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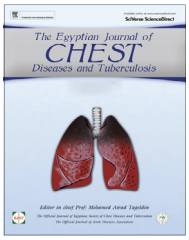

ORIGINAL ARTICLE

Prevalence of venous thrombo-embolism in acute exacerbations of chronic obstructive pulmonary disease

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KEYWORDS

COPD;
Venous thrombo-embolism (VTE);
Exacerbation;
CTPA

Abstract *Objectives:* To determine the prevalence of venous thrombo-embolism in patients with acute exacerbations of COPD.

Subjects and methods: This was a cross-sectional study involving 105 patients hospitalized with exacerbations of COPD. Clinical and hematological parameters on admission were collected. Multislice computed tomographic pulmonary angiography (CTPA) and ultrasonographic examination of lower limbs, for pulmonary embolism and deep vein thrombosis respectively were done. Wells and Geneva scores were calculated.

Results: This study was conducted on 105 COPD patients with acute exacerbations. All of them were males with mean age 49.3 + 8.43. Pulmonary embolism was found in 28.6% of COPD patients who were definitely diagnosed by CTPA while DVT was found in 26.7% of positive cases of pulmonary embolism detected by venous duplex. Wells and Geneva scores were calculated, high probability Wells score was found in 83.3% while Geneva score was likely in 90% of COPD patients proved to have pulmonary embolism. D-dimer and CBC were done; D-dimer was found negative in 90.0% in patients proven not to have pulmonary embolism while was positive in 100% of the diagnosed patients. Regarding CBC; polcythemia was found in 73.3% of diagnosed cases.

Conclusion: VTE appeared to be a common problem in COPD patients with exacerbations. The role of CTPA is the cornerstone in the diagnosis of pulmonary embolism. DVT of lower limbs was not essential in all cases of proven pulmonary embolism. Serum D-dimer, Wells criteria and Geneva score are useful bedside criteria that may help to assess the occurrence of VTE in such patients.

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Introduction

COPD is a major health burden worldwide. It is the fourth leading cause of mortality, accounting for >3 million deaths annually; and by 2020, COPD will be the third leading cause of death, trailing only ischemic heart disease and stroke [1].

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Most COPD related-deaths occur during periods of exacerbations. Sapey and Stockley estimated that 50–70% of all COPD exacerbations are precipitated by an infectious process, while 10% are due to environmental pollution. Up to 30% of exacerbations are caused by an unknown etiology [2]. Exacerbations of COPD are episodes of acute deterioration in respiratory symptoms [3] that are accompanied by physiological changes [4], and associated with increase in airway and systemic inflammation [5]. These episodes are responsible for considerable morbidity and mortality, especially in patients with more severe COPD [6]. There is consequently much interest in understanding the underlying pathophysiology of exacerbations and determining their triggers, so that appropriate interventions can be designed to prevent these events, reduce their severity and thus improve health status [7].

Acute pulmonary embolism (PE) and deep venous thrombosis (DVT) are manifestations of the overall disease known as venous thrombo-embolism (VTE) [8]. Chronic obstructive pulmonary disease (COPD) is a moderate predisposing factor for VTE, principally when associated with hospitalization [9]. *Post hoc* analyses of administrative healthcare databases using diagnostic codes suggest that the increased risk of VTE in COPD patients may be predominantly manifested in the form of PE rather than DVT [10]. An increased expression of VTE as PE in COPD patients may be problematic since the mortality of COPD patients with PE is particularly high [11], and COPD has been integrated in prognostic scores such as the Simplified Pulmonary Embolism Severity Index [12]. COPD has also been associated with inappropriate management in the case of suspected PE [13] and the suggestion of PE may be challenging in COPD patients [14] because of the similarities in symptoms. The former consideration may particularly apply during COPD exacerbation [15], a situation in which undiagnosed PE was found in an autopsy study in up to 30% of COPD patients who died [16]. Finally, COPD has been associated with an increased risk of unsuspected fatal PE [17]. Confirming the increased rate of PE in COPD patients, this should prompt clinicians to enhance PE suspicion in COPD patients at risk for VTE [18].

Sidney et al. [19] suggested that patients with COPD have approximately twice the risk of pulmonary embolism (PE) and other venous thrombo-embolic events rather than those without COPD. Since thrombo-embolic events can lead to cough and dyspnea (just like infectious events), PE may be another common cause of COPD exacerbations [20]. However dissimilar to infectious etiologies, which are effectively treated by antimicrobials and systemic corticosteroids, thrombo-embolic diseases require anticoagulant therapy and significant delays in treatment are associated with poor outcomes [21]. Owing to multiple perfusion and ventilation abnormalities frequently observed in COPD lungs (even the absence of VTE), noninvasive diagnosis of PE using imaging modalities was a significant challenge until quite recently. With the advent of contrast-enhanced multi-detector CT angiography, it is now possible to reliably diagnose PE in COPD subjects with minimal discomfort or risk to the patients [22].

Table 1 The simplified Geneva score.

Variable	Score
Age > 65	1
Previous DVT or PE	1
Surgery or fracture within 1 month	1
Active malignancy	1
Unilateral lower limb pain	1
Hemoptysis	1
Pain on deep vein palpation of lower limb and unilateral edema	1
Heart rate 75 to 94 bpm	1
Heart rate greater than 94 bpm[a]	+1

Patients with a score of 2 or less are considered unlikely to have a current PE. Authors suggest that the likelihood of patients having a PE with a simplified Geneva score less than 2 and a normal D-dimer is 3%.[24].

[a] Heart rates of 75 to 94 bpm receive 1 point, while heart rates higher than 94 bpm receive a further point (i.e. 2 points in total).

Table 2 Wells score.

Points of wells score	
Clinically suspected deep vein thrombosis (DVT)	3
Alternative diagnosis less likely than PE	3
Rapid heart rate	1.5
Immobilization within past 4 weeks	1.5
History of DVT	1.5
Hemoptysis	1
Malignancy	1

A total score greater than 6 indicates a high probability of a PE, a score between 2 and 6 moderate probability and a score below 2 low probability [25].

Aim of work

To determine the prevalence of venous thrombo-embolism in COPD patients suffering from acute exacerbations requiring hospitalization.

Subjects and methods

This was a cross-sectional study involving 105 patients hospitalized with exacerbations of COPD. It was carried out in Kasr El-Aini Hospital, Faculty of Medicine, Chest and Radiology departments during the period from June 2011 till June2012. All patients underwent the following:

1. Detailed medical history and epidemiological data.
2. Detailed physical examination
3. Analysis of resting arterial blood gas levels while breathing room air.
4. Detailed biochemical and hematological parameters, including D-dimer levels, were performed immediately. D-dimer test measures the levels of a protein that is produced when blood clots are broken down by the body. A negative D-dimer test is a good assurance that you do not have a DVT or pulmonary embolism and do not require treatment for these conditions. However, a positive D-dimer test is not enough to diagnose blood clots, and further tests will be needed [23].
5. Conventional chest radiographs were done.
6. Calculation of Geneva and Wells scores (Tables 1 and 2).

7. Bilateral lower limb venous imaging *(duplex and CTV);* to detect venous thrombi in lower limbs. For detection of DVT, starting from the subdiaphragmatic level to the leg level, all veins were scanned 180 s after contrast material injection for CT pulmonary angiography, with a slice thickness of 5 mm and a slice interval of 5 mm. The diagnostic criteria for DVT on CT venography were the presence of an intra luminal 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 ultrasonography (ATL-HDI 3500; ATL, Seattle, WA, USA) was also utilized 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. No compressibility of the veins was considered to indicate DVT (Fig. 1).
8. Dynamic multi-slice computed tomography (MSCT) scanning (CT angiography) to reveal thrombus formation in the lower extremities and emboli in the lungs (light speed CT; GE medical systems, Milwaukee, WI, USA) within 24 h following hospitalization. CT scans of the thorax were performed during breath-holding, scanners are used to acquire the images of the thorax in a caudal-cranial direction. The caudal-cranial direction is used because most emboli are located in the lower lobes and, if the patient breathes during image acquisition, there is more excursion of the lower lobes compared with the upper lobes. For IV access, the antecubital vein and an 18- or 20-gauge catheter is preferred with an injection of 130 mL nonionic contrast material (iopromide; Ultravist-300; Schering, Baar, Switzerland) for patients with a body mass index of $\leqslant 30\ kg\ m^{-2}$, with a power injector at $3\ mL\ s^{-1}$ 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 $> 30\ kg\ m^{-2}$, and tube voltage to 140 kV. The reconstruction interval was 2 mm. PE was diagnosed if the contrast material outlined an intra-luminal defect, or if the vessel was totally occluded by a low-attenuation material. Multiplanar reformation images through the longitudinal axis of a vessel can be used to overcome some of the difficulties encountered with axial-orientated images of obliquely or axially orientated arteries. Also, reformatted images can help to differentiate between some patient,

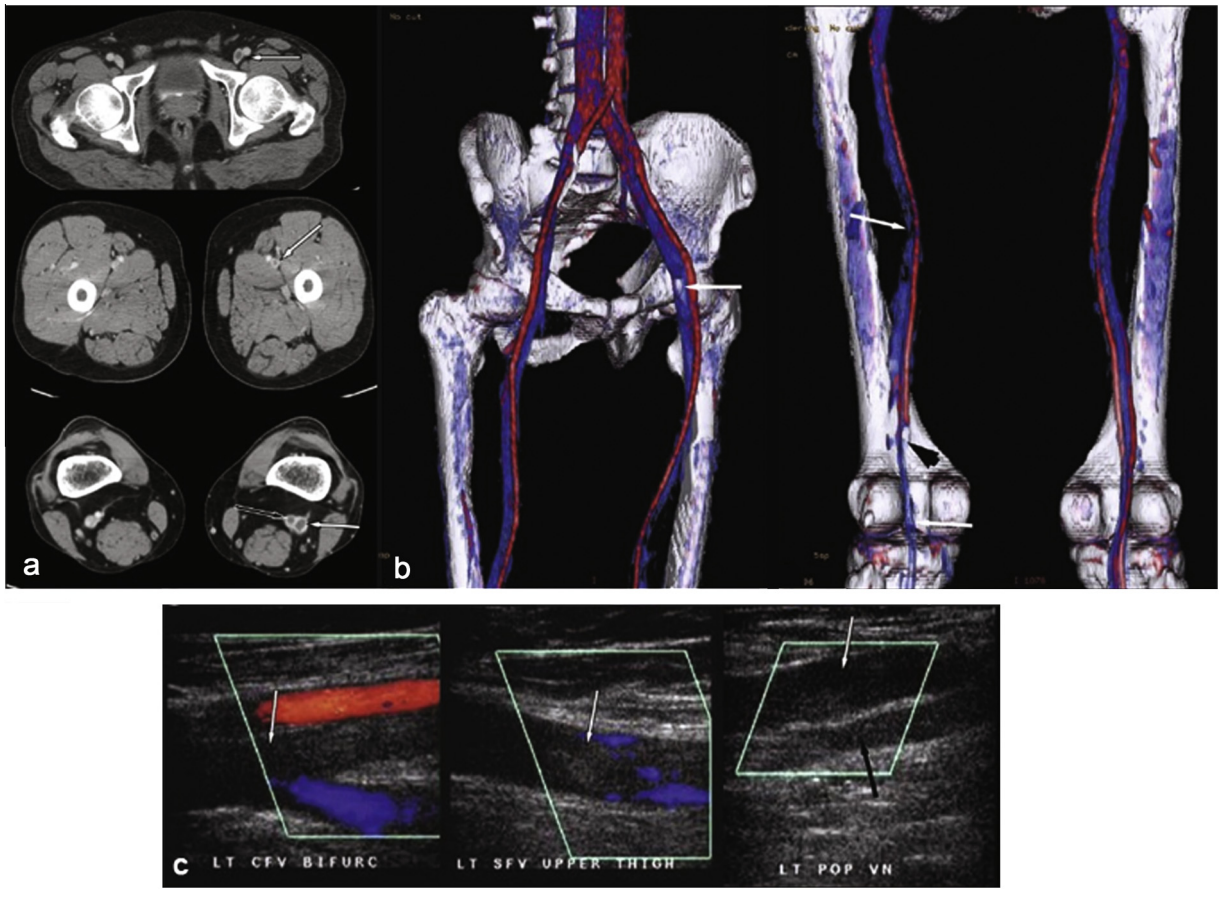

Figure 1 CTV and Doppler of lower limbs (a) CTV axial sections at level of upper thigh, mid thigh and popliteal fossa showing thrombus involving left common femoral vein, superficial femoral vein and popliteal vein (white arrows). In addition, thrombus is also seen in left popliteal artery (black arrow) (b): Volume rendered images in anterior and posterior view in the same patient showing filling defect in the region of left common femoral vein, superficial femoral vein, popliteal vein (white arrows) and left popliteal artery (black arrow) (c): Doppler USG of same patient at level left upper and mid thigh, and popliteal fossa showing thrombus filling left SFV and popliteal vein with absence of color filling. Left popliteal artery (black arrow) also showed no color fill in (thrombus) [26].

technical, anatomic, and pathologic factors that mimic pulmonary embolism and true pulmonary embolism (Figs. 2–4).

Results

Data were statistically described in terms of mean ± standard deviation (± SD), or frequencies (number of cases) and percentages when appropriate. A comparison of numerical variables between the study groups was done using Student *t* test for independent samples. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. Accuracy was represented using the terms sensitivity, specificity, +ve predictive value, −ve predictive value, and overall accuracy. *P* Values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

This study involved 105 male patients who were admitted with acute exacerbation of COPD. The ages ranged from 35–74 years old with a mean age of 49.3 + 8.43 (Tables 3–8).

Statistical methods were done to find correlations between patients with venous thrombo-embolism (as detected by CT-pulmonary angiography; most accurate method of detection) and other methods of diagnosis (Table 9–14).

Discussion

The chronic obstructive pulmonary disease (COPD) patient presenting with acute dyspnea can be a diagnostic challenge in both the outpatient and inpatient settings. Many cardiopulmonary diseases, including acute pulmonary embolism (PE), are worsened or masked by the presence of COPD. While diagnostic tests such as B-type natriuretic peptide have led to differentiating dyspnea in heart failure from COPD exacerbation, there are no proven clinical criteria to help delineating acute pulmonary embolism from COPD. This is attributable to the overlap and non-specificity of clinical features common to both diseases. The presentation of pulmonary embolism is similarly subtle with non-specific clinical features such as acute dyspnea, tachycardia, and pleuritic chest pain. While COPD remains a clinical diagnosis, PE requires objective confirmation of clots by an imaging study to warrant appropriate anticoagulation therapy. When recognizing that the mortality of untreated PE may be as high as 25%, it is crucial to incorporate PE into the differential diagnosis of a

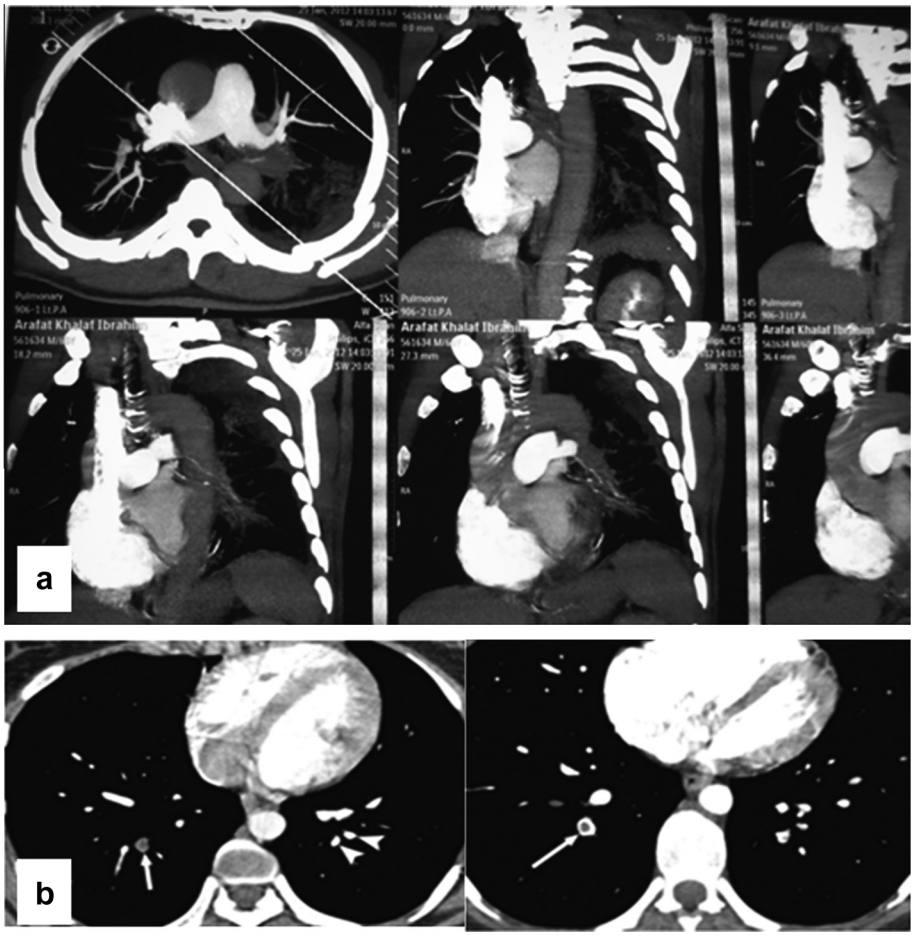

Figure 2 (a) the left main pulmonary artery shows a sizable hypodense filling defect filling the distal half and extending within the lower lobe branch. (b) Axial Images showing bilateral lower lobes emboli completely or partially occluding the lumen (arrow and arrow heads).

COPD exacerbation, and instructive to review the incidence of PE in COPD patients in the reported literature [27].

Thrombo-embolism represents a spectrum of disease, ranging from deep venous thrombosis (DVT) to PE and infarcts. Our study was done on patients with acute exacerbations of COPD. All of them were males with age ranging from 35 to 74 years with mean age 49.3 + 8.43. This mean age was similar to most of the studies addressing this issue as that done by Gershon et al. [28]. The predominance of males and older patients in the COPD group is easily understood as the prevalence of COPD increases with age and more common in males. Our study shows that the prevalence of pulmonary embolism among patients with acute exacerbations of COPD is 28.6% being surely diagnosed by CTPA. DVT prevalence diagnosed by lower limb venous duplex is 10.5%. Other diagnostic tools may help in the diagnosis of pulmonary embolism as D-dimer which is positive in all cases of pulmonary embolism (sensitivity 100%). Not only this, but there are clinical scores which may help in the diagnosis of pulmonary embolism namely Geneva and Wells scores. In our study, Geneva score is significantly associated (likely incidence of PE) in 90% of cases with proven pulmonary embolism and was unlikely in 88% of cases proved not to have PE while Wells score shows a high probability in 83.3% of proven cases. The presence of polycythemia is a constant finding in 73.3% of cases with positive pulmonary embolism highlighting a significant laboratory criterion in patients with proven pulmonary embolism.

The prevalence of PE in patients with COPD is important because of combined morbidity and mortality. In a follow-up of 1487 patients from the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, Carson et al. [29] found an adjusted estimated relative risk of death at one year with COPD and PE of 1.94, compared with 1.1 for patients with PE alone. The one year mortality of those with COPD and PE was 53.3%, in contrast to 15% of those with PE alone [27]. As there is clinical difficulty in diagnosing PE

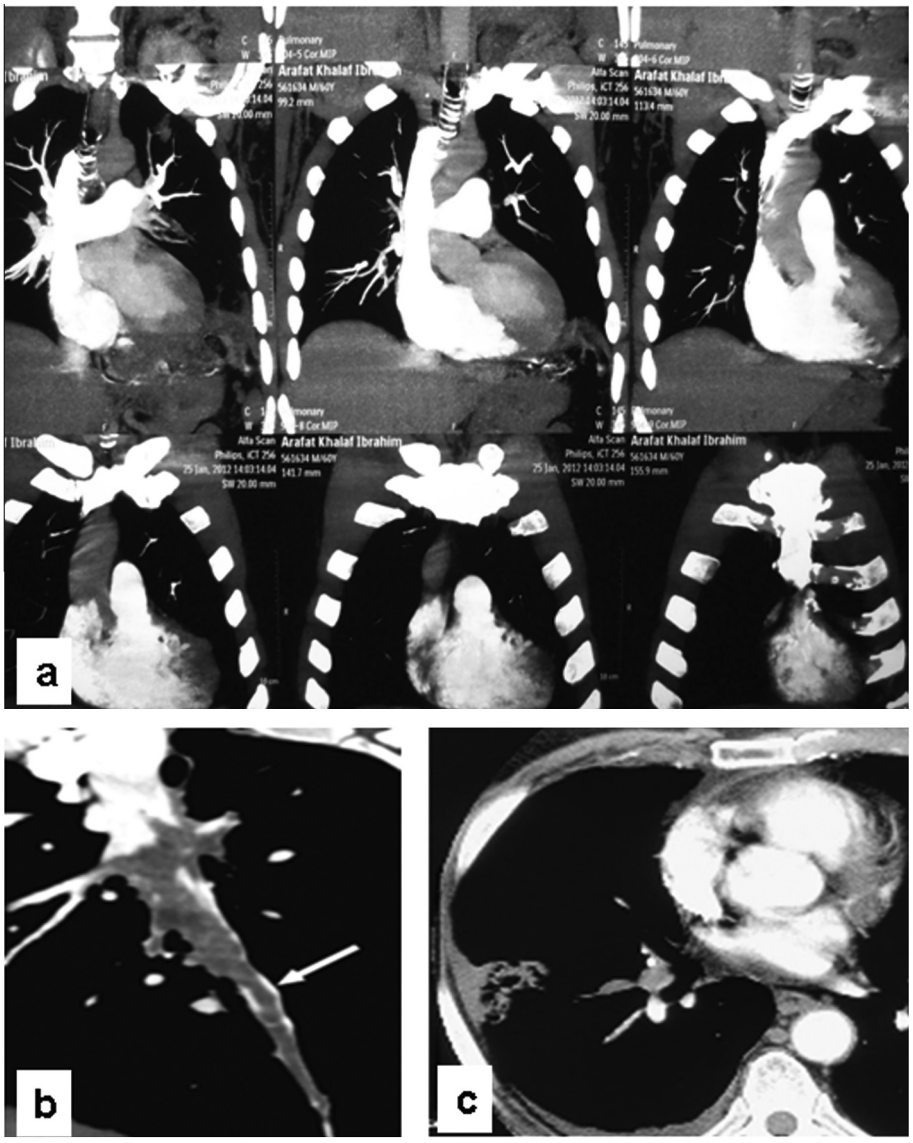

Figure 3 (a) showed bilateral pulmonary embolism more on left side with pulmonary infarcts. (b) reformatted image of left lower lobe branch filling defect, arrow (c) axial CT image of right lower lobe with distal lung infarction and minimal pleural effusion.

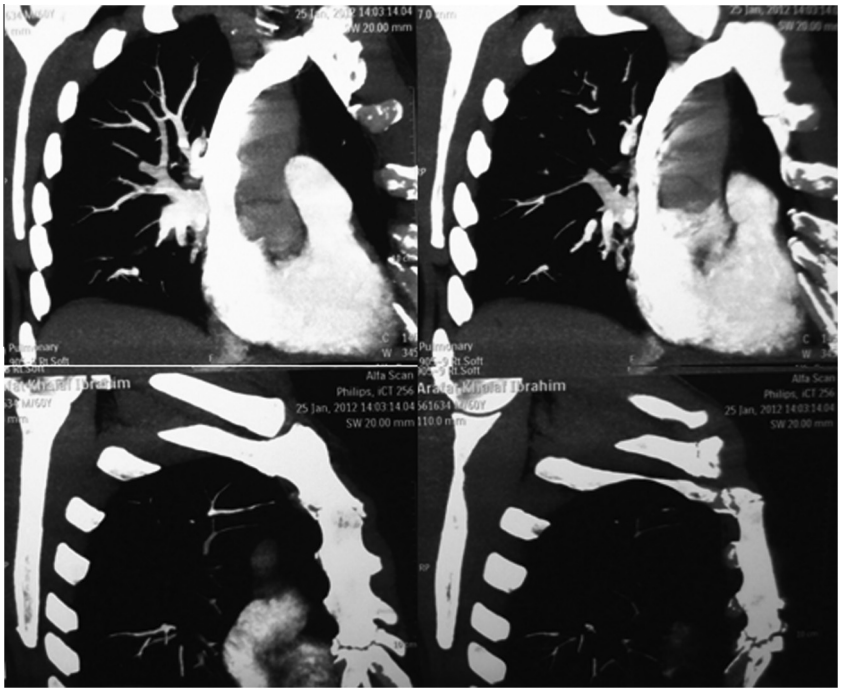

Figure 4 The branches of right lower lobe are variably attenuated and occluded.

Table 3 CBC in patients with acute exacerbation of COPD.

CBC	Frequency	Percent
Anemia	7	6.7
Normal	55	52.4
Polycythemia	43	41.0
Total	105	100.0

Table 4 D-dimer in patients with acute exacerbation of COPD.

D-dimer	Frequency	Percent
Negative	68	64.8
Positive	37	35.2
Total	105	100.0

Table 5 Geneva score in patients with acute exacerbation of COPD.

Geneva score	Frequency	Percent
Likely	36	34.3
Unlikely	69	65.7
Total	105	100.0

Table 6 Wells score in patients with acute exacerbation of COPD.

Wells score	Frequency	Percent
Low/Moderate	80	76.2
High	25	23.8
Total	105	100.0

Table 7 Duplex in patients with acute exacerbation of COPD.

Duplex	Frequency	Percent
Negative	94	89.5
Positive	11	10.5
Total	105	100.0

Table 8 Multislice CT pulmonary angiography results (CTPA) in patients with acute exacerbation of COPD.

CTPA-PE	Frequency	Percent
Negative	75	71.4
Positive	30	28.6
Total	105	100.0

in the setting of COPD as was described by Sharma and Sasahara [30] it is crucial to incorporate PE into the differential diagnosis of a COPD exacerbation. Our study showed that the prevalence of PE in cases of COPD exacerbations was 28.6%, similarly as Tillie-Lebond et al. [31] who reported 25% prevalence of pulmonary embolism in patients with COPD hospitalized with severe exacerbations. In contrast, Rutschmann et al. [32] concluded that the prevalence of pulmonary embolism was 6.2% in patients with COPD with clinical suspicion, and only 1.3% where there was no clinical

Table 9 Results of CBC in relation to CTPA findings.

			CTPA-PE		Total
			Negative	Positive	
CBC	Anemia	Count	7	0	7
		% Within CTPA-PE	9.3%	0.0%	6.7%
	Normal	Count	47	8	55
		% Within CTPA-PE	62.7%	26.7%	52.4%
	Polycythemia	Count	21	22	43
		% Within CTPA-PE	28.0%	73.3%	41.0%
Total		Count	75	30	105
		% Within CTPA-PE	100.0%	100.0%	100.0%

P-Value: 0.000, sensitivity: 73.33, specificity: 72.0.

Table 10 Results of D-dimer in relation to CTPA findings.

			CTPA-PE		Total
			Negative	Positive	
D-dimer	Negative	Count	68	0	68
		% Within CTPA-PE	90.7%	0.0%	64.8%
	Positive	Count	7	30	37
		% Within CTPA-PE	9.3%	100.0%	35.2%
Total		Count	75	30	105
		% Within CTPA-PE	100.0%	100.0%	100.0%

P-Value: 0.000, sensitivity: 100.00, specificity: 90.67.

Table 11 Geneva score in relation to CTPA findings.

			CTPA-PE		Total
			Negative	Positive	
Geneva	Likely	Count	9	27	36
		% Within CTPA-PE	12.0%	90.0%	34.3%
	Unlikely	Count	66	3	69
		% Within CTPA-PE	88.0%	10.0%	65.7%
Total		Count	75	30	105
		% Within CTPA-PE	100.0%	100.0%	100.0%

P-Value: 0.000, sensitivity: 90.00, specificity: 88.00.

Table 12 Wells Score in relation to CTPA findings.

			CTPA-PE		Total
			Negative	Positive	
Wells	Low/Moderate	Count	75	5	80
		% Within CTPA-PE	100.0%	16.7%	76.2%
	High	Count	0	25	25
		% Within CTPA-PE	0.0%	83.3%	23.8%
Total		Count	75	30	105
		% Within CTPA-PE	100.0%	100.0%	100.0%

P-Value: 0.000, sensitivity: 83.33, specificity: 100.

suspicion of pulmonary embolism and this was owed to the patients selected who were in the emergency department.

Regarding D-dimer, it was found that it is negative in 90.7% of cases without pulmonary embolism and positive in 100% of positive cases of pulmonary embolism. Hartmann et al. [33] Moua and Wood [27] similarly reported that D-dimer is the preferred diagnostic tool in the outpatient setting and emergency department for DVT and PE and also that

Table 13 Lower limb venous duplex results in relation to CTPA findings.

			CTPA-PE		Total
			Negative	Positive	
Duplex	Negative	Count	72	22	94
		% Within CTPA-PE	96.0%	73.3%	89.5%
	Positive	Count	3	8	11
		% Within CTPA-PE	4.0%	26.7%	10.5%
Total		Count	75	30	105
		% Within CTPA-PE	100.0%	100.0%	100.0%

P-Value: 0.002, sensitivity: 26.67, specificity: 96.00.

Table 14 Age characteristics in COPD patients with and without pulmonary embolism.

	CTPA-PE	*N*	Mean	Standard deviation	Standard error of mean
Age	Negative	75	50.52	8.934	1.032
	Positive	30	46.27	6.153	1.123

P-Value: 0.007.

COPD had no influence on the diagnostic accuracy of the test for thrombo-embolic disease. A systematic review found a negative D-dimer to be as diagnostically useful as a normal lung perfusion scan or negative duplex ultrasonography in the setting of low pretest probability [34].

The majority of pulmonary emboli (87–97%) originate from the lower extremities, particularly the deep veins of the thigh. Our study showed that lower limb duplex was positive in 26.7% of positive cases and negative in 96% of cases without pulmonary embolism which means that thrombo-embolism had occurred as a result of other causes related to COPD itself i.e. hypoxemia and polycythemia which in turn leads to hypercoaguable state. Similarly, among 29 patients with COPD exacerbations, Winter et al. [35] had found 13 patients with DVT; two of which were later found to have PE postmortem. Of these patients, none presented with clinical signs of DVT. Also Erelel et al. [36] followed up 56 patients with hospitalized COPD and detected DVT by ultrasound in eight. Five were subsequently diagnosed with pulmonary embolism by high probability V/Q scanning. Ambrosetti et al. [37] suggested 10% of patients with COPD have concomitant DVT, though this number may far underestimate actual prevalence. The risk of DVT appears increased due to poor mobility with worsening respiratory status, chronic steroid use, and active smoking [36].

Our study showed that pulmonary embolism was found in 28.6% of COPD patients as diagnosed by CTPA and negative in 71.4%. However, *Rutschmann* et al. [32] found only four cases of computed tomography (CT) proven PE out of 123 consecutive patients presenting with COPD exacerbation, representing a prevalence of 3.3%.

During our study, we found that polycythemia was present in 73.3% of proven cases of PE. Biswas et al. [38] showed that hypoxemia stimulates bone marrow leading to increase in red cells which in turn leads to polycythemia. This may explain the hypercoagulable state leading to thrombotic events in a large proportion of our patients.

Because symptoms of PE may be non-specific, clinical prediction rules are used to reduce the need for imaging. Our study showed that the likely high probability Geneva score was significantly associated with 90% of positive cases. On the other hand; Gunen et al. [39] had found it significant with 33% of patients with pulmonary embolism only. In the study done by Monreal et al. [40], Geneva score was positive in 11% of COPD patients with pulmonary embolism. However, a direct comparison of the results may not be appropriate due to major methodological variations between the studies and differences between the patient populations. Wells criteria was significantly high in 83.3% of COPD cases with pulmonary embolism with specificity 100.00 i.e. there was never a high probability of the Wells score in patients with negative CTPA findings for Pulmonary Embolism. These results were similar to those in the study done by Gunen et al. [39].

Of the studies that were assessed, only one study applied a validated clinical prediction probability of PE (i.e., a Geneva score) to determine the pretest probability of PE. It found that even patients in low-risk category (a Geneva score 4) had a substantive prevalence of PE (approximately 9%), although the prevalence was lower compared to those in high-risk category (a score 9; 46% prevalence). These data suggest that the Geneva risk scores may not be optimal in risk stratifying COPD patients for PE. Alternative instruments include the Wells criteria and the decision rule had been developed by Miniati et al. [41], but none of these have been well validated in COPD patients during exacerbations. Despite these shortcomings, the judicious use of these validated instruments in the context of a careful clinical and laboratory assessment may be helpful in avoiding unnecessary imaging studies.

In conclusion, patients with COPD exacerbations appear to experience PE at high rates. Since the presenting symptoms, signs and laboratory data are similar in COPD patients with and without VTE, it may not be easy to exclude VTE in the differential diagnosis. So, COPD patients hospitalized with an exacerbation of any origin should be evaluated for throm-

bo-embolic events unless serum D-dimer level and Wells criteria indicate otherwise.

Conflict of interest

The authors declare that there are no conflict of interest.

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