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Pulmonary Embolism in Patients with Unexplained Exacerbation of Chronic Obstructive Pulmonary Disease: Prevalence and Risk Factors

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Background: Diagnosis of pulmonary embolism (PE) is difficult in patients with chronic obstructive pulmonary disease (COPD) and exacerbation.

Objective: To evaluate PE in patients with COPD and exacerbation of unknown origin and explore factors associated with PE.

Design: Prospective cohort study.

Setting: University-affiliated hospital in France.

Patients: 211 consecutive patients, all current or former smokers with COPD, who were admitted to the hospital for severe exacerbation of unknown origin and did not require invasive mechanical ventilation.

Measurements: Spiral computed tomography angiography (CTA) and ultrasonography within 48 hours of admission and assessment of the Geneva score. Patients were classified as PE positive (positive results on CTA or negative results on CTA and positive results on ultrasonography) or PE negative (negative results on CTA and negative results on ultrasonography or negative results on CTA and no recurrence of PE at follow-up 3 months later).

Results: 49 of 197 patients (25% [95% CI, 19% to 32%]) met the diagnostic criteria for PE. Clinical factors associated with PE were previous thromboembolic disease (risk ratio, 2.43 [CI, 1.49 to 3.94]), malignant disease (risk ratio, 1.82 [CI, 1.13 to 2.92]), and decrease in $Paco_2$ of at least 5 mm Hg (risk ratio, 2.10 [CI, 1.23 to 3.58]). A total of 9.2% (CI, 4.7% to 15.9%) of patients with a low-probability Geneva score received a diagnosis of PE. An exploratory analysis suggested that substituting malignant disease for recent surgery in the Geneva score might improve its performance in excluding PE in this sample who were more likely to have malignant disease than to have had recent surgery. However, this improvement seems insufficient to exclude PE with enough certainty to withhold therapy for low-risk patients on the basis of the modified score.

Limitations: This study was done in only 1 center. Patients with COPD requiring invasive mechanical ventilation in the intensive care unit were not included. The upper bound of the 95% CI for the low probability of PE according to the Geneva score is too high to rule out PE. The classification of COPD exacerbation of unknown origin was based on the clinician's assessment, not on a standard evaluation for all patients.

Conclusion: This study showed a 25% prevalence of PE in patients with COPD hospitalized for severe exacerbation of unknown origin. Three clinical factors are associated with the increased risk for PE. The Geneva score and the modified Geneva score should be prospectively evaluated in patients with COPD.

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The management of patients with suspected acute pulmonary embolism (PE) has greatly improved in recent years because of clinical assessment of the probability of PE, pretest probability, ultrasonography, ventilation–perfusion scanning, and spiral computed tomography angiography (CTA) (1, 2). However, clinical diagnosis of acute PE is difficult in patients with chronic obstructive pulmonary disease (COPD). Pulmonary embolism resembles COPD exacerbation so closely that these 2 entities are often impossible to distinguish clinically (3). The reported incidence of PE in studies done postmortem of patients with COPD ranges from 28% to 51% (4, 5). Pulmonary embolism is known to increase the rate of death from COPD at 1 year (6), but the clinical probability of PE and the value of noninvasive tests to rule out the diagnosis in patients with COPD have not yet been clearly assessed. To date, 2 studies have evaluated PE in patients with this disorder (3, 7). In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, Lesser and colleagues (3) examined the characteristics of 108 patients with COPD and suspected PE; 21 (19%) received diagnoses of PE by pulmonary angiography. In this population, risk factors, symptoms, and arterial blood gas values were similar in patients with and without PE. The second study (7) showed that the presence of COPD does not affect the diagnostic performance of D-dimer testing, CTA, or pulmonary angiography for PE (7). The true frequency of PE in patients with COPD in whom PE is clinically suspected ranges from 19% to 29% (3, 7–9). Thus, clinical detection of PE in these patients is particularly difficult. In this study, we prospectively evaluated PE in patients with COPD exacerbation of unknown origin and examined factors associated with the presence of PE, including the Geneva score (1).

METHODS

Study Objectives

The objectives of our study were to assess the presence of PE in patients with COPD exacerbation of unknown

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origin and to explore factors associated with the presence of PE, including the Geneva score.

Study Group

Between April 1999 and December 2002, all consecutive patients with COPD referred to the Lung Department at the 59-bed Lille University Hospital for severe exacerbation of unknown origin were assessed for PE. Chronic obstructive pulmonary disease was diagnosed and its severity was determined according to the criteria of the American Thoracic Society (10). All patients smoked or were former smokers. Patients with asthma were not included in the study. Severe exacerbation was defined as acute deterioration from a stable condition that required hospitalization. The absence of a lower respiratory tract infection (increased sputum volume and/or increased sputum purulence, fever, history of cold, and sore throat); absence of pneumothorax and iatrogenic intervention; presence of parenchymal condensation without fever and chills; or presence of a discrepancy between clinical and radiologic features and hypoxemia severity classified the exacerbation as of "unknown origin." Physicians were required to discuss each case of COPD with 1 of the referring physicians. Patients requiring invasive mechanical ventilation were referred to the intensive care unit and were not included in the study.

Intervention

All patients were examined within 48 hours of admission to the hospital and had spiral CTA of pulmonary circulation and color Doppler and venous lower-limb ultrasonography. These are the first-line diagnostic tests for acute PE at our institution. The decision to perform additional examinations, including D-dimer determination and ventilation–perfusion scanning, was left to the discretion of the attending physician.

Our local ethics committee approved the study protocol, which did not require informed patient consent.

Spiral CTA

In 1999, spiral CTA of pulmonary circulation was performed with a 5Somaton Plus 4A (Siemens Medical Systems, Forchheim, Germany) using a collimation of 3 mm × 3 mm, a pitch of 2, and a scanning time of 0.75 second per revolution. The results were read during the clinical work-up as previously described (9, 11–13). Because the equipment at our institution was upgraded during this study, spiral CTA of pulmonary circulation between January 2000 and December 2002 was performed with a multislice spiral computed tomography (CT) scanner, using a collimation of 4 mm × 1 mm, a pitch of 2, and a rotation time of 0.5 second. All patients with negative results on spiral CTA had a 3-month follow-up visit after inclusion in the study to assess critical events that were potentially related to PE. A chest physician reported death, subsequent admission to the hospital, new symptoms, and use of anticoagulant medications.

Context

Pulmonary embolism (PE) is common in patients with chronic obstructive pulmonary disease (COPD) exacerbations, and the 2 conditions present similarly.

Content

For 45 months, every patient presenting with severe COPD exacerbation of unknown cause received an evaluation for PE that included a spiral computed tomography scan and color Doppler ultrasonography of the legs. Twenty-five percent of 197 patients had PE. Malignant disease, history of thromboembolism, and a decrease in $Paco_2$ level relative to baseline were the only factors associated with PE.

Cautions

This was a single-center study.

Implications

We need additional studies to confirm the high prevalence of PE in unexplained severe exacerbations of COPD and to study the value of routine testing for PE in patients with this clinical presentation.

—The Editors

Ultrasonography

Venous compression ultrasonography of both legs was done from the common femoral vein and including the calf vein. Lack of compressibility was considered to indicate deep venous thrombosis.

Definition

Patients were classified as PE positive (positive results on spiral CTA or negative results on spiral CTA and positive results on ultrasonography) or PE negative (negative results on spiral CTA and negative results on ultrasonography or negative results on spiral CTA and no recurrence of PE at follow-up 3 months later).

Assessment of the Geneva Score

Because the Geneva score (1) was published by the time our study ended in 2001, we evaluated this score a posteriori in our sample before reviewing the data on PE. The probability of PE was expressed as low (a score ≤ 4), intermediate (a score of 5 to 8), or high (a score ≥9) (**Table 1**) (1).

Statistical Analysis

Statistical analysis was done by using Epi Info software, version 3.3.2 (Centers for Disease Control and Prevention, Atlanta, Georgia), and CIs were calculated with StatExact and Stata, version 7 (Stata Corp., College Station, Texas). We calculated risk ratios and exact CIs for the various risk factors and clinical symptoms and determined *P* values using the Fisher exact test. A *P* value less than 0.05 indicated statistical significance.

Role of the Funding Source

No funding was received for this study.

RESULTS

Study Group

A total of 211 consecutive patients with COPD were referred for severe exacerbation of unknown origin. Fourteen patients were not included in the study because the results of the spiral CTA and ultrasonography were inconclusive (8 patients) or because of iodine intolerance (6 patients). Thus, the study group included 197 patients with COPD and severe exacerbation of unknown origin. There were 165 men and 32 women, and their mean age was 60.5 years (SD, 12.1). A total of 136 patients (69%) were referred from the emergency department, and 61 (31%) were inpatients who developed severe exacerbation while hospitalized. Arterial blood gas values on room air were 61.9 mm Hg (SD, 10.9) for Pa_{O_2} and 42 mm Hg (SD, 9) for Pa_{CO_2}. The mean number of risk factors for PE per patient was 0.87 (SD, 0.7).

In 160 of the 197 study patients, results of a pulmonary function test performed within 3 months of the severe exacerbation were available. The mean FEV_1 was 1.56 L (SD, 0.6), 52% (SD, 19%) of the predicted value. The mean FEV_1–vital capacity ratio was 56.4% (SD, 14.8%). The severity of respiratory disease was assessed according to the criteria of the American Thoracic Society (10): grade I, FEV_1 greater than 50% of the predicted value (66 patients [41%]); grade II, FEV_1 between 35% and 50% of predicted (67 patients [42%]); and grade III, FEV_1 less than 35% of predicted (27 patients [17%]). Forty-nine (25%) patients were receiving long-term oxygen therapy.

Table 1. **The Geneva Score and the Modified Geneva Score***

Variable	Score
Age	
60–79 y	1
>79 y	2
Previous PE or deep venous thrombosis	2
Recent surgery (replaced by malignant disease in the modified Geneva score)	3
Pulse rate >100 beats/min	1
$Paco_2$	
<36 mm Hg	2
36–39 mm Hg	1
Pao_2	
<50 mm Hg	4
50–60 mm Hg	3
61–72 mm Hg	2
73–83 mm Hg	1
Findings on chest radiography	
Platelike atelectasis	1
Elevation of hemidiaphragm	1

* The original Geneva score is discussed in reference 1. A score of 0 to 4 indicates low risk for PE, a score of 5 to 8 indicates intermediate risk, and a score of 9 to 16 indicates high risk. PE = pulmonary embolism.

Table 2. **Results of Spiral Computed Tomography Angiography in Patients Initially Referred for Suspected Acute Pulmonary Embolism***

Symptoms	Patients with COPD (n = 197)
Presence of PE, *n (%)*	43 (22)
Central, *n (%)*	20 (46)
Segmental, *n (%)*	21 (49)
Isolated subsegmental, *n (%)*	2 (5)
Absence of PE, *n (%)*	154 (78)
CT scan negative to the segmental level, *n*	84
CT scan negative to the subsegmental level, *n*	70

* COPD = chronic obstructive pulmonary disease; CT = computed tomography; PE = pulmonary embolism.

Pulmonary Embolism

All patients had spiral CTA (37 patients had a single-slice CT scan, and 160 had a multislice CT scan), and 180 had venous ultrasonography (**Table 2**). None of the 197 study patients were thought to have clinical recurrence of PE during the 3 months of follow-up. Forty-three patients had positive results on CT. Twenty-five patients had deep venous thrombosis on ultrasonography; of these patients, 6 had negative results on spiral CTA. Nineteen (44%) of the 43 patients with positive results on spiral CTA also had positive results on ultrasonography. One hundred forty-eight patients did not have PE, on the basis of negative results on CT and ultrasonography and negative findings at 3-month follow-up. Thus, the prevalence of PE in our study group was 49 of 197 patients (25% [95% CI, 19% to 32%]).

Clinical Characteristics according to the Presence or Absence of Pulmonary Embolism

The 49 patients with COPD who had PE did not differ statistically significantly from the 148 patients with COPD who did not have PE in terms of referral location (data not shown). We performed a bivariate analysis of baseline characteristics (**Table 3**) and clinical characteristics at admission (**Table 4**) that were potentially associated with PE. Clinical symptoms, such as change in dyspnea, pleuritic pain, hemoptysis, tachycardia (pulse rate >100 beats/min), and edema of the lower limbs, were not associated with PE. The need for long-term oxygen therapy was not associated with PE. At admission, the level of hypoxemia on arterial blood gas, with a cutoff of 50 mm Hg (risk ratio, 0.96 [CI, 0.5 to 2]; $P = 1.0$) or 60 mm Hg (**Table 4**), was not associated with PE. The level of Pa_{CO_2} on arterial blood gas at admission, with a cutoff of 36 mm Hg (risk ratio, 1.14 [CI, 0.64 to 2.02]; $P = 0.68$) or 39 mm Hg (**Table 4**), was not associated with PE. Recent trauma or surgery was not identified as a risk factor, but both events were rare in our patients.

In contrast, a decrease in $PaCO_2$ of at least 5 mm Hg from baseline values (risk ratio, 2.1 [CI, 1.23 to 3.58]; $P = 0.034$), previous thromboembolic disease (risk ratio, 2.43 [CI, 1.49 to 3.94]; $P = 0.004$), and malignant disease (risk ratio, 1.82 [CI, 1.13 to 2.92]; $P = 0.018$) were associated with PE (**Tables 3** and 4).

Evaluation of the Geneva Score

According to the Geneva score (1), 119 (60%) patients had a low probability of PE (a score ≤4); of these, 11 (9%) had confirmed PE. Seventy-five patients (38%) had an intermediate probability of PE (a score of 5 to 8); of these, 35 (46%) had confirmed PE. All 3 patients (100%) with a high probability of PE (a score ≥ 9) had confirmed PE.

As expected, the age and smoking habits of our study sample accounted for a high rate of underlying malignant disease (29%). Twenty patients had lung cancer, 7 had breast cancer, 5 had bowel cancer, 2 had gastric cancer, 11 had prostate cancer, 8 had head and neck cancer, and 4 had other types of cancer. We recalculated the Geneva score by replacing "surgery" with "associated underlying malignant disease" (**Table 5**). This modification was exploratory and was developed after reviewing the study data.

DISCUSSION

In this study, we showed that the frequency of PE was 25% in a series of 197 consecutive patients with COPD referred for severe exacerbation of unknown origin. This is similar to the value of 27% reported in the Geneva study (1). In contrast with the clinical scores recently developed for diagnosing PE in unselected patients, the Geneva score (1) and the score reported by Wells and colleagues (2), we found that only 3 factors predicted PE: history of thromboembolism, malignant disease, and a decrease in $PaCO_2$ of at least 5 mm Hg. Recent surgery, which was rare in the patients in our study group, was not identified as a risk factor for PE. Conversely, the clinical symptoms supporting the suspicion of PE, such as hemoptysis, chest pain, and edema of the lower limbs, did not definitively indicate PE in our study group. We did not identify age, long-term oxygen therapy, and severity of COPD as risk factors for PE. Similarly, right-heart failure identified in 26 patients at admission was not associated with PE. Only 1 study (14) has shown that a majority of patients (23 of 26) with emphysema and PE had clinical right-heart failure on admission. Of note, this study was conducted in patients with life-threatening PE and was based on autopsy data. The present study did not include patients who required invasive mechanical ventilation or fibrinolysis, and our conclusions are therefore not valid for such populations.

Among the 933 patients in the PIOPED study, the clinical criteria for PE were evaluated in a subset of 108 patients with COPD. In this subset, 19% received diagnoses of PE. Risk ratios were not calculated (3). Risk factors for PE identified in the present study—malignant disease and history of thromboembolism—were not identified as risk factors in the PIOPED study (3). Hypoxemia and hypocapnia are usually associated with PE (1, 8). We evaluated various intervals of values for PaO_2 and $PaCO_2$, but only the decrease in $PaCO_2$ compared with the baseline value was associated with PE in our study group. Lesser

Table 3. **Bivariate Analysis of Baseline Characteristics of the 197 Patients with Chronic Obstructive Pulmonary Disease according to the Presence or Absence of Pulmonary Embolism***

Patient Characteristics	Patients with COPD, *n* (%)	Patients with PE, *n* (%)	Risk Ratio for PE (95% CI)	*P* Value (Fisher Exact Test)
Age			0.99 (0.60–1.63)	0.99
<60 y	73 (37)	18 (37)		
≥60 y	124 (63)	31 (63)		
Sex			1.39 (0.65–2.99)	0.50
Male	165 (84)	43 (88)		
Female	32 (16)	6 (12)		
Long-term oxygen therapy	49 (25)	12 (25)	0.98 (0.56–1.72)	0.99
Severity of COPD†			1.68 (0.95–2.95)	0.087
Grade I	66 (44)	20 (54)		
Grade II/III‡	94 (56)	17 (46)		
Risk factors				
Previous PE or deep venous thrombosis§	23 (12)	12 (25)	2.43 (1.49–3.94)	0.004
Malignant disease§	57 (29)	21 (43)	1.82 (1.13–2.92)	0.018
Thrombophilia‖	1	1	–	–
Trauma	1	0	–	–
Surgery	5 (3)	2 (4)	1.63 (0.54–4.92)	0.59
Obesity	30 (15)	4 (8)	0.49 (0.19–1.27)	0.167
Immobilization >7 d	12 (6)	5 (10)	1.75 (0.85–3.59)	0.177

* There were 49 patients with PE and 148 patients without PE. COPD = chronic obstructive pulmonary disease; PE = pulmonary embolism.
† For severity of COPD, data were missing for 12 patients with PE.
‡ Data were missing for 37 patients overall.
§ Data were missing for 2 patients without PE.
‖ Data were missing for 18 patients.

Table 4. **Bivariate Analysis of Clinical Characteristics at Admission of the 197 Patients with Chronic Obstructive Pulmonary Disease according to the Presence or Absence of Pulmonary Embolism***

Patient Characteristics	Patients with COPD, *n* (%)	Patients with PE, *n* (%)	Risk Ratio for PE (95% CI)	*P* Value (Fisher Exact Test)
Pao_2†			1.4 (0.86–2.28)	0.187
<60 mm Hg	88 (45)	26 (53)		
≥60 mm Hg	109 (55)	23 (47)		
$Paco_2$†			1.26 (0.77–2.06)	0.38
<39 mm Hg	66 (33)	19 (39)		
≥39 mm Hg	131 (67)	30 (61)		
Decrease in $Paco_2$ ≥ 5 mm Hg‡	15 (8)	9 (27)	2.1 (1.23–3.58)	0.034
Dyspnea				
Recent onset	47 (24)	12 (25)	1	0.408§
Worsening	118 (60)	32 (65)	1.02 (0.82–1.27)	
No change	32 (16)	5 (10)	0.71 (0.2–1.56)	
Cough‖	120 (61)	35 (71)	1.56 (0.9–2.7)	0.126
Pleuritic pain¶	74 (37)	20 (41)	1.11 (0.68–1.81)	0.73
Edema of lower limb**	50 (25)	17 (35)	1.46 (0.89–2.38)	0.187
Hemoptysis‖	15 (8)	5 (10)	1.36 (0.64–2.92)	0.53
Palpitations††	31 (18)	8 (17)	1.01 (0.53–1.95)	0.99
Pulse rate >100 beats/min	38 (19)	13 (26)	1.51 (0.89–2.56)	0.147
Right-heart ventricular failure‡‡	22 (11)	4 (8)	0.65 (0.26–1.63)	0.44

* There were 49 patients with PE and 148 patients without PE. COPD = chronic obstructive pulmonary disease; PE = pulmonary embolism.
† Arterial blood gas values are reported assuming a fraction of inspired oxygen of 21% at admission.
‡ Decrease in $Paco_2$ of at least 5 mm Hg with respect to previous arterial blood gas values. Data were missing for 98 patients, 16 of whom had PE.
§ *P* value computed by using a chi-square test.
‖ Data were missing for 2 patients without PE.
¶ Data were missing for 4 patients without PE.
** Data were missing for 10 patients without PE.
†† Data were missing for 11 patients without PE and 2 patients with PE.
‡‡ Data were missing for 14 patients without PE.

and colleagues (3) did not find a difference in mean Pao_2 and $Paco_2$ levels between patients with COPD with and without PE. Previous reports showed that a decrease in $Paco_2$ during COPD exacerbation may indicate PE (15–17). In patients with underlying cardiopulmonary disease, a normal level of $Paco_2$ was found in 67% of those with PE; the specificity of this variable to exclude PE was low (49%) (18). Prediletto and colleagues (19) showed that arterial blood gas tests seem to have limited value in diagnosing PE when not included in a clinical score of probability. Rodger and colleagues (17) showed that the negative predictive value of the end-tidal alveolar dead space measurement was 90.7% in a general population. In a previous study (20), alveolar arterial gradients of Co_2 during forced expiration in patients with COPD did not support the use of this technique for diagnosing PE in those with severe exacerbation of unknown origin.

Patients were compared on the basis of results of spiral CT scans and ultrasonography. Venous thrombosis in patients with COPD and exacerbation was evaluated in 2 studies, using different techniques (21, 22). In 13 of 29 patients with COPD and exacerbation, venous thrombosis was diagnosed by using autologous platelet labeling with indium-111 (21). Prescott and colleagues (22) identified 4 cases of deep venous thrombosis in 45 patients with decompensated COPD, which was diagnosed by ^{125}I-labeled fibrinogen scanning, contrast venography, or both. In our study, color Doppler and venous ultrasonography identified deep venous thrombosis in 51% of patients with PE. These findings are consistent with those observed in a gen-

Table 5. **Probabilities of Pulmonary Embolism for the 197 Patients with Chronic Obstructive Pulmonary Disease Computed from the Geneva Score and from the Modified Geneva Score***

Clinical Risk	Geneva Score		Modified Geneva Score†	
	Patients, *n* (%)	Patients with PE (95% CI), %	Patients, *n* (%)	Patients with PE (95% CI), %
Low	119 (60)	9.2 (4.7–15.9)	93 (47)	3.2 (0–9.1)
Intermediate	75 (38)	46.7 (35–58.6)	88 (45)	38.6 (28.4–49.6)
High	3 (1.5)	100 (NA)	16 (8)	75 (47.6–92.7)

* We calculated exact 95% CIs for the Geneva score and for the modified Geneva score. The original Geneva score is discussed in reference 1. NA = not applicable; PE = pulmonary embolism.
† Recent surgery, used in the Geneva score, was replaced by malignant disease in the modified Geneva score (Table 1).

eral population (23, 24). Color Doppler and venous ultrasonography must be done as first-line tests in patients with COPD and suspected PE.

Spiral CT technology has gradually replaced pulmonary angiography in many institutions. It now is possible to obtain uniform opacification of pulmonary vessels, as small as 2 to 3 mm in diameter, and to analyze peripheral pulmonary circulation in greater anatomic detail than was possible with conventional techniques (11, 12). In this study, we used thin-collimation, single-slice CT and multislice spiral CTA to evaluate patients with suspected acute PE. It was therefore possible to select high-resolution acquisition protocols. The increasing amount of data for thin-collimation, single-slice CT is still debated (9, 25, 26). The negative predictive value of multislice spiral CTA should be higher than that of single-slice CT. Multislice spiral CT accurately evaluates pulmonary arteries to the subsegmental level in a substantially higher proportion of patients than does thin-collimation, single-slice CT (13, 25, 27). Perrier and colleagues (27) showed that lower-limb ultrasonography is not needed to rule out PE when multidetector-row CT is used. There is continuing concern about the accuracy of single-detector spiral CT for PE (28). For this reason, in addition to the use of high-resolution CT protocols, we also followed our patients for 3 months to exclude the possibility of false-negative CT results at presentation. Moreover, the diagnosis of PE was not limited to a single diagnostic test; lower-limb ultrasonography was done as a first-line diagnostic procedure in 92% of our study group. Six patients who received diagnoses of PE had isolated positive results on ultrasonography, although CT results were negative.

Pulmonary embolism was observed in many patients identified as having low probability with the Geneva score (risk ratio, 9.2 [CI, 4.7 to 15.9]). Because the upper bound of the CI for probability of PE is 15.9%, the false-negative rate is too high to adequately exclude PE. In our study group, a low-probability Geneva score could not rule out PE and the use of the modified Geneva score was exploratory. The samples included in the Geneva study (1) and in the present study differ. Seven percent of patients in the Geneva study but only 3% of patients in our study had had recent surgery. In contrast, malignant disease was less common in the Geneva study (13%) than in our sample of patients who smoked (29%). In our group, malignant disease was associated with PE.

We modified the Geneva score by substituting malignant disease for surgery (**Table 1**). For low-risk patients, the modified Geneva score yielded a probability of PE of 3.2% (CI, 0% to 9.1%) (**Table 5**). This indicates that the best estimate for the unknown true probability is 3.2%, but probabilities up to 9.1% cannot be excluded. The possibility that the actual false-negative rate has an upper CI as high as 9.1% limits the clinical utility of the modified score.

Our results might be challenged on the basis of 4 potential limitations. First, patients with COPD and severe exacerbation requiring invasive mechanical ventilation in the intensive care unit were not included in the study. Second, the upper bound of the CI for the low-probability Geneva score is too high (15.9%) to rule out PE. Third, although the modified score had a lower false-negative rate than the Geneva score, this analysis is exploratory and requires additional study. Fourth, the classification of COPD exacerbation of unknown origin was based on empirical assessment.

In conclusion, this study showed a 25% prevalence of PE in patients with COPD who were hospitalized for severe exacerbation of unknown origin, confirming previous data (3, 7). When severe exacerbation occurred without purulence of sputum, history of a cold or sore throat, pneumothorax, or iatrogenic intervention, or when there was a discrepancy between the clinical and radiologic features and hypoxemia severity, PE was identified in 1 of 4 patients. In this study group, the risk was higher when patients had previous thromboembolic disease, malignant disease, and decrease in $PaCO_2$ from baseline. Color Doppler and venous lower-limb ultrasonography should be done as a first-line evaluation because deep venous thrombosis was identified in 51% of patients receiving PE diagnoses.

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