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VENOUS THROMBOEMBOLI AND EXACERBATIONS OF COPD

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ABSTRACT:

Objectives: We aimed to determine prevalence and risk factors of venous thromboemboli (VTE) in exacerbations of chronic obstructive pulmonary disease (COPD).

Patients and Methods: COPD patients hospitalized with exacerbation were consecutively included. Symptoms, signs, clinical, haematological and epidemiological parameters on admission were noted. All patients underwent CT angiography and ultrasound examination for deep vein thrombosis (DVT) and pulmonary emboli (PE). Wells and Geneva scores were calculated. Patients were followed-up for 1-year to determine mortality.

Results: DVT and PE were detected in 14 and 18 patients respectively. Prevalence of VTE was three times higher in patients with exacerbation of unknown origin than patients with exacerbation of known origin (p=0.016). Twenty patients (95%) with VTE had high D-dimer levels. Negative predictive value of D-dimer testing was 0.98. Although moderate and high risk categories of both Wells and Geneva methods covered all PE patients, Wells method identified 49% less potential patients for PE investigation. One-year mortality was higher in VTE patients (61.9% versus 31.8%) (p=0.013).

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

Key Words: COPD, exacerbation, pulmonary emboli, deep vein thrombosis, mortality

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of mortality and morbidity worldwide (1). Once hospitalized due to COPD exacerbation of any cause, 5 to 10% of patients die despite every effort (2). Among the triggering factors of COPD exacerbation, the role of pulmonary emboli (PE) has not been clearly determined yet. In the previous studies, only the patients hospitalized with undetermined cause of exacerbation were included (3-7). However, in addition to having very strong common risk factors like being very elderly and immobile, the excluded patient groups (having exacerbation due to bronchitic infections, pneumonia, cardiac failure) are actually under an increased risk for development of pulmonary thromboemboli. On the other hand, 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 limited number of participants in the former studies have not enabled the investigators to make strong comments on how to approach the exacerbating COPD patients from venous thromboemboli (VTE) perspectives so far. Hence, we designed a new study to explore the frequency of VTE in all COPD patients hospitalized with exacerbation. In addition to this, we also aimed to determine its impact on mortality and related factors in its occurrence.

PATIENTS and METHODS

The study was conducted at the pulmonary department of Inonu University Hospital. This hospital serves as the largest regional hospital, and majority of COPD patients with exacerbation in the region are hospitalized at this unit. All patients hospitalized from the outpatients clinics of pulmonary medicine or department of emergency medicine due to COPD exacerbation were consecutively enrolled in this study in a prospective manner.

According to the social security system, around 70% of the patients in the region can apply directly to the university hospital without needing any referral. The study protocol was approved by the ethics committee of the center and informed consent was obtained from all participants. The diagnosis of COPD was made depending upon the combination of patient characteristics like the past-medical history (previous diagnosis, hospitalizations, outpatient clinics visits and patients' and relatives' statements), available official medical records (pulmonary function tests, chest films and blood gases) and medications utilized. Determination of hospitalization was made 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 comorbidities; failure to respond to initial treatment; judgment that treatment at home will be insufficient; acidosis; persistent or worsening hypoxemia and/or severe or worsening hypercapnia and new onset arrhythmias. Patients with exacerbation due to pneumothorax or iatrogenic reasons were excluded.

After hospitalization, initial detailed clinical evaluations including the calculations for PE risk stratifications were made by at least two clinicians. These clinicians were blinded to the results of VTE investigations. All patients underwent detailed physical examination and questioning for medical history. Epidemiological data, characteristics of exacerbation and immobile patients were noted. Analysis for resting arterial blood gases while breathing room air and for detailed biochemical and hematological parameters including D-dimer levels were performed immediately. D-dimer levels below 0.5 mcg/ml was considered to be within the normal range (STA Liatest D-Di, Diagnostica Stago Inc., NJ, USA). Conventional chest films and spirometric measurements were obtained. For each patient, classification of COPD severity was made according to GOLD criteria depending upon the stable state spirometric measurements, long term oxygen consumption and presence of previous diagnosis of chronic

respiratory insufficiency (1). Then, the patients were divided into 2 sub-groups; 1) patients hospitalized with exacerbation of known etiology, 2) patients hospitalized with exacerbation of unknown etiology. Etiological determination was made according to the presence of infection signs (increased sputum and/or purulence, fever, chills, sore throat, presence of evident upper respiratory tract infection, consolidation in chest films for pneumonia), objective findings for heart failure, and exposure to inhalational irritant particles or toxic gases, patient statement for incompliance with drug or oxygen treatment, neglect of scheduled pulmonary rehabilitation, and evident problems in nutritional status and patient's home care. According to the data abovementioned, the patients were classified using Wells and Geneva criteria as low, moderate and high risk for pulmonary emboli as described in detail elsewhere (9, 10). All patients underwent dynamic computerized tomography scanning (CT angiography) to show thrombus formation in the lower extremities and emboli in the lungs (Spiral CT, Philips Secura, Netherland) within 24-hour after hospitalization. Computed tomography scans for thorax were performed in breath hold, with injection of 130 ml of non-ionic contrast material (iopromide – Ultravist-300, Schering, Baas, Switzerland) for patients with body mass index of $\leq$30 kg/m^2, with a power injector at 3 ml/s, using a slice thickness of 3 mm, tube voltage of 120 kV and tube current of 240 mA. Injection volume of contrast material was increased to 150 ml for patients with body mass index of >30 kg/m^2, and tube voltage to 140 kV. Reconstruction interval was 2 mm. Pulmonary embolism was diagnosed if contrast material outlined an intraluminal defect, or if vessel was totally occluded by low-attenuation material. For detection of DVT, starting from subdiaphragmatic level to popliteal level, all veins were scanned 180 seconds after the contrast material injection for pulmonary CT angiography, with a slice thickness of 5 mm and slice interval of 5 cm. Diagnostic criteria of DVT on CT venography were presence of an intraluminal filling defect in an opacified vein, or a localized 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 ultrasound (ATL-HDI 3500, USA) was also utilized in identification of thrombi in the lower extremities as a standard method. 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 functions were evaluated further with ECG recordings and echocardiographic examination (ATL-HD 5000, USA) to reveal direct and indirect signs of pulmonary emboli, like direct visualization of emboli in pulmonary arteries, leftward bulging of interventriculer septum, hypokinesis of right ventricle on echocardiography, and sinus tachycardia, atrial fibrillation, T wave abnormalities, S1Q3T3 pattern, right ventricular strain and right bundle branch block, and right axis deviation on ECG. Evaluation sequence of the study population is described in the flowchart (fig. 1).

In the comparison of independent group rates, Chi-square tests were utilized. Mean values of the groups were compared using student-t test. ROC analysis was performed in determination of sensitivity and specificity for D-dimer levels. Positive predictive values (PPV) and negative predictive values (NPV) were calculated for different D-dimer thresholds. ROC was also used in the calculation of AUC values for the clinical probability criteria for pulmonary embolism (Wells and Geneva criteria). To determine the influence of VTE on 1-year mortality, a Cox proportional hazards model was run. In addition to presence or absence of VTE, our model included widely accepted classical parameters (age, sex, smoke load, serum albumin, FEV1, PaO2, PaCO2, body mass index and systolic pulmonary artery pressure). Survival of the patients with and without thromboembolic event was analyzed using Kaplan-Meier method. P values less than 0.05 was considered to be statistically significant.

RESULTS

One-hundred and thirty-eight patients who gave informed consent were included in the study. Seven patients were dropped out due to technical problems in their angiographic and ultrasonographic scans (n=4), and contrast allergy (n=3). One-hundred and thirty-one patients completed the study. Twenty-seven patients were female (20.6%). The mean age of the participants was 67.1±10.1 years. Thirty-four patients (26%) were non-smoker. Admission characteristics of the patients are shown in table 1.

In 21 patients (16%; 95% CI:9.7% to 22.3%), VTE (deep vein thrombosis and/or pulmonary emboli) were detected. While PE was detected in 18 patients (13.7%; 95% CI:7.8% to 19.6%), DVT was detected in 14 patients (10.6%; 95% CI:5.3% to 15.9%). CT venography and Doppler ultrasound showed DVT in the lower extremities in 10 and 11 patients respectively. DVT was detected in 11 patients with PE (61.1%). As efficacy of these 2 techniques for detection of DVT was similar, their complementary role to each other was found to be 27.2% and 40% respectively. Table 2 shows the localizations of PE cases. Three of the four cases with subsegmental PE were agreed by the readers (observer agreement 0,75). While one DVT lesion was found bilateral, 6 and 7 lesions were right and left sided respectively.

Sixty patients were evaluated as COPD exacerbation of unknown etiology (45.8%), and 71 patients were evaluated as COPD exacerbation of known etiology (54.2%). Triggering factors for exacerbations of known etiology were described in table 3. Venous thromboemboli was detected in 15 (25%; 95% CI:14% to 36%) and 6 (8.5%; 95% CI:2% to 15%) patients in exacerbating patients hospitalized with unknown and known etiologies respectively. Distribution of the patients according to unknown and known etiologies were statistically significant (p=0.016).

Stable state postbronchodilator spirograms could be obtained in 116 patients who completed the study. Classification of COPD severity according to GOLD guidelines was described in table 4. Venous thromboembolism was detected in 1, 8 and 12 patients in stage II, III and IV patients respectively. Distribution of VTE among these groups were not statistically significant ($p>0.05$)

Except female gender, chest pain, syncope and hypotension, any significant relationship could not be established between epidemiological, hematological, biochemical and arterial blood gas and spirometric parameters and occurrence of VTE (table 1). While 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 interventriculer septum in 5 of the patients with PE (27.7%) as the indicators of acute right heart failure ($p=0.0001$) (table 1). Then, all of these patients were evaluated to have massive ($n=3$) and submassive ($n=2$) PE according to their clinical and radiological findings.

Mean D-dimer level was significantly higher in VTE group (5.2±4.5 mcg/ml versus 1.2±1.8 mcg/ml ($p<0.001$).Except one, D-dimer levels were positive (>0.5 mcg/ml) in all patients with VTE. At this cut-off level, sensitivity, specificity, positive and negative predictive values were 0.95, 0.37, 0.22 and 0.98 respectively. Analysis of D-dimer levels for better sensitivity, specificity, positive and negative predictive values did not demonstrate any better cut-off values at other D-dimer levels.

According to Wells criteria, none of the patients with low risk determination ($n=71$), 20.7% of the patients with moderate risk determination ($n=53$), and all of the patients with high risk determination ($n=7$) were found to have PE (table 5). In a similar manner, Geneva risk determination yielded PE in none of the low risk patients ($n=14$), in 11.7% of the moderate risk patients ($n=111$) and 83.3% of the high risk patients ($n=6$). Using ROC curves, value of

these 2 methods for diagnosing PE was compared. As a test probability criteria, AUC was significantly higher for Wells method [AUC for Wells method: 0.882 (95% CI:0.819-0.945); AUC for Geneva method: 0.663 (95% CI:0.532-0.794)] (p=0.018).

Hospitalization period was significantly longer in patients with VTE (13.4±5.0 days versus 9.0±5.6 days) (p=0.001). Fifty-one percent of the patients had one or more co-morbidity like, cardiac disorders of extra-pulmonary origin, malignancies, hypertension, diabetes mellitus, and cerebrovascular accidents and connective tissue disorders. Eleven of the patients died during index hospitalization (8.4%). Five of these patients were in the group with VTE (p=0.016). Pulmonary emboli were present in all of these patients, two of them being massive and sub-massive emboli. All patients were followed-up for 1 year and the mortality rate was significantly higher in patients with VTE (61.9% versus 31.8%) (p=0.013) (fig. 2). Our Cox regression model revealed that presence of VTE was the only parameter which had significant influence on 1-year mortality (p=0.022) (table 6).

DISCUSSION

Our results have shown that VTE was present in 16% of COPD patients hospitalized due to exacerbation as a complicating or triggering factor. Although the prevalence of VTE was shown to be higher in COPD exacerbations of unknown etiology, VTE prevalence found in patients with exacerbation of known etiology was also considerable. For the first time it was demonstrated that, life expectancy is remarkably low in exacerbating patients with VTE in one year.

Pulmonary embolism may worsen the symptoms in COPD patients, even leading to death in some, and differentiation of pulmonary emboli may be impossible from other causes of exacerbation in any clinical grounds. Despite this widely accepted classical knowledge, prevalence and role of PE have not been determined precisely in COPD exacerbations yet.

Limited number of studies on this issue addressed quite different prevalence rates varying between 0% and 29% (3-8). In autopsy series, this rate increases 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, overall prevalence of PE in COPD exacerbations was defined as 20% in patients with unknown cause of exacerbation (13). Deep vein thrombosis is even a less frequently addressed issue in COPD exacerbations, and its prevalence was reported between 1.6 and 12.7% in COPD patients with exacerbation (5-8). However it is obvious that PE and DVT have common underlying factors and mechanisms.

In our 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 the rate in patients with unknown cause of exacerbation (25%), it seems high enough to suggest that these patients should not be directly excluded from the 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 ones. Interestingly, all current guidelines on VTE recommend such patients to be evaluated as high risk for development of VTE. It is not reasonable to think that COPD patients to be excluded from this list. There is not enough data yet, but it might be a better approach to consider an exacerbation of any origin itself as a risk factor for development of VTE in COPD patients, and VTE should be particularly considered during their evaluation.

Interestingly, the multiple parameters, we analyzed to predict patients with VTE, did not reveal any significant result, except female gender, chest pain, syncope, hypotension and atrial fibrillation on ECG and right heart failure findings on echocardiography (table 1). Due to the limited number of female patients in our study group (n=28), appropriate subgroup analysis to explain the relationship between occurrence of VTE and female gender could not be made. Unless the same relationship will be shown in larger groups, it seems to be a better

approach to consider it coincidental rather than cause related. Amongst many symptoms and signs on admission (dyspnea, cough, sputum, hemoptysis, wheezing, cyanosis, fever), chest pain, syncope and hypotension are not unexpected ones to have some correlation with thromboembolic event. However, ECG findings are not in concordance with the classical knowledge for patients with PE. Except atrial fibrillation, none of the other PE indicators on ECG could reach a significant level in our patients. Since ECG findings in PE and COPD exacerbation are somewhat similar, ECG findings related to right ventricular strain in patients with exacerbation may 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 our patients.

Pulmonary embolism is a common disorder, and a quarter of patients with PE die in one year (14). Although not defined in any specifically designed clinical trial yet, the expected mortality rates should be higher in patients with COPD. Nevertheless, a highly selective subgroup analysis of COPD patients (n=45) in PIOPED study revealed a mortality rate of 53.3% in one year (15). This rate was twice higher than the rates in both general PIOPED patients with PE and in COPD patients without PE. In concordance with these findings, we also found that both in-hospital and 1-year mortality rates are significantly higher in COPD patients with VTE. Additionally, our Cox regression model yielded that presence of VTE was the only parameter which had statistically significant relationship with mortality in 1-year after hospitalization (table 6) ($p=0.022$). One-year mortality rate was twice higher in VTE subgroup of COPD patients hospitalized with exacerbation (31.8% versus 61.9) (fig.2). In addition to increased mortality, the length of hospital stay was 4-5 days longer in our patients with VTE ($p=0.001$). There is no doubt that increased hospitalization period in this sub-group of patient with VTE will create a considerable impact on total cost of hospital care.

For the first time, we utilized and compared both Wells and Geneva criteria in predicting pulmonary emboli in COPD patients. Both sensitivity and positive predictive value of Wells criteria for moderate and high probability cases (n=60) are higher than those of Geneva criteria (n=117) (table 5). While thirty-nine percent of the COPD patients with PE met the high probability criteria of Wells (100% PPV), rest of the PE patients were diagnosed with moderate probability criteria of Wells (22% PPV). On the other hand, high probability criteria of Geneva could be met by 33% of all patients with PE (83% PPV). Although moderate probability criteria covered rest of the patients with PE in this method too, PPV could only be 12%. In the study by Monreal et al, high probability category of Geneva method could cover only 11% of COPD patients with PE (16). However, direct comparison of the results may not be appropriate due to major methodological variations between the studies and differences between the patient populations. Pulmonary emboli estimation models (Geneva and Pisa models only) have been utilized in an extremely limited number of studies addressing COPD patients with exacerbation so far (6,16). Wells method yielded an excellent PPV for high probability category patients in our study, and such a strong predictive value was not described in the previous studies. This might be due to the fact that the parameters included in Wells method are more appropriate for the assessment of PE in COPD patients. However, regarding the limited number of patients falling into high probability category in our pioneer study on Wells method, we think that further prospective studies confirming our result are needed before making strong comments on the issue.

A low D-dimer level still stands to be the single most haematological parameter to exclude the patients with VTE. Our findings simply pointed out that general rules for the other populations with suspected VTE completely apply in patients with COPD exacerbation too. That is to say, if D-dimer level is within normal range, evaluation for VTE should be done only in exceptional patients. Moreover, combined consideration of Wells criteria (moderate

and high probability) and high D-dimer level further reduces the total number of COPD patients with potential PE to be evaluated by 20% (from 60 patients to 47 patients). In the same manner, the combination of Geneva Criteria (moderate and high probability) with high D-dimer levels could reduce the potential number of patients with PE by 28% (from 117 patients to 84 patients) This also shows that even when used in combination with high D-dimer level, discriminative power of Geneva criteria for PE is almost one half of Wells criteria. Thus Wells criteria appear to be a significantly better tool in exploring COPD patients for PE.

In conclusion, our findings yielded that VTE is a common pathology in COPD patients hospitalized with an exacerbation. Moreover, for the first time, in-hospital and long term mortality were found significantly higher in COPD patients differentiated to have VTE. Since 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 hospitalized with an exacerbation of any origin should be evaluated for thromboembolic event unless serum D-dimer level and Wells criteria indicate otherwise.

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TABLE 1. Admission characteristics of the patients with and without venous thromboembolism**.**

	Patients without VTE (n=110)	**Patients with VTE (n=21)**	**P value**
Age yrs	67.1±10.1	67.5±10.3	NS
Gender female/male	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 (n)	47	6	NS
Immobility (n)	25	9	NS
Chest pain (n)	44	17	0.0007
Hemoptysis (n)	12	3	NS
Palpitation (n)	86	18	NS
Lower extremity complaints (n)	35	11	NS
Syncope (n)	3	5	0.0027
Hypotension (n)	1	3	0.013
Atrial fibrillation on ECG	2	4	0.006
S1Q3T3 pattern on ECG	1	2	NS
PAPs on ECHO mmHg	45.2±13.6	50.0±18.2	NS
Acute right heart failure findings on ECHO	0	5	0.0001
Leucocyte 10^3.dL^{-1}	14±6.5	11.2±5.6	NS
Hematocrit	44.8±6.6	42.0±11.1	NS
D-dimer mcg.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
Creatinin 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
Pa,O_2 mmHg	48.1±7.0	50.2±9.1	NS
Pa,CO_2 mmHg	47.5±14.0	42.9±9.3	NS
FEV_1 % predicted	38.8±13.9	39.4±8.8	NS
Malignancy	4	3	NS
Congestive heart failure	16	3	NS
Previous thromboemboli	1	2	NS

VTE: venous thromboemboli, NS: not significant, BMI: body mass index,
LTOT: long term oxygen treatment, ECG: electrocardiography, PAPs: systolic pulmonary artery pressure, ECHO:echocardiography, BUN: blood urea nitrogen.
Mean values of the continuous variables were presented with their standard deviations (±SD).
Multiple other characteristics not listed in the table are not statistically significant.

TABLE 2. Localizations of pulmonary emboli lesions detected with CT angiography

Localizations of pulmonary emboli lesions	n
Bilateral	9
Right sided only	7
Left sided only	2
Centrally located	9
Segmental	5
Subsegmental	4

TABLE 3. Triggering factors for COPD exacerbations

Causes of exacerbations	n
Tracheobronchitis	45
Pneumonia	6
Cardiac disorders	5
Exposure to irritant inhalants	1
Incompliance with the treatment	5
Presence of multiple triggering factors	9

TABLE 4. Classification of COPD severity according to GOLD guideline

COPD severity	%
Stage I (mild)	-
Stage II (moderate)	12%
Stage III (severe)	20%
Stage IV (very severe)	68%

TABLE 5. Pulmonary emboli risk determination according to Wells and Geneva criteria.

	PE percentage in low risk patients	PE percentage in moderate risk patients	PE percentage in high risk patients
Wells Criteria	0 in 71 (0%)	11 in 53 (20.7%)	7 in 7 (100%)
Geneva Criteria	0 in14 (0%)	13 in 111 (11.7%)	5 in 6 (83.3%)

PE**:** pulmonary emboli

TABLE 6. Multivariate Cox proportional hazard analysis for multiple independent parameters associated with 1-year mortality.

	Relative risk	**95% CI**	**p-value**
Age	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 %predicted	0.990	0.961-1.021	NS
Pa,O_2 mmHg	0.982	0.934-1.031	NS
Pa,CO_2 mmHg	1.002	0.976-1.029	NS
Body mass index $kg.m^{-2}$	0.956	0.891-1.026	NS
Venous thromboembolism	2.528	1.144-5.588	0.022

NS: not significant.

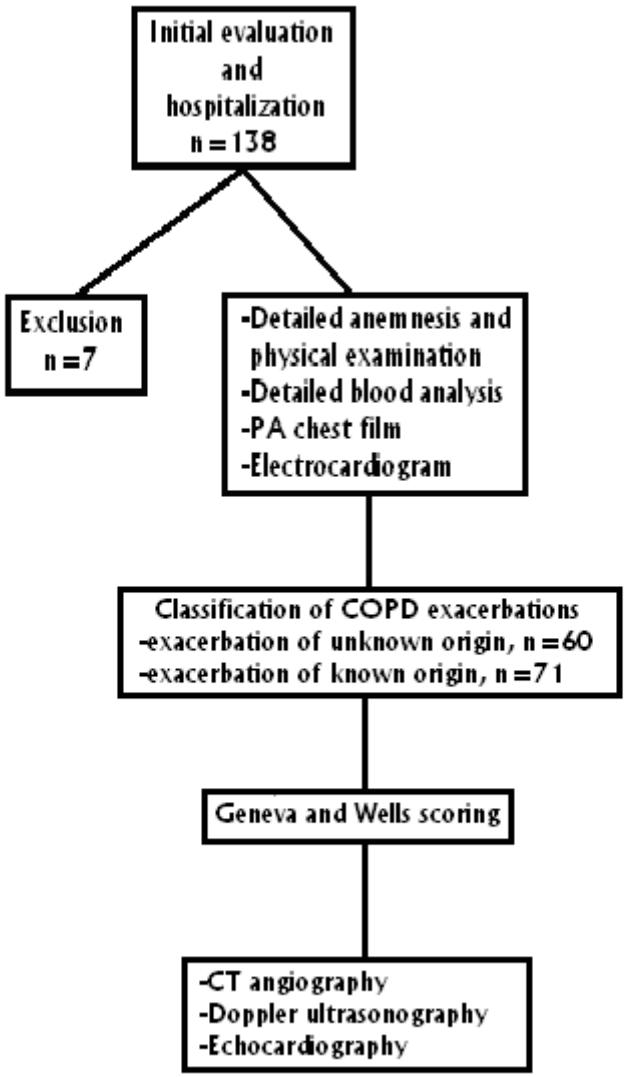

FIGURE 1. Flowchart showing the evaluation sequence of the study population

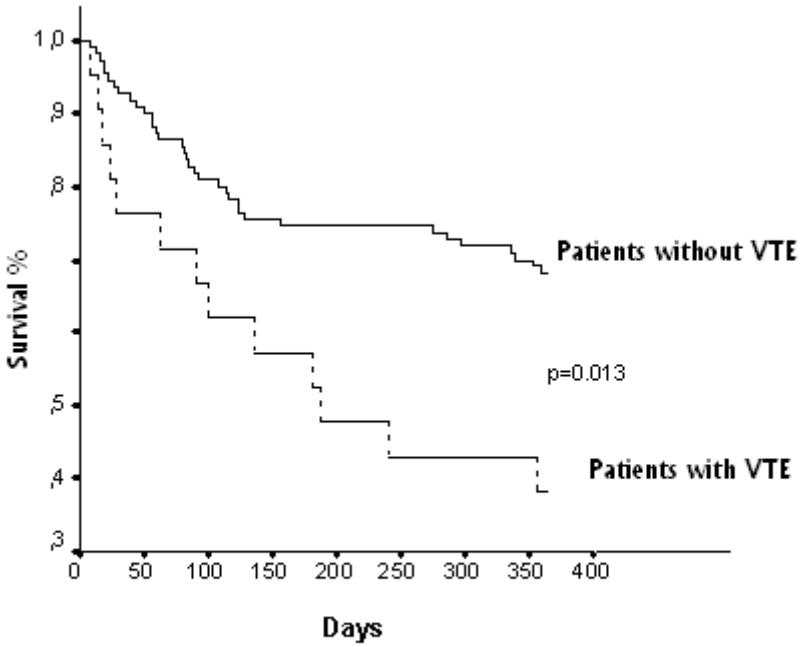

Figure 2. Kaplan-Meier curves showing the mortality rates in COPD patients with and without venous thromboembolism (VTE)