁴ and the decision rule developed by Miniati et al,¹⁵ although none of these have been well validated in COPD patients during exacerbations. Despite these shortcomings, the judicious use of these validated instruments in the context of a careful clinical and laboratory assessment may be helpful in avoiding unnecessary imaging studies.

Interestingly, we found that the prevalence of DVT was lower than that of PE in the same population. Although imaging techniques such as spiral CT scans are sensitive in detecting a filling defect in pulmonary arteries, a clear separation between *in situ* thrombosis and embolism (from peripheral veins) is not always possible. In one study¹⁶ of 27 consecutive patients with stable COPD (mean FEV₁, 52% of predicted) who did not have any history of VTE, transesophageal echocardiography revealed a lesion in central pulmonary arteries consistent with a thromboembolic event in 48% of these patients. Seventy-five percent of these lesions were flat or rounded and totally adherent to the right pulmonary artery, suggesting *in situ* thrombosis (rather than an embolic phenomenon). These findings in conjunction with data from the present study, which indicates a higher rate of PE than that of DVT raise the possibility that some of the PE cases may represent *in situ* thrombosis. This hypothesis will need to be validated in a prospective study.

There are several salient caveats to our findings. Firstly, all of the studies included in this analysis had relatively small sample sizes, making the prevalence estimates unstable. However, in studies that included hospitalized patients, the lower limit of the 95% CI was 18%, which suggests that even using a conservative approach, PE is likely to be common in acute exacerbations. Notably, there was one study¹¹ that evaluated patients in the emergency department and found a PE prevalence of 3.3%. Since patients requiring hospitalization are generally sicker, frailer, and have more comorbidities than those who do not, these findings suggest that other risk factors such as prolonged immobilization, cardiovascular disease, and cancer play important roles in the risk of PE during acute exacerbations.¹⁷ Secondly, there are major clinical factors that modulate the risk for VTE,

and these factors could not be adequately evaluated in our study. For instance, one study¹⁰ excluded subjects with low d-dimer levels, while another study¹² had an extraordinary high rate of malignancy in the population. Not surprisingly, the highest occurrence of VTE was observed in these two studies. It should also be noted that blood d-dimer levels have a high negative but a low positive predictive value for PE in COPD exacerbations because a multitude of different inflammatory and infectious etiologies can cause blood d-dimers to rise.¹⁸

Notwithstanding these limitations, our findings may have some management implications for patients with COPD who require hospitalization. The standard in-hospital management of COPD exacerbations consists of bronchodilators, systemic corticosteroids, antimicrobials, and occasionally noninvasive mechanical ventilation.¹⁹ While subcutaneous heparin may be administered in “prophylactic” doses, therapeutic doses are not routinely provided unless VTE is diagnosed. PEs are associated with high morbidity and mortality with a 3-month mortality rate of 15 to 18% even with adequate anticoagulant therapy.²⁰ In COPD patients, the risk of mortality nearly doubles.²⁰ Any delays in the diagnosis of PE or initiation of treatment significantly amplifies the risk of mortality.⁶ In view of the high prevalence of VTE in COPD patients who require hospitalization and the mortality risk associated with undiagnosed VTE, PE should be carefully considered especially in those who have an intermediate-to-high pretest probability of PE based on clinical assessment.

Our study findings also highlight the urgent need for a large-scale, multicenter study to evaluate the prevalence of VTE in COPD patients who do and do not require hospitalization. While systematic reviews and metaanalyses are useful tools to synthesize the existing body of evidence, they cannot substitute findings from well-conducted, large (multicenter) clinical studies.²¹ Given the therapeutic and prognostic importance of a prompt diagnosis of PE during exacerbations, there is a pressing need to determine the prevalence as well as the clinical manifestations of PE-related exacerbations in patients with COPD. In the meantime, our study findings suggest that one in four patients with an acute exacerbation of COPD may have PE. Thus, clinicians should consider PE in the diagnostic workup of COPD exacerbations, especially in patients where the underlying etiology is not apparent and in whom there is a history of malignancy or other additional risk factors that may increase the clinical likelihood of PE.

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