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Prevalence and risk factors of pulmonary embolism in acute exacerbation of chronic obstructive pulmonary disease and its impact on outcomes: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: The current study aimed to pool data for the prevalence of pulmonary embolism (PE) in acute exacerbation of chronic obstructive pulmonary disease (AE-COPD). We also aimed to assess the risk factors of PE and its impact on the outcomes of AE-COPD.

MATERIALS AND METHODS: PubMed, Embase, and CENTRAL databases were searched up to 1st January 2021 for prospective, retrospective, and cross-sectional studies reporting the prevalence of PE in AE-COPD based on computed tomography (CT) data.

RESULTS: Sixteen studies were included. Pooled data of 5035 patients indicated the prevalence of PE in AE-COPD to be 12.9% (95% CI: 8.9%-18.4%). In studies wherein, all patients underwent CT the prevalence was 19.4% (95% CI: 13.4%-27.4%). On the other hand, the prevalence of PE was 7.8% (95% CI: 3.7%-15.7%) in studies where CT was carried out only after screening patients based on study-specific diagnostic protocol. Multiple studies indicated that recent immobilization, increased D-dimer levels, lower limb edema, older age and the concomitant presence of deep vein thrombosis were independent risk factors for PE in AE-COPD. Pooled analysis indicated that PE was associated with a significantly increased risk of mortality (OR: 3.21 95% CI: 1.86, 5.54 I2=52% p<0.0001) and longer ICU/hospital stay (MD: 3.26 95% CI: 1.93, 4.58 I2=0% p<0.00001) in AE-COPD.

CONCLUSIONS: The prevalence of PE in AE-COPD is estimated to be 12.9%. This figure, however, varies based on the PE workup protocol. Higher prevalence (19.4%) was noted when all patients underwent CT as compared to when a study-specific diagnostic protocol was followed (7.8%). Recent immobilization, increased D-dimer levels, lower limb edema, older age and the concomitant presence of deep vein thrombosis are important independent risk factors for PE in patients with AE-COPD. Patients diagnosed with PE have increased mortality and longer ICU/hospital stay as compared to non-PE patients.

Key Words:
Chronic obstructive lung disease, Venous thromboembolism, Prevalence, Acute Exacerbation, Risk-factors, Mortality.

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease characterized by chronic inflammation of the respiratory tract and lungs resulting in limitation of airflow and subsequent destruction of lung tissue[1]. According to estimates, the disease affects more than 210 million individuals globally and would be the third most common cause of death in the world by 2030[2]. A common presentation of the disease is an acute exacerbation of COPD (AE-COPD) which manifests as rapid-onset dyspnea, often accompanied by productive cough, bronchospasm, deterioration of respiratory function, and poor prognosis[3,4]. Bronchial infection and air pollution are recognized as the major cause of AE-COPD, however, in about 30% of cases, no clear etiology is identifiable[5]. The signs and symptoms of AE-COPD can overlap several other clinical conditions like heart failure, asthma, pneumonia, and pulmonary embolism (PE) making overt clinical diagnosis difficult[6].

PE is a condition characterized by obstruction of pulmonary vasculature by a thromboembolism[7]. COPD patients are at particular risk of venous thromboembolism (VTE) due to factors like immobility, advanced age, smoking, infection, heart failure, and venous stasis[8]. Chen et al[9] have indicated that COPD patients have a four-times increased

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risk of PE as compared to the general population. However, as PE presents with similar signs and symptoms as AE-COPD, differentiating between the two conditions is often difficult[10]. The prevalence of PE in AE-COPD has been reported by several studies[11,12] in literature but with differences in the study population, design, and methodology. Aleva et al[12] in a systematic review and meta-analysis published in 2017 reported the prevalence of PE in AE-COPD to be 16.1%. However, the study could include only seven studies with a total of 880 patients which significantly limits the strength of the results. Also, the study could not conduct a meta-analysis on the impact of PE on outcomes of AE-COPD. Given several new publications in recent years, there is a need to update the past review[12] and provide comprehensive high-level evidence to clinicians involved in the management of AE-COPD. Therefore, the primary aim of the current study was to systematically search the literature for studies reporting the prevalence of PE in AE-COPD and pool data for a meta-analysis. Our review also aimed to provide a detailed description of the risk factors of PE and assess the impact of PE on the outcomes of AE-COPD.

Materials and Methods

Inclusion Criteria

Guidelines of the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[13] were followed during the conduct of this review. However, the protocol was not registered.

We developed the following inclusion/exclusion criteria to select studies for the review:

Inclusion criteria: 1) prospective, retrospective, and cross-sectional studies reporting the prevalence of PE in patients with AE-COPD; 2) studies were to diagnose PE based on computed tomography data.

The following studies were excluded: 1) studies reporting the prevalence of PE in COPD patients and not during AE-COPD; 2) studies diagnosing PE *via* other diagnostic methods; 3) review articles, editorials, and case reports were also excluded. If there were two or more studies which had duplicate or overlapping data, the study with a larger sample size was to be chosen for inclusion. No restriction was placed on the language of publication, and the sample size of the study.

Search Strategy

Two independent reviewers searched the databases of PubMed, Embase, and CENTRAL to identify relevant studies. All databases were screened electronically on the database websites from inception and the last search was conducted on 1st January 2021. Keywords used in different combinations were: "pulmonary embolism", "thromboembolism", "chronic obstructive pulmonary disease", and "acute exacerbation COPD". The search strategy and the combination of keywords used have been presented in **Supplementary Table I**. Search results were screened by their titles and abstracts to identify studies relevant to the review. Full texts of these studies were assessed based on the inclusion and exclusion criteria and the article fulfilling all the criteria was finally selected for this review. Any disagreements were resolved by discussion. We also performed a hand-search of the bibliography of included studies to look for any additional references which may have been missed in the electronic search.

Data Extraction

We prepared a data extraction form at the beginning of the review to extract relevant details from the studies. Details of the first author, publication year, study type, study location, inclusion criteria, the definition of AE-COPD, sample size, demographic details, PE diagnosis protocol, and prevalence of PE and DVT were extracted. In studies wherein baseline differences between PE and non-PE subjects were compared, we extracted data on those variables which were significantly different between the two groups. Furthermore, where available, we also extracted multivariable-adjusted odds ratios (OR) of independent predictors of PE, and mortality and length of hospital stay.

The primary outcome of interest was to assess the prevalence of PE in AE-COPD patients. Secondly, we qualitatively assessed baseline differences between PE and non-PE patients and independent predictors of PE in AE-COPD. Lastly, a quantitative analysis was conducted for the difference in mortality and length of intensive care unit (ICU)/hospital stay between PE and non-PE patients.

Risk of bias analysis

Since all included studies were observational in design, we assessed the risk of bias in included studies using the STROBE-score[14]. The STROBE-score was created to ascertain clear presentation of observational studies and to enable critical appraisal of the research. The score has a maximum of 22 points based on a pre-defined checklist. The checklists consist of several guidelines on the overall structure and reporting of the study. The STROBE-

score has been used to assess risk of bias in prior reviews assessing the prevalence of AE-COPD[12].

Statistical Analysis

We used the software "Open MetaAnalyst" for calculating the prevalence of PE in AE-COPD[15]. For the primary outcomes, we extracted prevalence of PE in AECOPD from the included studies. Then, using the meta-analysis software we calculated point estimates with 95% confidence intervals (CI) of the prevalence data. Data were then transformed using the logit transformation for pooling the proportions using the DerSimonian-Laird random-effects meta-analysis model. This gave us the pooled prevalence of PE in AE-COPD. Secondly, we explored the heterogeneity in the prevalence of PE in AE-COPD amongst included studies by segregating them based on the different PE workup criteria used in the study. As some studies conducted CT examination in all AE-COPD patients, while others carried out CT scans only after other diagnostic tests, we performed a sub-group analysis based on these different PE workup criteria to provide clarity on current evidence.

For analyzing data on difference in mortality and length of hospital stay between AE-COPD and non AE-COPD patients, we used the software "Review Manager" (RevMan, version 5.3; Nordic Cochrane Centre [Cochrane Collaboration], Copenhagen, Denmark; 2014) for the meta-analysis. Dichotomous data on mortality were pooled to calculate OR with 95% CI. To assess the heterogeneity amongst included studies, we performed a sub-group analysis based on follow-up duration. Mean and standard deviation (SD) of the length of hospital stay were pooled to calculate the mean difference (MD) with 95% CI. In some studies, mean and SD values were not provided for length of hospital stay. In such cases, we calculated mean and SD values from the reported median and interquartile range values using methods developed by Wan et al[16]. A random-effects model was preferred for the meta-analysis. The I^2 statistic was used to assess inter-study heterogeneity. I^2 values of 25-50% represented low, values of 50-75% medium, and more than 75% represented substantial heterogeneity.

Results

Figure 1 presented the study flow-chart. A total of 28 articles were screened by their full texts of which 12 were excluded with reasons. Sixteen articles fulfilled the inclusion criteria for the review[17-32]. Details of the included studies are presented in Table I. The majority were prospective studies while four were retrospective and two were cross-sectional studies. The studies were carried out in different parts of the world. The sample size varied from 49 to 1144. The PE workup protocol differed across studies. In seven studies, CT was carried out in all patients for the diagnosis of PE. In the remaining studies, selective patients underwent CT based on the discretion of the physician[18,22,23,31,] Geneva score[24,33], Wells score[20,34], echocardiography criteria[21], lower limb ultrasonography (USG)[20] or D-dimer levels[25,32]. The reported prevalence of PE varied from 2.1% to 33% in the included studies. Some studies also reported the prevalence of DVT based on ultrasonography findings, which varied from 1.4% to 29.1%. STROBE score was ≥18 for all studies.

Prevalence of PE

On the meta-analysis of data from 5035 patients, the pooled prevalence of PE in AE-COPD was 12.9% (95% CI: 8.9%-18.4%) (Figure 2). As mentioned in Table I, the protocol for diagnosis of PE in AE-COPD patients differed across included studies. Owing to such heterogeneity in the PE workup amongst included studies, a sub-group analysis was performed to estimate the prevalence of PE in studies with similar PE workup protocol (Figure 1). In studies wherein all patients underwent CT without any other diagnostic protocol or physician's discretion, the prevalence was found to be 19.4% (95% CI: 13.4%-27.4%). On the other hand, the prevalence of PE was 7.8% (95% CI: 3.7%-15.7%) in studies where CT was carried out only after screening patients based on the study-specific diagnostic protocol, i.e., after evaluation of Geneva score[24,33] or Wells score[20,34], echocardiography criteria[21], lower limb ultrasonography (USG)[20] or D-dimer levels[25,32] (Table I). In three retrospective studies[18,22,23]mean p <0.05, only patients undergoing CT based on physician's discretion were selected and the pooled prevalence was found to be 14.1% (95% CI: 9.7%-20.1%).

Risk Factors for PE

Details of statistically significant differences in clinical characteristics between PE and non-PE AE-COPD patients as reported by the included studies are presented in Table II. Several different variables were found to be significantly different between the two groups. Variables reported by multiple studies that were associated with PE in-

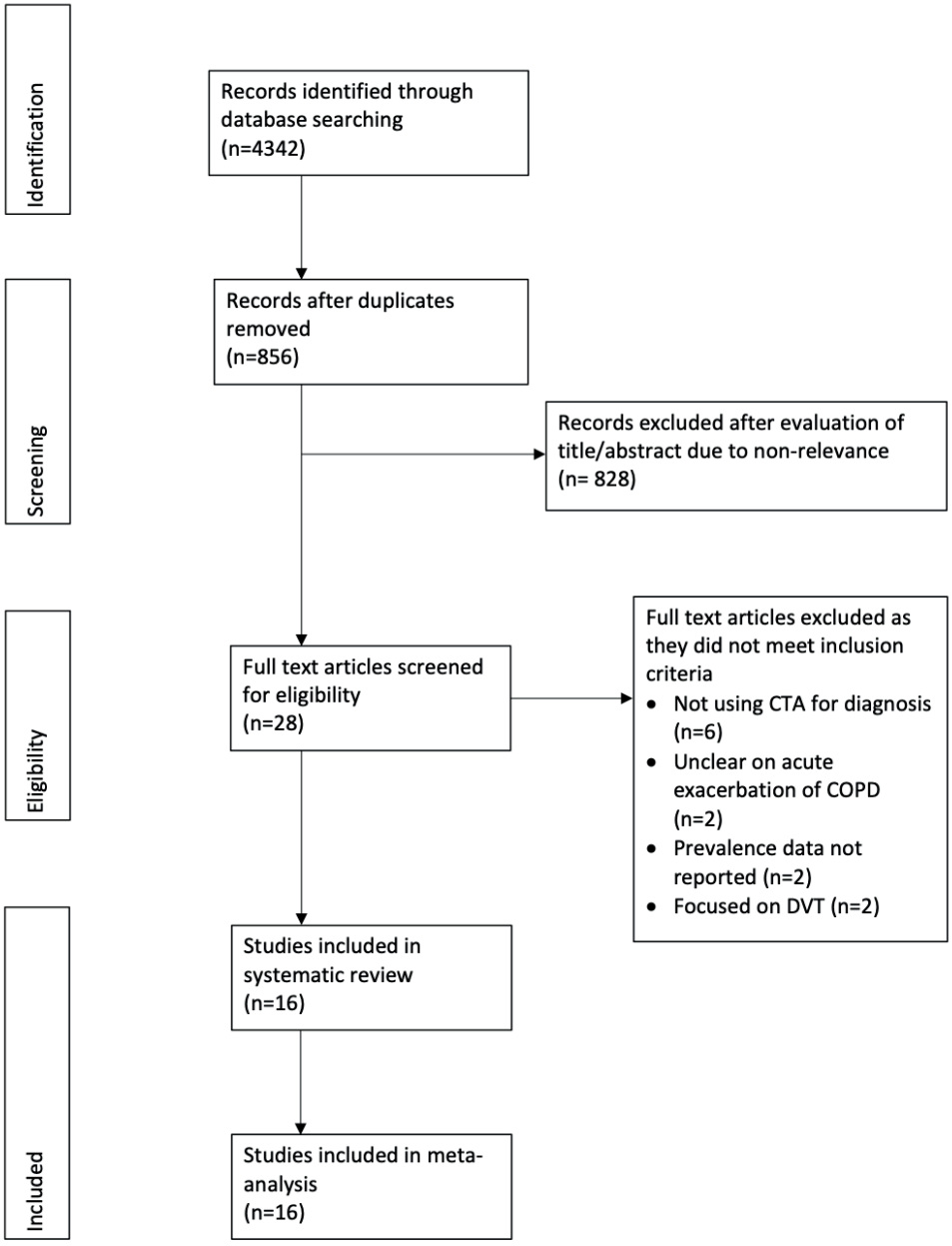

Figure 1. Study flow-chart.

cluded: high D-dimer levels (5 studies), low $PaCO_2$ values (4 studies), prior history of VTE (4 studies), higher age (4 studies), recent immobility/bed rest (3 studies), lower limb edema (3 studies), male gender (2 studies), chest pain (2 studies), syncope (2 studies), low blood pressure (2 studies), higher arterial blood pH (2 studies), higher heart rate (2 studies), presence of DVT (2 studies), atrial fibrillation (2 studies), and higher N-terminal pro-Brain natriuretic peptide (2 studies). Since these variables were unadjusted, we also extracted data on independent predictors of PE in AE-COPD as reported by the studies[17,18,20,21,23,28,30] (Table III). Recent immobilization, higher D-dimer level, and lower limb edema were found to be independent predictors of PE by ≥3 studies. Older age and the presence of DVT were found to be independent predictors by two studies.

Impact of PE on Outcomes of AE-COPD

Data on outcomes were reported by a limited number of studies. Of the seven studies reporting

mortality data, four reported in-hospital mortality, two reported mortality at three months while one reported mortality at one year. Pooled analysis indicated that PE was associated with a significantly increased risk of mortality in AE-COPD (OR: 3.21 95% CI: 1.86, 5.54 I^2=52% p<0.0001) (Figure 3). The difference was significant for both in-hospital mortality (OR: 2.81 95% CI: 1.20, 6.55 I^2=56% p=0.02) and mortality up to 1 year (OR: 3.91 95% CI: 1.99, 7.66 I^2=40% p<0.0001) (Figure 3). Pooled analysis of five studies indicated that length of ICU/hospital stay was significantly longer in PE patients as compared to non-PE patients (MD: 3.26 95% CI: 1.93, 4.58 I^2=0% p<0.00001) (Figure 4).

Discussion

The diagnosis of PE in a setting of AE-COPD patients has always been challenging as both AE-COPD and PE present with a common spectrum of symptoms, including tachycardia, dyspnea, and tachypnea[10]. Furthermore, distinguishing the two based on physical signs, chest X-ray, and arterial blood gas analysis is also difficult[6]. Baum and Fisher[35] have indicated PE prevalence of up to 50% in patients with AE-COPD. However, according to our results, the prevalence of PE in AE-COPD in clinical practice is estimated to be 12.9% ranging from 8.9% to 18.4%. The overall prevalence in our study was lower as compared to the previous meta-analysis [16.1% (95% CI 8.3%-25.3%)][12]. The variation may be explained by a significant difference in the power of the two studies (880 *vs.* 5035). We were able to add nine more studies to our analysis thereby strengthening the overall evidence. Also, unlike the past review, we attempted to explore the heterogeneity in the prevalence of PE amongst the included studies based on the PE workup protocol. In studies in which CT was ordered for all patients, the prevalence of PE was found to be on the higher side at 19.4% (95% CI: 13.4%-27.4%). In contrast, studies[20,21,24,25,31,32] utilizing a pre-defined protocol for recommending a CT reported a lower prevalence of PE at 7.8% (95% CI: 3.7%-15.7%). In the three retrospective studies[18,22,23] wherein all patients underwent CT based on clinical suspicion by the physician, a prevalence of 14.1% (95% CI: 9.7%-20.1%) was noted.

CT angiogram (CTA) remains the gold-standard in the diagnosis of PE. However, concerns regarding radiation exposure, allergy to contrast media, contrast-induced nephropathy, and cost of the procedure limits the widespread use of CTA[36]. In this context, several clinical scoring systems and less noxious diagnostic tools have been developed to screen AE-COPD patients for PE and subsequent confirmation by CTA. The Wells score and Geneva score are clinical prediction rules which are widely used for stratifying the risk of PE[37]. However, as these rules were developed on a general population without COPD[38], concerns have been raised if they can be applied for evaluating the presence of PE in AE-COPD patients[22,29]. The diagnostic accuracy of these scores for the presence of PE in AE-COPD has been reported in literature, but results have not been encouraging. In one of the included studies, Furcada et al[22] reported the sensitivity and specificity of Wells score (cut-off >4) for diagnosis of PE in AE-COPD to be 24% and 90% and for the Geneva score (cut-off≥3) to be 59% and 43% respectively. Similar low diagnostic accuracy for these rules has been reported by other included studies as well[27,29]. In our review, Couturaud et al[24] used a very high Geneva score (≥11) for the initial screening of AE-COPD patients while the remaining patients were further screened by D-dimer levels. Elevated levels of D-dimer, which is a fibrin-degradation product, are found during active clot remodeling like during acute PE. However, the high rate of false-positive results on D-dimer testing especially in AE-COPD patients is a cause of concern[32]. Several studies[39,40] have demonstrated that due to the hypercoagulable state in COPD, D-dimer levels may be increased even in stable COPD patients as compared to controls. To overcome this, studies[40,41] have indicated the use of higher cut-offs of D-dimer and even age-adjusted D-dimer levels to reduce the use of confirmatory CTA in such patients. Considering the variations reported in the prevalence of PE on our sub-group analysis with the different PE workup protocols and limitations of existing screening tools, it is evident that selecting patients based on various screening criteria is bound to underestimate the prevalence of PE in AE-COPD. However, as routine CTA cannot be used for all patients, clinicians should use multiple screening tools and have a high degree of suspicion based on risk factors of PE in AE-COPD to recommend further confirmatory testing.

Amongst the several clinical differences reported between PE and non-PE patients by individual studies on bivariate analysis, only a few of them

Table I. Details of included studies.

Study	Location	Study type	Inclusion criteria	Definition of AE-COPD	Sample size	Mean age (years)	Male gender (%)	PE workup	PE (%)	DVT (%)	STROBE score
Tillie-Leblond 2006[26]all current or former smokers with COPD, who were admitted to the hospital for severe exacerbation of unknown origin and did not require invasive mechanical ventilation. Measurements: Spiral computed tomography angiography (CTA	France	P	Consecutive COPD patients admitted to the hospital for severe exacerbation of unknown origin. COPD diagnosed by ATS criteria.	Acute deterioration from a stable condition that required hospitalization	197	60.5± 12.1	83.6	All patients underwent CTA and lower limb USG Doppler within 48 hours of admission	25	12.7	21
Rutschmann 2007[25]	Switzerland	P	Consecutive patients admitted for moderate to very severe AE-COPD. COPD diagnosed by GOLD criteria.	Worsening of dyspnea that required admission to the Emergency Department	123	71± 8	68	If D-dimer >500 mg/l then lower-limb USG and thoracic helical CT scan	3.3	2.2	20
Gunen 2010[27]	Turkey	P	Consecutive patients admitted for AE-COPD. COPD diagnosed by medical history and records.	Acute deterioration from a stable condition that required hospitalization	131	67± 10.1	79.4	All patients underwent CTA and lower limb Doppler USG	13.7	10.6	19
Wang 2012[17]	China	P	Consecutive patients hospitalized for severe AE-COPD	Acute deterioration from a stable condition that required hospitalization	208	62± 12	NA	All patients underwent CTA and lower limb USG	33	NR	19
Choi 2013[28]	South Korea	P	Consecutive patients hospitalized for AE-COPD	Acute deterioration from a stable condition that required hospitalization	103	71± 6	70	All patients underwent CTA and indirect CT venography within 24 hours of admission	5	6	19
Kamel 2013[29]	Egypt	CS	Patients hospitalized for AE-COPD	NR	105	49.3± 8.4	100	All patients underwent CTA, lower limb Doppler USG and CT venography within 24 hours of admission	28.6	10.5	18
Akpinar 2014[30]	Turkey	P	Consecutive patients admitted for AE-COPD. COPD diagnosed by medical history and records.	Worsening in respiratory symptoms beyond normal day- to-day variations that led to a change in medication	172	71.3± 9.6	82.6	All patients underwent CTA and lower limb Doppler USG	29.1	29.1	20
Bahloul 2014[31]Tunisia	Tunisia	R	Patients hospitalized in ICU for AE-COPD. COPD diagnosed by clinical history, physical examination, arterial blood gas results and chest radiograph.	Presence of at least two of the following signs and symptoms: change in baseline dyspnea, cough, and sputum quantity or purulence	131	68.6± 9.2	90	Only patients with suspicion of PE based on symptoms of right ventricular dysfunction, chest X-ray findings, arterial blood gas results and electrocardiography abnormalities underwent CTA	17.5	NR	18
Shapira-Rootman 2014[32]	Israel	P	Consecutive patients admitted for AE-COPD. COPD diagnosed by spirometry.	Worsening of dyspnea that required admission to the hospital	49	65.5± NR	71.4	If D-dimer >500 mg/l then chest CTA scan	18.4	NR	19
Li 2016[18]mean P<0.05	China	R	All patients admitted for AE-COPD and those who underwent CTA.	Acute deterioration from a stable condition that required hospitalization	522	72± 9	NA	Only patients with CTA included. CTA performed at the discretion of the physician.	10.3	NR	19
Davoodi 2018[19]	Iran	CS	Consecutive patients admitted for AE-COPD. COPD diagnosed by medical records and spirometry.	NR	68	67.7± 9.2	55.9	All patients underwent CTA within 72 hours of admission	7.4	NR	18

Table continued

Table I. ***(Continued).*** Details of included studies.

Study	Location	Study type	Inclusion criteria	Definition of AE-COPD	Sample size	Mean age (years)	Male gender (%)	PE workup	PE (%)	DVT (%)	STROBE score
Pang 2018[21]	China	P	Consecutive patients admitted for AE-COPD. COPD diagnosed by GOLD criteria.	Severely increased symptoms and failure to respond to initial treatment or treatment at home	1144	72± 9.1	67.3	Pulmonary artery pressure measured by echocardiography. CTA performed for patients with moderate-to-severe pulmonary hypertension (systolic pulmonary artery pressure ≥40mmHg)	2.1	5.6	20
Hassen 2019[20]risk factors, and impact of PE during COPD exacerbation requiring mechanical ventilation. METHODS: This prospective cohort study was conducted between March 2013 and May 2017. Subjects with severe COPD exacerbation requiring mechanical ventilation were included. A lower-limb ultrasonography or a multidetector helical computed tomography scan (MDCT	Tunisia	P	Consecutive patients admitted to ICU for severe AE-COPD. COPD diagnosed by medical records and spirometry.	Based on GOLD criteria	131	68± 13	79	Wells score measured on admission. For scores >2, CTA performed. For others, lower limb USG performed, in case of incomplete compressibility of the vein, CTA performed	13.7	NR	20
Dentali 2020[23]	Italy	R	All patients admitted for AE-COPD and those who underwent CTA. COPD diagnosed by GOLD criteria, based on previous hospitalization for COPD or on treatment for COPD	NR	1043	75.8± 9.7	65.5	Only patients with CTA included. CTA performed at the discretion of the physician.	12.6	-*	20
Furcada 2020[22]Argentina. We estimated the area under the receiver operating characteristic curves (AU-ROC	Argentina	R	Patients admitted for AE-COPD and those who underwent CTA	NR	168	74 [66-81]^	63	Only patients with CTA included. CTA performed at the discretion of the physician.	22	NR	18
Couturaud 2021[24]	France	P	Consecutive patients admitted for AE-COPD. COPD diagnosed by spirometry or prior diagnosis by pulmonologist needed	Worsening in respiratory symptoms beyond normal day- to-day variations that led to treatment modification	740	68.2± 10.9	63	All patients assessed for PE probability by Geneva score. For scores ≥11, CTA and lower limb USG performed. For remaining, D-dimer testing done and for D-dimer >500 mg/l, chest CTA performed	5.9	1.4	21

*only a limited number of patients underwent lower limb USG, hence data was excluded; ^Median [Interquartile range]; P, Prospective; R, retrospective; CS, cross-sectional; NR, not reported; AE, acute exacerbation; COPD, chronic obstructive pulmonary disease; CTA, computed tomography angiography; USG, ultrasonography; PE, pulmonary embolism; DVT, deep vein thrombosis; ICU, intensive care unit; ATS, American Thoracic Society; GOLD, Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease.

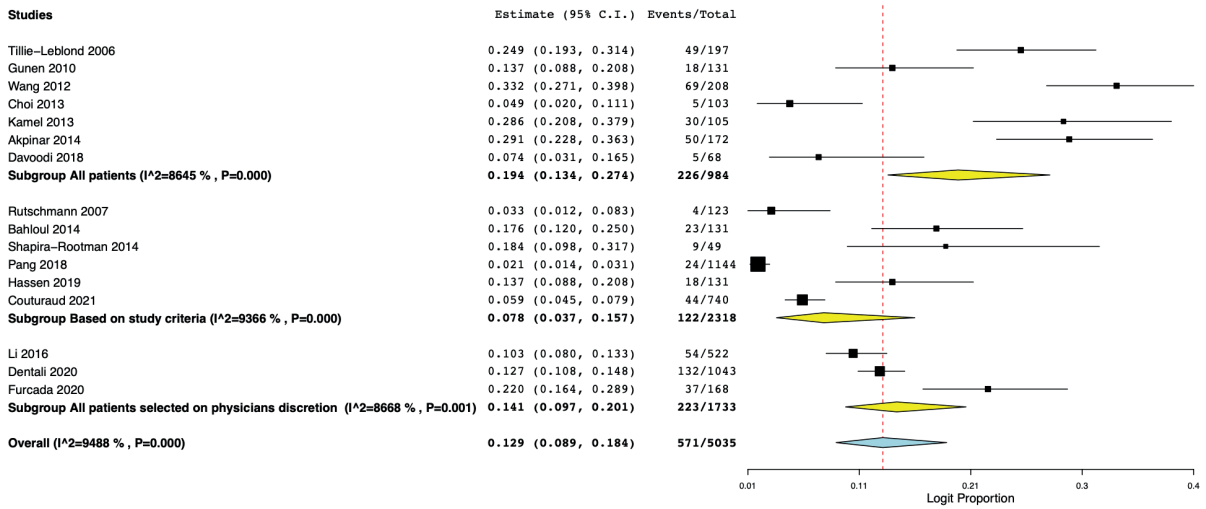

Figure 2. Meta-analysis of prevalence of PE in patients with AE-COPD with sub-group analysis based on PE workup protocol.

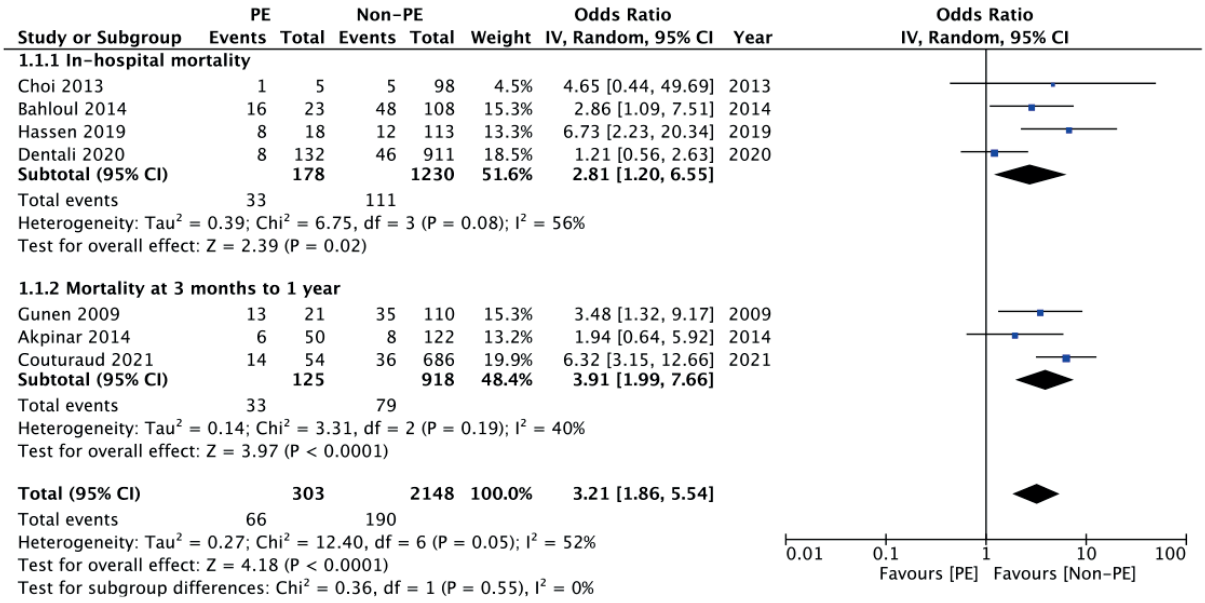

Figure 3. Meta-analysis of difference in mortality between PE and non-PE AE-COPD patients with sub-group analysis based on follow-up duration.

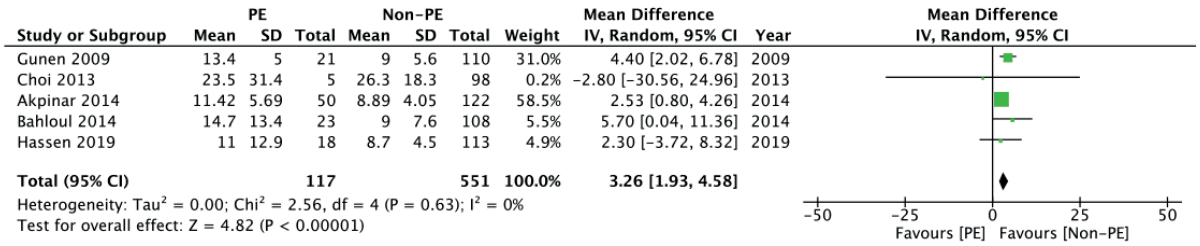

Figure 4. Meta-analysis of difference in length of ICU/hospital stay between PE and non-PE AE-COPD patients.

Table II. QRT-PCR primer sequences.

Study	Variable	PE	Non-PE	*p*-value
Tillie-Leblond 2006[26*]	Previous PE or DVT	12 (25%)	23 (12%)	0.004
	Malignant disease	21 (43%)	57 (29%)	0.018
	Decrease in $PaCO_2$ ≥5mmHg from previous arterial blood gas values	9 (27%)	15 (8%)	0.034
Gunen 2010[27^]	Male gender	13 (61.9%)	91 (82.7%)	0.041
	Chest pain	17 (80.9%)	44 (40%)	0.0007
	Syncope	5 (23.8%)	3 (2.7%)	0.0027
	Hypotension	3 (14.3%)	1 (0.9%)	0.013
	Atrial fibrillation on ECG	4 (19%)	2 (1.8%)	0.006
	Acute right heart failure on echocardiography	5 (23.8%)	0	0.0001
	D-dimer (μg/mL)	5.2± 4.5	1.2± 1.8	0.001
Choi 2013[28]	Symptoms of respiratory infection	1 (20%)	80 (83%)	0.001
	D-dimer (μg/L)	1479± NR	378± NR	0.01
Akpinar 2014[30]	D-dimer (μg/mL)	2.38± 2.8	1.06± 1.51	<0.001
	Pleuritic chest pain	12 (24%)	14 (11.5%)	0.038
	Lower limb asymmetry	11 (22%)	7 (5.7%)	0.002
	N-terminal pro-Brain natriuretic peptide (pg/L)	1664± 3247	1188± 3233	0.006
	Arterial blood pH	7.47± 0.0072	7.4± 0.039	<0.01
	$PaCO_2$ (mmHg)	34± 20	37.5± 10.1	<0.05
Bahloul 2014[31]	Shock	23 (100%)	84 (77.7%)	0.012
	Coma	6 (26%)	9 (8.3%)	0.01
Li 2016[18]	Age ≥70 years	41 (70.7%)	287 (61.3%)	0.036
	Immobility ≥3 days	13 (24.1%)	8 (1.7%)	<0.001
	History of VTE	6 (11.1%)	7 (1.4%)	<0.001
	DVT	12 (22.2%)	21 (4.5)	<0.001
	D-dimer ≥2000 μg/L	30 (55.6%)	98 (20.9%)	<0.001
	N-terminal pro-Brain natriuretic peptide ≥1200 pg/L	24 (44.4%)	78 ((16.7%)	0.001
	Pneumonia	24 (44.4%)	130 (27.8%)	0.01
	Atrial fibrillation	5 (9.2%)	13 (2.8%)	0.03
	Lower extremity edema	39 (72.2%)	117 (25%)	<0.001
Davoodi 2018[19]	Systolic blood pressure mmHg	88.3± 1.53	118.3± 20.18	<0.001
	Heart rate	132± 7.21	90.33± 12.07	<0.001
	Arterial blood pH	7.46± 0.03	7.36± 0.06	0.024
	PaCO2 (mmHg)	42.33± 2.52	51.43± 11.91	0.002
	Arterial blood HCO3	2.3± 0.0	3.25± 9.44	<0.01
	LVEF	35± 5	46.94± 8.27	0.038
	Mitral regurgitation	0	12 (19%)	0.039
Pang 2018[21^]	Age (years)	74.3± 7.9	71.8± 9.2	0.019
	Syncope	4 (5.1%)	15 (1.4%)	0.035
	Lower limb swelling	41 (52.6%)	356 (33.4%)	<0.001
	Walking difficulty	18 (23.1%)	90 (8.4%)	<0.001
	Lower limb pain	14 (18.4%)	30 (3%)	<0.001
	Hemoglobin (g/L)	189 [128.3-243.5]~	190 [143-241]~	0.014
	D-dimer (μg/dL)	0.8 [0.4-1.5]~	0.3[0.2-0.7]~	<0.001
	History of VTE	33 (42.9%)	32 (3%)	<0.001
	Diuretics treatment	27 (34.6%)	231 (22.4%)	0.014
	Bedridden/immobility ≥3 days	30 (46.9%)	180 (19.1%)	<0.001

Table continued

Table II. ***(Continued).*** QRT-PCR primer sequences.

Study	Variable	PE	Non-PE	*p*-value
Hassen 2019[20]	Age (years)	75± 7	67± 14	0.005
	Simplified Acute Physiology Score II	35 [21-42]~	26[20-35]~	0.036
	Dyspnea at rest	12 (67%)	34 (30%)	0.01
	Dyspnea on activity	6 (38%)	79 (70%)	0.005
	Cough	9 (50%)	101 (89%)	<0.001
	Increased sputum volume	5 (28%)	85 (75%)	<0.001
	Heart rate	109± 16	100± 18	0.042
Dentali 2020[23]	Age (years)	78.9± 8.7	75.3± 9.7	<0.0001
	Male gender	66 (50%)	617 (67.7%)	<0.0001
	Recent bed rest ≥3 days	45 (34.1%)	214 (23.5%)	0.01
	History of VTE	22 (16.7%)	72 (7.9%)	0.001
	Hypertension	45 (34.1%)	224 (24.6%)	0.02
	Purulent sputum	22 (16.7%)	229 (25.1%)	0.03
	Clinical signs of DVT	33 (25%)	55 (6%)	<0.0001
	Atleast 1 ECG abnormality suggestive of PE*	35 (26.5%)	168 (18.6%)	0.03
	PaCO2< 40mmHg*	72 (60%)	380 (46.6%)	0.01
	Normal chest X-ray*	39 (34.8%)	158 (19.2%)	0.0001
Furcada 2020[22]	Isolated dyspnea	34 (91.9%)	82 (62.6%)	0.001
	Outpatient status	35 (94.5%)	102 (77.9%)	0.021

Data reported as number (percentage) or Mean± Standard deviation; *missing data for baseline variables; ~Median [Interquartile range]; ^Comparison of VTE vs non-VTE groups instead of PE vs non-PE groups; PE, pulmonary embolism; DVT, deep vein thrombosis; VTE, venous thromboembolism; ECG, electrocardiogram; PaCO2, partial pressure of carbon dioxide; LVEF, left ventricular ejection fraction.

were found to be independent predictors of PE and were repeated across multiple studies. Our qualitative analysis indicated that recent immobilization, increased D-dimer levels, lower limb edema, older age and the concomitant presence of DVT are important factors that should raise the suspicion of PE in AE-COPD patients. The majority of these factors are inter-dependent and have been verified to be important risk factors of VTE even in the general population[42,43]. Immobilization is known to cause a prethrombotic state in COPD patients and prolonged immobilization (more than 3-7 days) significantly increases the risk of VTE[21]. According to data from the RIETE registry, more than 30.5% of COPD patients had a history of immobilization for ≥4 days in the two months preceding the diagnosis of VTE[44].

Our results also demonstrated that the presence of PE significantly increases the mortality rates and length of ICU/hospital stay in AE-COPD patients. It is important to note that only unadjusted data were pooled in our meta-analysis and these outcomes may have been confounded by other factors. Couturaud et al[24] reported increased cancer-related deaths in patients with PE and AE-COPD. It is known that VTE is associated with poor prognosis in patients with cancer[45]. However, increased mortality with combined PE and COPD has been reported by other studies[46,47] as well. de-Miguel-Diez et al[46] in a nation-wide study of 47,190 PE patients have reported 2.8 times increased risk of mortality in PE patients with COPD as compared to non-COPD patients. Similarly, Carson et al[47] have reported that the combination of PE and COPD has increased mortality as compared to COPD patients without PE as well as non-COPD patients.

The limitations of our review need to be mentioned. Foremost, there was inter-study heterogeneity concerning study design, methodology, inclusion/exclusion criteria, and PE workup protocol amongst the included studies. This may have led to wide variations in the individual results. Secondly, unlike the previous review, we also included retrospective studies in our analysis for providing comprehensive evidence. However, the inherent bias of retrospective studies might have skewed results. Furthermore, several of the included studies were of a small sample size which may have underestimated or overestimated the actual prevalence of PE in their cohort. Thirdly, only a limited number of

studies were included in the meta-analysis on outcomes due to the paucity of data.

The strengths of our review include the large number of studies included in the analysis significantly raising the power of our review. Our analysis presents the largest pooled data of PE prevalence in AE-COPD to date. Unlike previous studies[11,12], we presented separate prevalence rates based on PE workup protocol, thereby providing clarity to readers. Lastly, a detailed review of risk factors and a meta-analysis of the impact of PE on outcomes was also carried out.

Conclusions

The results of our updated systematic review and meta-analysis indicate that the prevalence of PE in AE-COPD is 12.9%. This figure, however, varies based on the PE workup protocol. Higher prevalence (19.4%) was noted when all patients underwent CT as compared to when a study-specific diagnostic protocol was followed (7.8%). Recent immobilization, increased D-dimer levels, lower limb edema, older age and the concomitant presence of DVT are important independent risk factors for PE in patients with AE-COPD. Patients diagnosed with PE have increased mortality and longer ICU/hospital stay as compared to non-PE patients.

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