Original Article

A Cross-sectional Study for the Evaluation of Pulmonary Embolism in Unexplained Dyspnea in Acute Exacerbation of Chronic Obstructive Pulmonary Disease

Anshika Jindal, Yogendra Singh Rathore, Vinod Joshi, Shubhra Jain, Narendra Khippal

Department of Respiratory Medicine, Institute of Respiratory Diseases, SMS Medical College, Jaipur, Rajasthan, India

Abstract

Context: An acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a common condition seen in emergency. Clinical conditions which mimic AECOPD are congestive heart failure, pneumonia, pneumothorax, pleural effusion, and pulmonary embolism (PE). Early recognition of PE can be difficult due to overlap in clinical symptoms of AECOPD. This should prompt clinicians to enhance PE suspicion in AECOPD patients of unknown origin. **Aims:** The aim of the study was to assess the prevalence of PE in unexplained acute exacerbation of COPD, severity, duration of hospital admission, and to explore factors associated with co-existing disease. **Patients and Methods:** This was a hospital-based cross-sectional study, conducted at a tertiary care center of Rajasthan. One hundred and ten cases of AECOPD of unknown origin hospitalized in the department of pulmonary medicine during the study period were included after conforming to the inclusion and exclusion criteria. **Results:** In our study, the prevalence of PE in unexplained AE-COPD was 18%. Clinically, chest pain and hemoptysis were present in 80% and 12% of the patients with PE, compared with 49% and 5% of the patients without PE, respectively. The mean duration of hospital stay of AECOPD patients without PE was 2.69 ± 1.08 compared to 6.65 ± 1.56 in PE, which is a highly statistically significant difference ($P < 0.001$) in the study population. **Conclusion:** Clinicians should be alert toward the presence of PE in patients with unexplained AECOPD, especially when chest pain, hemoptysis, disproportionate tachycardia, and signs of right ventricular failure are present and no clear infectious origin can be identified.

Keywords: Acute exacerbation of chronic obstructive pulmonary disease, deep venous thrombosis, pulmonary embolism

Introduction

Exacerbations of chronic obstructive pulmonary disease (COPD) lead to worsening of respiratory symptoms[1] due to changes in pathophysiology[2] such as increase in airway and systemic inflammation.[3,4] Acute exacerbation of COPD (AECOPD) is a frequent reason for visit to the emergency. Hence, it is important to determine their triggers so that appropriate interventions can be adopted to prevent these events. Most common triggers of exacerbations are infections of the tracheobronchial tree[4] and air pollution.[5] However, 30% of cases may have indeterminate causes.[6] Clinical conditions that mimic AECOPD are congestive heart failure, pneumonia, pneumothorax, pleural effusion, and pulmonary embolism (PE). Sidney *et al*.[7] suggested that patients with COPD have approximately twice the risk of PE and other venous thromboembolic events compared to those without COPD. Early recognition of PE is of vital importance but difficult due to overlap in clinical symptoms. This should prompt clinicians to enhance PE suspicion in AECOPD patients of unknown origin.

Patients and Methods

One hundred and ten cases of AECOPD of unknown origin that met the inclusion and exclusion criteria were hospitalized in the department of pulmonary medicine during the study period. All

Address for correspondence: Dr. Yogendra Singh Rathore, Institute of Respiratory Diseases, SMS Medical College, Jaipur - 302 016, Rajasthan, India.
E-mail: yrjsr108@gmail.com

How to cite this article: Jindal A, Rathore YS, Joshi V, Jain S, Khippal N. A cross-sectional study for the evaluation of pulmonary embolism in unexplained dyspnea in acute exacerbation of chronic obstructive pulmonary disease. Indian J Respir Care 2020;9:191-5.

Received: 11-01-2020 **Revised:** 13-01-2020
Accepted: 02-03-2020 **Published:** 07-07-2020

Access this article online

Quick Response Code:

Website: www.ijrconline.org

DOI: 10.4103/ijrc.ijrc_1_20

patients who had AECOPD according to the Global initiative for chronic Obstructive Lung Disease (GOLD 2018) criteria were included in the study. Those with obvious alternative causes were excluded from the study. Approval was obtained from Institutional Ethics Committee to conduct the study.

The following evaluations were done to rule out the etiology of AECOPD: (i) discontinuation of COPD medication was identified to rule out exacerbation due to cessation of regular medication; (ii) symptoms such as fever, purulent sputum, sore throat, myalgia, or rhinorrhea to rule out upper or lower respiratory tract infection; (iii) chest X-ray showing pleural effusion and pneumothorax to rule out obvious alternative causes of exacerbation; and (iv) computed tomography (CT) scan revealing consolidation, ground-glass opacity, tree-in-bud pattern, or centrilobular nodules was examined to rule out pneumonia or tracheobronchitis. CT findings suggestive of pulmonary edema and echocardiography (Echo) suggestive of left ventricular dysfunction were obtained to rule out cardiogenic pulmonary edema. The etiology was considered unknown when no cause could be determined. Patients with renal failure (plasma creatinine >150/micromol/L), allergy to intravenous contrast medium, long term anticoagulant therapy and who were not giving consent were excluded.

After giving a full explanation regarding the study, written consent was obtained from all enrolled AECOPD patients of unknown origin. A detailed history, clinical examination (including general, respiratory, and other systemic examinations) findings, and Wells score were assessed for each patient. Chest radiography and other relevant investigations were carried out in each patient to rule out other alternative diagnoses. Depending on the results of the initial evaluation, patients of AECOPD having increased dyspnea of unknown origin underwent detailed investigations such as arterial blood gas levels, biochemical and hematological parameters (liver function tests, renal function tests, complete blood count), D-dimer, cardiac function (electrocardiogram, two-dimensional-Echo), and CT pulmonary angiography (CTPA).

Results

A total of 110 patients of AECOPD were referred for unexplained dyspnea after applying inclusion and exclusion criteria. Of these, 20 patients of AECOPD were diagnosed with PE (18%). No statistically significant differences were seen between both the groups of patients in terms of age groups and sex ratio. The mean age of AECOPD patients was 63.93 ± 11.93 years and that of AECOPD patients with PE was 64.55 ± 8.97 years. Both the groups were male dominant.

A few differences were observed in the clinical presentation: chest pain and hemoptysis were present in 80% and 12% of the patients with PE, compared with 49% and 5% of the patients without PE, respectively. There was a statistically significant difference in the mean heart rate, which was 111.18 ± 9.75 beats/min (mean ± standard deviation [SD]) in AECOPD patients without PE and was 138.40 ± 10.99 beats/min (mean ± SD) in AECOPD patients with PE [Table 1].

Severe hypoxemia was more frequent in patients having PE: half of the AECOPD patients with PE had moderate (50%) and half had severe hypoxemia (50%). None of the patients of PE had mild hypoxemia. Most of the patients (72.22%) of AECOPD without PE had mild hypoxemia [Table 2].

We also observed that signs of deep vein thrombosis (DVT) and signs of right ventricular failure (RVF) were present in only 4.44% and 27.78% of AECOPD cases without PE, respectively, whereas signs of DVT and RVF were present in 10% and 50% of cases of PE, respectively. Of two cases of prior DVT/PE, one had PE. Four patients of PE (20%) had immobilization of 3 days or more and none of the patients of AECOPD without PE had immobilization of at least 3 days. According to our study**,** comorbidities were more common in AECOPD patients with PE than without PE [Table 3].

The mean duration of hospital stay of AECOPD patients without PE was 2.69 ± 1.08 days compared to 6.65 ± 1.56 days in PE. Patients of PE had significantly longer hospital stay than patients of AECOPD without PE [Table 1].

Wells score: Among 91 patients with low suspicion of PE in AECOPD, 9.89% of them had PE. Among 17 cases of moderate risk of PE, 52.94% had PE, whereas both the cases considered at high risk of PE in AECOPD had PE [Figure 1].

Regarding D-dimers, among 21 AECOPD patients who had D-dimer >2 μg/ml, 17 patients (maximum) were confirmed with PE and the rest 4 were not. Seventy-one patients had D-dimer value between 0.5 and 2 mg/ml, but two patients were confirmed with PE. Eighteen patients of AECOPD had D-dimer <0.5 mg/ml, but one of them had PE [Table 4]. When the D-dimer cutoff value was kept at 0.5, it gave 95% sensitivity and 74.2% specificity [Figure 2].

CT scan of the lungs showed 20 patients with PE. Among these, 15 cases had thrombus in the main pulmonary artery and one case had thrombus in both the right and left main pulmonary arteries. Twenty-five percent of cases had thrombus in the lobar branches and none were found in the segmental and subsegmental branches [Table 5].

Discussion

One hundred and ten cases of AECOPD with unknown origin were investigated for pulmonary embolism, and the prevalence of PE observed was 18.1%. This high prevalence may be due to the fact that some of the inflammatory markers are responsible for coagulation.[8] The prevalence was similarly higher in five studies.[9-13] The prevalence of PE in COPD patients was reported to be 3.3% in Rutschmann *et al*.'s study (2007).[14] Reason of low prevalence observed may be because the authors did not further evaluate the COPD patients who had low D-dimer levels (<0.5 μg/mL). We evaluated all

Table 1: Comparison of patient characteristics between acute exacerbation of chronic obstructive pulmonary disease without and with pulmonary embolism

Patient characteristics	AECOPD without PE (*n*=90)	AECOPD with PE (*n*=20)	*P*
Age in years, mean±SD	63.93±11.93	64.55±8.97	0.376 (NS)
Gender, *n* (%)			
Male	62 (68.89)	15 (75)	0.787 (NS)
Female	28 (31.11)	5 (25)	
Smoking, *n* (%)			
Smoker	43 (47.78)	6 (30)	0.109 (NS)
Nonsmoker	6 (6.67)	4 (20)	
Ex-smoker	41 (45.56)	10 (50)	
Clinical symptoms			
Dyspnea	90 (100)	20 (100)	
Cough	74 (82.22)	17 (85.00)	0.976 (NS)
Chest pain	44 (48.89)	16 (80.00)	0.023 (S)
Hemoptysis	5 (5.56)	12 (60.00)	0.001 (S)
Treated pulmonary tuberculosis	33 (36.67)	9 (45.00)	0.660 (NS)
Heart rate at admission, mean±SD	111.18±9.75	138.40±10.99	0.001 (S)
Polycythemia, *n* (%)	18 (20)	15 (75)	<0.001 (S)
Pulmonary arterial pressure (mmHg), mean±SD	33.87±12.83	66.60±15.87	<0.001 (S)
FEV_1 %, mean±SD	34.90±12.92	28.80±9.96	0.322 (NS)
ABG, mean±SD			
PaO_2 (mmHg)	70.38±10.68	40.33±9.18	<0.001 (S)
pH	7.39±0.06	7.36±0.16	0.285 (NS)
$PaCO_2$ (mmHg)	49.71±10.83	42.53±23.20	0.104 (NS)
HCO_3 (mmol/L)	23.74±4.27	21.53±6.79	0.172 (NS)
Hospital stay (days), mean±SD	2.69±1.08	6.65±1.56	<0.001 (S)

AECOPD: Acute exacerbation of chronic obstructive pulmonary disease, SD: Standard deviation, FEV_1: Forced expiratory volume in 1 s, PE: Pulmonary embolism, S: Significant, NS: Not significant, ABG: Arterial blood gas

Table 2: Comparison of arterial oxygen tension (PaO_2) between acute exacerbation of chronic obstructive pulmonary disease without and with pulmonary embolism

PaO_2 (mmHg)	AECOPD without PE (*n*=90), *n* (%)	AECOPD with PE (*n*=20), *n* (%)
<40 (severe hypoxia)	2 (2.22)	10 (50.00)
40-60 (moderate hypoxia)	13 (14.44)	10 (50.00)
60-80 (mild hypoxia)	65 (72.22)	0 (0.00)
80-100 (normal)	10 (11.11)	0 (0.00)
Mean±SD	70.38±10.68	40.33±9.18
P	<0.001 (S)	

AECOPD: Acute exacerbation of chronic obstructive pulmonary disease, PE: Pulmonary embolism, SD: Standard deviation, S: Significant

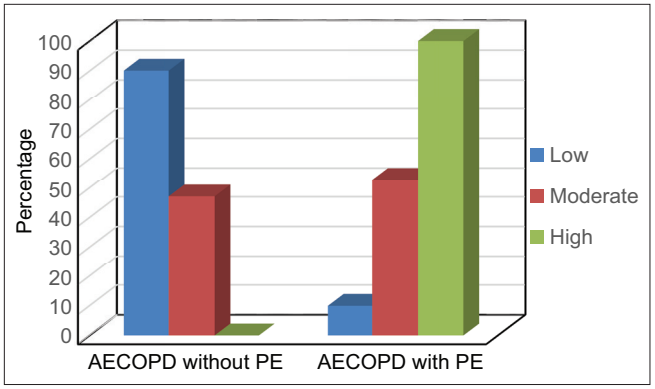

Figure 1: Wells score (risk stratification) and pulmonary embolism

AECOPD patients of unknown origin in spite of low D-dimer values. Another reason may be due to the selection of patients. We excluded patients with increased sputum volume and/or increased sputum purulence, fever, history of cold, and sore throat. Patients whose X-ray had consolidation picture were included in the study.

Our study had more number of males and mostly in the range of 50–70 years, as the prevalence of COPD is more in elderly male patients. However, the rates of diagnosis of PE in COPD were similar for elderly men and women as also observed by Akpinar *et al*. 2014.[12] Clinically, there was a statistically significant difference in chest pain and hemoptysis between AECOPD patients with and without pulmonary embolism. Tachycardia was present in both the groups, but the mean heart rate was significantly higher in patients with pulmonary embolism. Hence, according to our study, pulmonary embolism should be more frequently suspected in the presence of unexplained dyspnea, chest pain, hemoptysis, and disproportionate tachycardia and in the absence of purulent sputum or fever. PE can worsen AECOPD patients and even lead to death because their clinical features are almost similar. Hence, PE might remain underdiagnosed in patients with unexplained AECOPD. Similar results were observed by Akpinar *et al*.

Table 3: Comparison of patient comorbidities *n* (%) between acute exacerbation of chronic obstructive pulmonary disease without and with pulmonary embolism

Patient characteristics	AECOPD without PE (*n*=90)	AECOPD with PE (*n*=20)
Signs of DVT	4 (4.44)	2 (10)
Signs of RVF	25 (27.78)	10 (50)
Prior DVT/PE	1 (1.11)	1 (5)
Immobilization	0 (0)	4 (20)
IHD	1 (1.11)	2 (10)
DM	15 (16.67)	6 (30)
HTN	25 (27.78)	6 (30)
Malignancy	0 (0.00)	4 (20)
OSA	3 (3.33)	6 (30)
None	57 (63.33)	5 (20)

AECOPD: Acute exacerbation of chronic obstructive pulmonary disease, PE: Pulmonary embolism, DM: Diabetes mellitus, HTN: Hypertension, OSA : Obstructive sleep apnoea, IHD: Ischaemic heart diseases, DVT : Deep vein thrombosis, RVF: Right ventricular failure

Table 4: D-Dimer values in acute exacerbation of chronic obstructive pulmonary disease without pulmonary embolism and acute exacerbation of chronic obstructive pulmonary disease with pulmonary embolism along with the ROC curve

D dimer (microgram/ml)	AECOPD without PE (*n*=90), *n* (%)	AECOPD with PE (*n*=20), *n* (%)
<0.5	17 (18.89)	1 (5.00)
0.5-2	69 (76.66)	2 (10.00)
>2	4 (4.44)	17 (85.00)
Mean±SD	1.08±0.59	4.38±2.52
P	<0.001 (S)	

ROC: Receiver operating characteristic, SD: Standard deviation, AECOPD: Acute exacerbation of chronic obstructive pulmonary disease, PE: Pulmonary embolism, S: Significant

Table 5: Localization of thrombus

CTPA	Number (percentage) of cases
Main pulmonary artery	
Right	7 (35)
Left	7 (35)
Both	1 (5)
Lobar branches	5 (25)
Segmental and subsegmental branches	0 (0)

CTPA: Computed tomography pulmonary angiography

2014.[12] By Wells score, 82.72% of all AECOPD cases had low risk and 15.45% had a moderate risk of pulmonary embolism. In cases of AECOPD with pulmonary embolism, 45% had a low risk and 45% had a moderate risk. In short, most of the patients of AECOPD with PE had low and moderate pretest probabilities for PE. The presence of common symptoms in COPD exacerbation and PE is the reason for maximum patients coming under low-risk probability. In the present study, the Wells method yielded an excellent positive predictive for

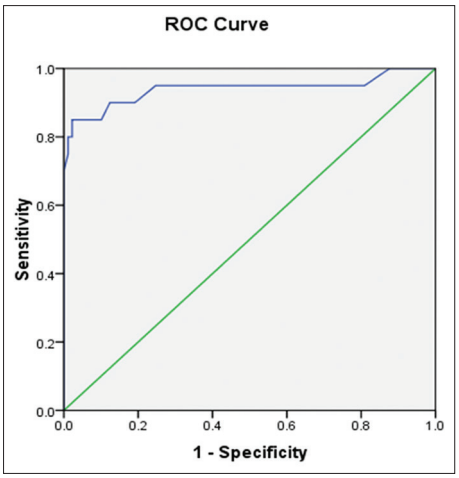

Figure 2: Diagonal segments are produced by ties

high-probability category patients. This is possibly because the parameters included in the Wells method are more appropriate for the assessment of PE in COPD patients.

Severe hypoxemia was seen in AECOPD patients with pulmonary embolism. Regarding $PaCO_2$, in AECOPD with pulmonary embolism, majority of the patients (40%) had $PaCO_2$ in the range of 25–45 mmHg, whereas, in AECOPD patients without pulmonary embolism, majority of the patients (54.44%) had $PaCO_2$ in the range of 45–65 mmHg. The mean values, however, were similar, as supported by Gunen *et al*.'s[10] study. Maximum patients of AECOPD without PE (64.44%) and with PE (60.00%) had HCO_3 in the range of 20–30 mmol/L. Hypoxemia stimulates bone marrow leading to increase in red cells which, in turn, leads to polycythemia.[15] This may explain the hypercoagulable state leading to thrombotic events in a large proportion of our patients, which was supported by our study.

D-dimer is the preferred diagnostic tool in the outpatient setting and emergency department for DVT and PE.[16] In our study, 71 AECOPD patients had D-dimer value between 0.5 and 2 mg/ml, but of that, only two patients were confirmed with pulmonary embolism. It was negative (<0.5 mg/ml) in 18.89% of the AECOPD cases without pulmonary embolism and positive in 95% of the positive cases of pulmonary embolism. At D-dimer cutoff value of 0.5 mg/ml, sensitivity was 95% and specificity was 74.2%, which was supported by Gunen 2010 *et al*.;[10] according to our observation, D-dimer cutoff value in AECOPD patients should be raised as to prevent excessive use of CTPA.

Some limitations of our study were that it was a single center study and the sample size is small. In addition, venous lower limb ultrasound examination was not performed. D-Dimer levels were not taken into consideration for imaging. All patients were evaluated and referred to CTPA. Adding such examination may prevent excessive use of CTPA in some cases. Patients with COPD requiring invasive mechanical ventilation in the intensive care unit were not included. The classification of COPD

exacerbation of unknown origin was based on only clinician's assessment.

Conclusion

Pulmonary embolism is common in unexplained AECOPD, with an estimated prevalence of 18%. These findings merit clinical attention as patients, with PE in unexplained AECOPD had increased length of hospital stay and poor prognosis. Pulmonary embolism should receive increased awareness in patients with unexplained AECOPD, especially when chest pain, hemoptysis, disproportionate tachycardia, and signs of right ventricular failure are present and no clear infectious origin can be identified. Furthermore, localization of PE is essential which has an important consequence on management.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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