Eur Respir J 2010; 35: 1243–1248
DOI: 10.1183/09031936.00120909


# Venous thromboemboli and exacerbations of COPD

**H. Gunen, G. Gulbas, E. In, O. Yetkin and S.S. Hacievliyagil**

**ABSTRACT: The aim of the present study was to determine the prevalence of and risk factors for venous thromboembolism (VTE) in exacerbations of chronic obstructive pulmonary disease (COPD).**

**COPD patients hospitalised with an exacerbation were included consecutively. Symptoms, signs and clinical, haematological and epidemiological parameters on admission were noted. All patients underwent computed tomographic angiography and ultrasonographic examination for deep vein thrombosis and pulmonary embolism (PE). Wells and Geneva scores were calculated. Patients were followed-up for 1 yr in order to determine mortality.**

**Deep vein thrombosis and PE were detected in 14 and 18 patients, respectively. The prevalence of VTE was three times higher in patients with an exacerbation of unknown origin than in patients with an exacerbation of known origin ($p=0.016$). Of patients with VTE, 20 (95%) had high D-dimer levels. The negative predictive value of D-dimer testing was 0.98. Although the moderate- and high-risk categories of both the Wells and Geneva methods covered all PE patients, the Wells method identified 49% less potential patients for PE investigation. Mortality at 1 yr was higher (61.9% *versus* 31.8%) in VTE patients ($p=0.013$).**

**VTE is a common problem in COPD patients hospitalised with an exacerbation, leading to high long-term mortality. D-dimer levels and the Wells criteria can be used to determine whether or not these patients are assessed for a thromboembolic event.**

**KEYWORDS: Chronic obstructive pulmonary disease, deep vein thrombosis, exacerbation, mortality, pulmonary emboli**

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of mortality and morbidity worldwide [1]. Once hospitalised due to COPD exacerbation of any cause, 5–10% of patients die despite every effort [2]. Among the triggering factors of COPD exacerbation, the role of pulmonary embolism (PE) has not yet been clearly determined. In previous studies, only patients hospitalised with an undetermined cause of exacerbation were included [3–7]. However, in addition to having very strong common risk factors, such as being very elderly and immobile, the excluded patient groups (with exacerbations due to bronchitic infections, pneumonia and cardiac failure) are indeed at increased risk of development of pulmonary thromboemboli. Conversely, a highly related entity, the occurrence of deep vein thrombosis (DVT) in COPD exacerbations, was assessed only in some of the studies on PE [5–7]. There is a single study addressing the presence of DVT in COPD exacerbations as a separate issue [8].

Methodological variations and the limited number of participants in the former studies have not permitted investigators to draw firm conclusions as to how to approach exacerbating COPD patients from the venous thromboembolism (VTE) perspective to date. Hence, the present study was designed to explore the frequency of VTE in all COPD patients hospitalised with an exacerbation. In addition to this, the aim was to determine its impact on mortality and related factors.

## PATIENTS AND METHODS

The present study was conducted in the pulmonary department of Inonu University Hospital (Malatya, Turkey). This hospital serves as the largest regional hospital, and the majority of COPD patients with an exacerbation in the region are hospitalised at this unit. All patients hospitalised from the outpatient clinics of pulmonary medicine or department of emergency medicine due to COPD exacerbation were consecutively enrolled into the present study in a prospective manner. According to the social security system, ~70% of the patients in the region can apply directly to the university hospital without needing

AFFILIATIONS
Dept of Pulmonary Medicine, Turgut Ozal Research Center, Inonu University, Malatya, Turkey.

CORRESPONDENCE
H. Gunen
Dept of Pulmonary Medicine
Turgut Ozal Research Center
Inonu University
44069
Malatya
Turkey
E-mail: hgunen@yahoo.com

Received:
July 29 2009
Accepted after revision:
Oct 12 2009
First published online:
Nov 19 2009

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

any referral. The study protocol was approved by the Malatya City Regional Ethics Committee of Turgut Ozal Research Center (Malatya, Turkey), and informed consent was obtained from all participants. The diagnosis of COPD was made dependent upon a combination of patient characteristics, such as medical history (previous diagnosis, hospitalisations, outpatient clinic visits and patient and relative statements), the available official medical records (pulmonary function test results, chest radiographs and blood gas levels) and medications utilised. Determination of hospitalisation was performed according to the presence of one or more of the following indications: severely increased symptoms; new onset of cyanosis and peripheral oedema; confusion; lethargy; coma; use of accessory muscles for ventilation; significant comorbid conditions; failure to respond to initial treatment; judgment that treatment at home would be insufficient; acidosis; persistent or worsening hypoxaemia and/or severe or worsening hypercapnia and new-onset arrhythmias. Patients with exacerbation due to pneumothorax or iatrogenic reasons were excluded.

After hospitalisation, detailed initial clinical evaluations, including the calculations for PE risk stratification, were performed by at least two clinicians. These clinicians were blinded to the results of VTE investigations. All patients underwent detailed physical examination and questioning regarding medical history. Epidemiological data, the characteristics of the exacerbation and immobile patients were noted. Analysis of resting arterial blood gas levels whilst breathing room air and detailed biochemical and haematological parameters, including D-dimer levels, were performed immediately. D-dimer levels of $<0.5$ $\mu g \cdot mL^{-1}$ were considered to be within the normal range (STA Liatest D-Di; Diagnostica Stago, Inc., Parsippany, NJ, USA). Conventional chest radiographs and spirometric measurements were obtained. For each patient, classification of COPD severity was made according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, dependent upon stable-state spirometric measurements, long-term oxygen consumption and the presence of a previous diagnosis of chronic respiratory insufficiency [1]. Subsequently, the patients were divided into two subgroups: 1) patients hospitalised with an exacerbation of known aetiology; and 2) patients hospitalised with an exacerbation of unknown aetiology. Aetiological determination was performed according to the presence of infection signs (increased sputum and/or sputum purulence, fever, chills, sore throat, presence of evident upper respiratory tract infection and consolidation on chest radiographs for pneumonia), objective findings for heart failure, exposure to inhalational irritant particles or toxic gases, patient statement regarding lack of compliance with drug or oxygen treatment, neglect of scheduled pulmonary rehabilitation and evident problems in nutritional status and the patient's home care. According to the above-mentioned data, patients were classified using the Wells and Geneva criteria as being at low, moderate and high risk of PE, as described in detail elsewhere [9, 10].

All patients underwent dynamic computed tomography (CT) scanning (CT angiography) to reveal thrombus formation in the lower extremities and emboli in the lungs (spiral CT; Philips Secura; Philips, Best, The Netherlands) within 24 h following hospitalisation. CT scans of the thorax were performed during breath-holding, with injection of 130 mL nonionic contrast material (iopromide; Ultravist-300; Schering, Baar, Switzerland) for patients with a body mass index of $\leqslant 30$ $kg \cdot m^{-2}$, with a power injector at 3 $mL \cdot s^{-1}$ and using a slice thickness of 3 mm, tube voltage of 120 kV and tube current of 240 mA. The injection volume of the contrast material was increased to 150 mL for patients with a body mass index of $>30$ $kg \cdot m^{-2}$, and tube voltage to 140 kV. The reconstruction interval was 2 mm. PE was diagnosed if the contrast material outlined an intraluminal defect, or if the vessel was totally occluded by low-attenuation material. For detection of DVT, starting from the subdiaphragmatic level to the popliteal level, all veins were scanned 180 s after contrast material injection for CT pulmonary angiography, with a slice thickness of 5 mm and slice interval of 5 cm. The diagnostic criteria for DVT on CT venography were the presence of an intraluminal filling defect in an opacified vein, or a localised non-opacified venous segment on at least two consecutive axial CT images if the vein distal and proximal to the non-opacified segment was opacified. Doppler ultrasonography (ATL-HDI 3500; ATL, Seattle, WA, USA) was also utilised as a standard method in the identification of thrombi in the lower extremities. From the common femoral vein to the popliteal vein of both lower extremities were examined using the venous compression technique with ultrasonography. Noncompressibility of the veins was considered to indicate DVT.

Cardiac function was evaluated further with ECG recordings and echocardiographic examination (ATL-HD 5000; ATL) to reveal direct and indirect signs of PE, such as direct visualisation of emboli in pulmonary arteries, leftward bulging of the interventricular septum, hypokinesis of the right ventricle on echocardiography and sinus tachycardia, atrial fibrillation, T-wave abnormalities, an S1Q3T3 pattern, right ventricular strain and right bundle branch block, and right axis deviation on ECG. The evaluation sequence of the study population is described in the flow chart (fig. 1).

In the comparison of independent group rates, Chi-squared tests were utilised. Group means were compared using an unpaired t-test. Receiver operating characteristic (ROC) analysis was performed to determine the sensitivity and specificity of D-dimer levels. Positive predictive values (PPVs) and negative predictive values (NPVs) were calculated for different D-dimer thresholds. The ROC analysis was also used in the calculation of areas under the curve (AUCs) for the clinical probability criteria for PE (Wells and Geneva criteria). In order to determine the influence of VTE on 1-yr mortality, a Cox's proportional hazards model was run. In addition to the presence or absence of VTE, the model included widely accepted classical parameters (age, sex, smoke load, serum albumin level, forced expiratory volume in 1 s, arterial oxygen and carbon dioxide tension, body mass index and systolic pulmonary arterial pressure). The survival of the patients with and without a thromboembolic event was analysed using the Kaplan–Meier method. A p-value of $<0.05$ was considered significant.

## RESULTS

Patients who gave informed consent (n=138) were included in the study. Seven patients were excluded due to technical problems with their angiographic and ultrasonographic scans

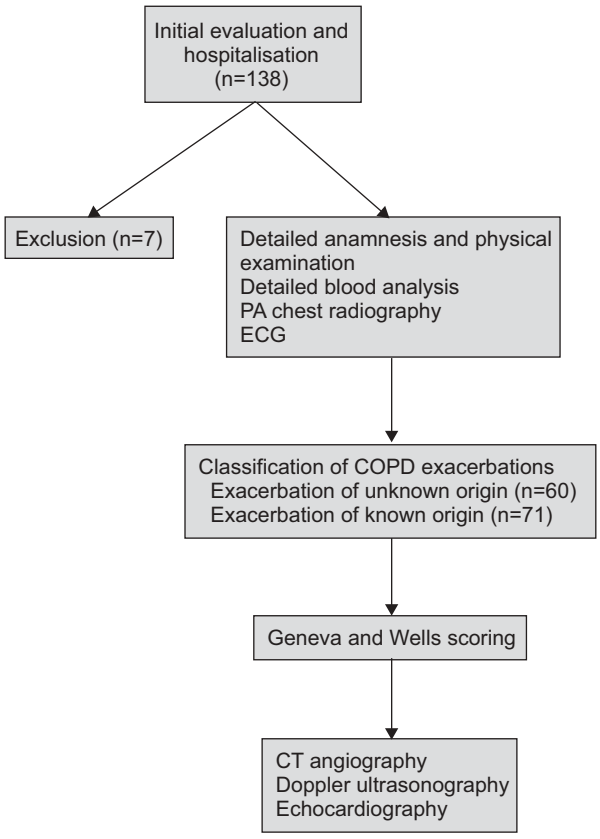


**FIGURE 1.** Flow chart showing the evaluation sequence of the study population. PA: posteroanterior; COPD: chronic obstructive pulmonary disease; CT: computed tomography.

(n=4) and contrast allergy (n=3), and 131 patients completed the study. The mean age of the participants was 67.1±10.1 yrs; 27 (20.6%) were female and 34 (26%) were nonsmokers. The admission characteristics of the patients are shown in table 1.

In 21 (16%; 95% CI 9.7–22.3%) patients, VTE (DVT and/or PE) was detected. Although PE was detected in 18 (13.7%; 95% CI 7.8–19.6%) patients, DVT was detected in 14 (10.6%; 95% CI 5.3–15.9%). CT venography and Doppler ultrasosonography revealed DVT in the lower extremities in 10 and 11 patients, respectively. DVT was detected in 11 (61.1%) patients with PE. As the efficacy of these two techniques for the detection of DVT was similar, their complementary role to each other was found to be 27.2 and 40% respectively. Table 2 shows the localisations of PE cases. Three of the four cases with subsegmental PE were agreed by the readers (observer agreement 0.75). Although one DVT lesion was found bilaterally, six and seven lesions were right and left sided, respectively.

A total of 60 (45.8%) patients were evaluated as having COPD exacerbations of unknown aetiology, and 71 (54.2%) were evaluated as having COPD exacerbations of known aetiology. The triggering factors for exacerbations of known aetiology are described in table 3. VTE was detected in 15 (25%; 95% CI 14–36%) and six (8.5%; 95% CI 2–15%) patients hospitalised with exacerbations of unknown and known aetiology, respectively. The distribution of the patients according to unknown and known aetiology was significant (p=0.016).

**TABLE 1** Admission characteristics of patients with and without venous thromboembolism (VTE)

| | VTE | No VTE | p-value |
|---|---|---|---|
| **Subjects** | 110 | 21 | |
| **Age yrs** | 67.1±10.1 | 67.5±10.3 | NS |
| **Sex females/males** | 19/91 | 8/13 | 0.041 |
| **Smoke load pack-yrs** | 44.8±32.2 | 42.2±33.6 | NS |
| **BMI kg·m$^{-2}$** | 23.0±5.0 | 25.1±5.0 | NS |
| **LTOT** | 47 | 6 | NS |
| **Immobility** | 25 | 9 | NS |
| **Chest pain** | 44 | 17 | 0.0007 |
| **Haemoptysis** | 12 | 3 | NS |
| **Palpitation** | 86 | 18 | NS |
| **Lower extremity complaints** | 35 | 11 | NS |
| **Syncope** | 3 | 5 | 0.0027 |
| **Hypotension** | 1 | 3 | 0.013 |
| **Atrial fibrillation on ECG** | 2 | 4 | 0.006 |
| **S1Q3T3 pattern on ECG** | 1 | 2 | NS |
| **$P_{pa,sys}$ on ECHO mmHg** | 45.2±13.6 | 50.0±18.2 | NS |
| **Acute right heart failure on ECHO** | 0 | 5 | 0.0001 |
| **Leukocyte 10$^3$ cells·dL$^{-1}$** | 14±6.5 | 11.2±5.6 | NS |
| **Haematocrit %** | 44.8±6.6 | 42.0±11.1 | NS |
| **D-dimer μg·mL$^{-1}$** | 1.2±1.8 | 5.2±4.5 | 0.001 |
| **Glucose mg·dL$^{-1}$** | 133±57 | 157±81 | NS |
| **BUN mg·dL$^{-1}$** | 27.7±15.2 | 29.4±12.1 | NS |
| **Creatinine mg·dL$^{-1}$** | 1.1±0.6 | 1.0±0.3 | NS |
| **Albumin g·dL$^{-1}$** | 3.2±0.4 | 3.1±0.5 | NS |
| **$P_{a,O_2}$ mmHg** | 48.1±7.0 | 50.2±9.1 | NS |
| **$P_{a,CO_2}$ mmHg** | 47.5±14.0 | 42.9±9.3 | NS |
| **$FEV_1$ % pred** | 38.8±13.9 | 39.4±8.8 | NS |
| **Malignancy** | 4 | 3 | NS |
| **Congestive heart failure** | 16 | 3 | NS |
| **Previous thromboemboli** | 1 | 2 | NS |

Data are presented as n, mean±SD (continuous variables), unless otherwise stated. Multiple other characteristics not listed in the table were nonsignificant (NS). BMI: body mass index; LTOT: long-term oxygen treatment; $P_{pa,sys}$: systolic pulmonary arterial pressure; ECHO: echocardiography; BUN: blood urea nitrogen; $P_{a,O_2}$: arterial oxygen tension; $P_{a,CO_2}$: arterial carbon dioxide tension; $FEV_1$: forced expiratory volume in 1 s; % pred: % predicted.

Stable-state post-bronchodilator spirograms could be obtained in 116 patients who completed the study. The classification of COPD severity according to GOLD guidelines is described in table 4. VTE was detected in one, eight and 12 GOLD stage II, III and IV patients, respectively. The distribution of VTE among these groups was nonsignificant (p>0.05).

Except for female sex, chest pain, syncope and hypotension, no significant relationship could be established between epidemiological, haematological, biochemical and arterial blood gas, and spirometric parameters and the occurrence of VTE (table 1). Although the prevalence of VTE was 29.6% in female patients, it was 12.5% in male patients (p=0.041). Among classical ECG findings of PE, only the presence of atrial fibrillation correlated with PE (p=0.006). Echocardiographic examination revealed right ventricular hypokinesia and leftward deviation of the interventricular septum in five (27.7%) of

**TABLE 2** Localisations of pulmonary embolism lesions detected using computed tomographic angiography

| | |
|---|---|
| **Bilateral** | 9 |
| **Right sided alone** | 7 |
| **Left sided alone** | 2 |
| **Centrally located** | 9 |
| **Segmental** | 5 |
| **Subsegmental** | 4 |

Data are presented as n.

**TABLE 3** Triggering factors for chronic obstructive pulmonary disease exacerbations

| | |
|---|---|
| **Tracheobronchitis** | 45 |
| **Pneumonia** | 6 |
| **Cardiac disorders** | 5 |
| **Exposure to irritant inhalants** | 1 |
| **Lack of compliance with treatment** | 5 |
| **Presence of multiple triggering factors** | 9 |

Data are presented as n.

the patients with PE, as indicators of acute right heart failure (p=0.0001) (table 1). All of these patients were subsequently evaluated as having massive (n=3) and submassive (n=2) PE according to their clinical and radiological findings.

The mean D-dimer level was significantly higher in the VTE group (5.2±4.5 *versus* 1.2±1.8 $\mu g \cdot mL^{-1}$; p<0.001). Except for one patient, D-dimer levels were elevated (>0.5 $\mu g \cdot mL^{-1}$) in all patients with VTE. At this cut-off level, the sensitivity, specificity, PPV and NPV were 0.95, 0.37, 0.22 and 0.98, respectively. Analysis of D-dimer levels for better sensitivity, specificity, PPV and NPV did not demonstrate any better D-dimer cut-off levels.

According to the Wells criteria, none (n=71) of the patients with low-risk determination, 20.7% (n=53) of the patients with moderate-risk determination and all (n=7) of the patients with high-risk determination were found to have PE (table 5). In a similar manner, Geneva risk determination yielded PE in none (n=14) of the low-risk patients, 11.7% (n=111) of the moderate-risk patients and 83.3% (n=6) of the high-risk patients. Using ROC curves, the value of these two methods in the diagnosis of PE were compared. As a test probability criteria, the AUC was significantly higher for the Wells method (0.882 (95% CI 0.819–0.945) *versus* 0.663 (95% CI 0.532–0.794) for the Geneva method; p=0.018).

The hospitalisation period was significantly longer in patients with VTE (13.4±5.0 *versus* 9.0±5.6 days; p=0.001). Of the patients, 51% had one or more comorbid conditions, such as cardiac disorders of extrapulmonary origin, malignancies, hypertension, diabetes mellitus, cerebrovascular accidents and connective tissue disorders. Of the patients, 11 (8.4%) died during index hospitalisation; five of these were in the group with VTE (p=0.016). PE was present in all of these patients, two of the emboli being massive and sub-massive. All of the patients were followed-up for 1 yr, and the mortality rate was significantly higher in patients with VTE (61.9 *versus* 31.8%; p=0.013) (fig. 2). The Cox's regression model revealed that the presence of VTE was the only parameter that had a significant influence on 1-yr mortality (p=0.022) (table 6).

## DISCUSSION

The present results showed that VTE was present in 16% of COPD patients hospitalised due to an exacerbation as a complicating or triggering factor. Although the prevalence of VTE was shown to be higher in COPD exacerbations of unknown aetiology, the VTE prevalence found in patients with an exacerbation of known aetiology was also considerable. For the first time, it was demonstrated that life expectancy is remarkably low in exacerbating patients with VTE at 1 yr.

PE may worsen symptoms in COPD patients, even leading to death in some, and differentiation of PE from other causes of exacerbation may be impossible on any clinical grounds. Despite this widely accepted classical knowledge, the prevalence and role of PE have not yet been determined precisely in COPD exacerbations. The limited number of studies on this issue found quite different prevalence rates, ranging 0–29% [3–8]. In autopsy series, this rate increases to up to 50% [11, 12]. The main reason for this variation seems to be related to the study populations selected. In a recent meta-analysis, the overall prevalence of PE in COPD exacerbations was defined as 20% in patients with an unknown cause of exacerbation [13]. DVT is an even less frequently addressed issue in COPD exacerbations, and its prevalence was reported to be 1.6–12.7% in COPD patients with an exacerbation [5–8]. However, it is obvious that PE and DVT have common underlying factors and mechanisms.

In the present study, patients with known causes of exacerbation were also included, and the prevalence of VTE in these patients was 8.4%. Although this rate was lower than that (25%) in patients with unknown causes of exacerbation, it seems high enough to suggest that these patients should not be directly excluded from future studies addressing the same issue. Amongst the known causes of exacerbation, lower respiratory tract infections and heart failure are always regarded as the most frequently encountered. Interestingly, all current guidelines on VTE recommend such patients to be evaluated as being at high risk of development of VTE. It is unreasonable to think that COPD patients should be excluded from this list. There is not enough data yet, but a better approach might be to consider an exacerbation of any origin as

**TABLE 4** Classification of chronic obstructive pulmonary disease severity according to Global Initiative for Chronic Obstructive Lung Disease guidelines

| | |
|---|---|
| **Stage I (mild)** | |
| **Stage II (moderate)** | 12 |
| **Stage III (severe)** | 20 |
| **Stage IV (very severe)** | 68 |

Data are presented as %.

**TABLE 5** Pulmonary embolism risk determination according to the Wells and Geneva criteria

| | Low-risk | Moderate-risk | High-risk |
|---|---|---|---|
| **Wells criteria** | 0/71 (0) | 11/53 (20.7) | 7/7 (100) |
| **Geneva criteria** | 0/14 (0) | 13/111 (11.7) | 5/6 (83.3) |

Data are presented as n/N (%), where N is the group size.

a risk factor for the development of VTE in COPD patients, and VTE should be particularly considered during their evaluation.

Interestingly, the multiple parameters analysed to predict patients with VTE did not reveal any significant result, except for female sex, chest pain, syncope, hypotension and atrial fibrillation on ECG and right heart failure on echocardiography (table 1). Since there were a limited number of female patients in the present study group (n=28), appropriate subgroup analysis to explain the relationship between the occurrence of VTE and female sex could not be undertaken. Unless the same relationship is shown in larger groups, it would seem to be a better approach to consider it coincidental rather than cause-related. Amongst the many symptoms and signs on admission (dyspnoea, cough, sputum, haemoptysis, wheezing, cyanosis and fever), chest pain, syncope and hypotension are not unexpected candidates for having some correlation with a thromboembolic event. However, ECG findings are not in concordance with classical knowledge for patients with PE. Apart from atrial fibrillation, none of the other PE indicators on ECG reached a significant level in the present patients. Since ECG findings in PE and COPD exacerbation are somewhat similar, ECG findings related to right ventricular strain in patients with an exacerbation might not be easy to differentiate from those in PE. Increased right ventricular strain arising from exacerbation itself probably mimicked the expected PE findings on ECG to reach a level of statistical significance in the present patients.

PE is a common disorder, and a quarter of patients with PE die within 1 yr [14]. Although not yet defined in any specifically designed clinical trial, the expected mortality rates should be higher in patients with COPD. Nevertheless, a highly selective subgroup analysis of COPD patients (n=45) in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study revealed a mortality rate of 53.3% in 1 yr [15]. This rate was twice as high as those in both general PIOPED patients with PE and COPD patients without PE. In concordance with these findings, the present study also found that both in-hospital and 1-yr mortality rates were significantly higher in COPD patients with VTE. Additionally, the Cox's regression model yielded the fact that the presence of VTE was the only parameter that had a significant relationship with mortality within 1 yr following hospitalisation (p=0.022) (table 6). The 1-yr mortality rate was twice as high in the VTE subgroup of COPD patients hospitalised with an exacerbation (31.8 *versus* 61.9%) (fig. 2). In addition to increased mortality, the length of hospital stay was 4–5 days longer in the patients with VTE (p=0.001). There is no doubt that the increased hospitalisation

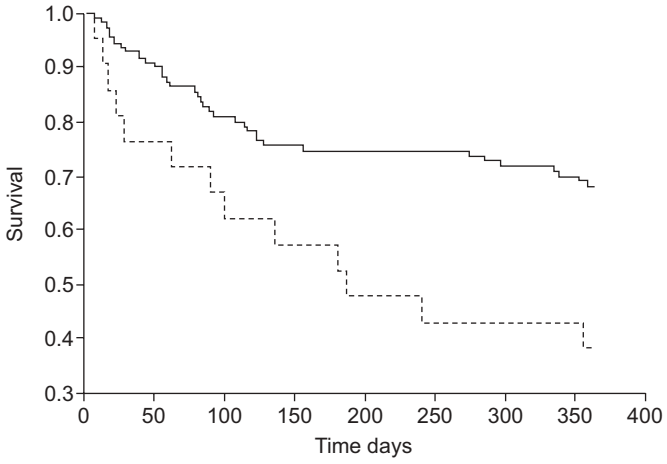


**FIGURE 2.** Kaplan–Meier curves showing the mortality rates in chronic obstructive pulmonary disease patients with (------) and without (——) venous thromboembolism. p=0.013.

period in this subgroup of patient with VTE creates a considerable impact upon the total cost of hospital care.

For the first time, both the Wells and Geneva criteria were utilised and compared in predicting PE in COPD patients. Both the sensitivity and PPV of the Wells criteria for moderate- and high-probability cases (n=60) are higher than those of the Geneva criteria (n=117) (table 5). Although 39% of the COPD patients with PE met the Wells high-probability criteria (100% PPV), the rest of the PE patients were diagnosed with the Wells moderate-probability criteria (22% PPV). Conversely, the Geneva high-probability criteria could be met by 33% of all patients with PE (83% PPV). Although the moderate-probability criteria also covered the rest of the patients with PE using this method, the PPV was only 12%. In the study of MONREAL *et al.* [16], the high-probability category of the Geneva method covered only 11% of COPD patients with PE. However, direct comparison of the results may not be appropriate due to major methodological variations between

**TABLE 6** Multivariate Cox's proportional hazard analysis for multiple independent parameters associated with 1-yr mortality

| | Relative risk (95% CI) | p-value |
|---|---|---|
| **Age yrs** | 1.029 (0.993–1.066) | NS |
| **Sex female/male** | 0.366 (0.120–1.123) | NS |
| **Smoke load pack-yrs** | 1.006 (0.993–1.019) | NS |
| **Albumin g·dL$^{-1}$** | 0.982 (0.485–1.991) | NS |
| **FEV$_1$ % pred** | 0.990 (0.961–1.021) | NS |
| **$P_{a,O_2}$ mmHg** | 0.982 (0.934–1.031) | NS |
| **$P_{a,CO_2}$ mmHg** | 1.002 (0.976–1.029) | NS |
| **BMI kg·m$^{-2}$** | 0.956 (0.891–1.026) | NS |
| **Venous thromboembolism** | 2.528 (1.144–5.588) | 0.022 |

FEV$_1$: forced expiratory volume in 1 s; % pred: % predicted; $P_{a,O_2}$: arterial oxygen tension; $P_{a,CO_2}$: arterial carbon dioxide tension; BMI: body mass index; NS: nonsignificant.

the studies and differences between the patient populations. To date, PE estimation models (Geneva and Pisa models only) have been utilised in an extremely limited number of studies addressing COPD patients with exacerbations [6, 16]. The Wells method yielded an excellent PPV for high-probability-category patients in the present study; such a strong predictive value was not described in the previous studies. This might be due to the fact that the parameters included in the Wells method are more appropriate for the assessment of PE in COPD patients. However, regarding the limited number of patients falling into the high-probability category in the present pioneer study on the Wells method, we think that further prospective studies confirming the present results are needed before drawing firm conclusions regarding this issue.

A low D-dimer level remains the single most useful haematological parameter for excluding VTE. The present findings have simply pointed out that the general rules for other populations with suspected VTE also apply completely in patients with COPD exacerbations. That is to say, if the D-dimer level is within the normal range, evaluation for VTE should be performed only in exceptional patients. Moreover, combined consideration of the Wells criteria (moderate and high probability) and a high D-dimer level further reduces the total number of COPD patients with potential PE to be evaluated by 20% (from 60 to 47 patients). In the same manner, the combination of the Geneva criteria (moderate and high probability) with high D-dimer levels could reduce the potential number of patients with PE by 28% (from 117 to 84 patients) This also shows that, even when used in combination with a high D-dimer level, the discriminative power of the Geneva criteria for PE is almost half that of the Wells criteria. Thus the Wells criteria appear to be a significantly better tool for exploring COPD patients for PE.

In conclusion, the present findings showed that VTE is a common pathology in COPD patients hospitalised with an exacerbation. Moreover, for the first time, in-hospital and long-term mortality were found to be significantly higher in COPD patients differentiated on the basis of having VTE. Since the presenting symptoms, signs and laboratory and epidemiological data are similar in COPD patients with and without VTE, it may not be easy to exclude VTE in the differential diagnosis. We think that all COPD patients hospitalised with an exacerbation of any origin should be evaluated for thromboembolic events unless serum D-dimer level and Wells criteria indicate otherwise.

## STATEMENT OF INTEREST

None declared.

## REFERENCES


1 Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. Updated 2006. www.goldcopd.com Date last updated: 2006. Date last accessed: January 14, 2008.

2 Gunen H, Hacievliyagil SS, Kosar F, *et al.* Factors affecting survival of hospitalized patients with COPD. *Eur Respir J* 2005; 26: 234–241.

3 Lesser BA, Leeper KV, Stein PD, *et al.* The diagnosis of acute pulmonary embolism in patients with chronic obstructive pulmonary disease. *Chest* 1992; 102: 17–22.

4 Hartmann IJC, Hagen PJ, Melissant CF, *et al.* Diagnosing acute pulmonary embolism. *Am J Respir Crit Care Med* 2000; 162: 2232–2237.

5 Erelel M, Cuhadaroglu C, Ece T, *et al.* The frequency of deep vein thrombosis and pulmonary embolism in acute exacerbations of chronic obstructive pulmonary disease. *Respir Med* 2002; 96: 515–518.

6 Leblond IT, Marquette CH, Perez T, *et al.* Pulmonary embolism in patients with unexplained exacerbation of chronic obstructive pulmonary disease: prevalence and risk factors. *Ann Intern Med* 2006; 144: 390–396.

7 Rutschmann OT, Cornuz J, Poletti PA, *et al.* Should pulmonary embolism be suspected in exacerbations of chronic obstructive pulmonary disease? *Thorax* 2007; 62: 121–125.

8 Schönhofer B, Köhler D. Prevalence of deep-vein thrombosis of the leg in patients with acute exacerbations of chronic obstructive pulmonary disease. *Respiration* 1998; 65: 173–177.

9 Wells PS, Anderson DR, Rodger M, *et al.* Excluding pulmonary embolism at 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: 98–107.

10 Wicki J, Perneger TV, Funod AF, *et al.* Assessing clinical probability of pulmonary embolism in the emergency ward. *Arch Intern Med* 2001; 161: 92–97.

11 Baum GL, Fisher FD. The relationship of fatal pulmonary insufficiency with cor pulmonale, right sided mural thrombi, and pulmonary emboli: a preliminary report. *Am J Med Sci* 1960; 240: 609–612.

12 Mitchell RS, Silvers GW, Dart GA, *et al.* Clinical and morphologic correlations in chronic airway obstruction. *Aspen Emphysema Conf* 1968; 9: 109–123.

13 Rizkallah J, Man SF, Sin DD. Prevalence of pulmonary embolism in acute exacerbations of chronic obstructive pulmonary disease. *Chest* 2009; 135: 786–793.

14 Carson JL, Kelley ML, Duff AE, *et al.* The clinical course of pulmonary embolism. *N Engl J Med* 1992; 326: 1240–1245.

15 Carson JL, Terrin ML, Duff A, *et al.* Pulmonary embolism and mortality in patients with COPD. *Chest* 1996; 110: 1212–1219.

16 Monreal M, Munoz-Torrero JFS, Naraine VS, *et al.* Pulmonary embolism in patients with chronic obstructive pulmonary disease or congestive heart failure. *Am J Med* 2006; 119: 851–858.