COPD exacerbation purulence status and its association with pulmonary embolism: a systematic review with meta-analysis

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Shareable abstract (@ERSpublications)
The risk of pulmonary embolism was clinically lower in patients with purulent acute exacerbation of COPD (AECOPD) compared to patients with nonpurulent/unknown aetiology AECOPD https://bit.ly/4leYsQt

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Abstract

Background Diagnosing pulmonary embolism (PE) in patients with acute exacerbation of COPD (AECOPD) is challenging. Finding predictors of PE could help improve diagnostic management of patients with AECOPD. The aim was to evaluate the association between AECOPD purulence status and the presence of PE.

Methods A systematic review with meta-analysis was conducted. Medline, Embase and CENTRAL were searched from inception to April 2024 for randomised trials, cohort or cross-sectional studies reporting on the prevalence of PE according to AECOPD purulence status. Relative risks with 95% confidence intervals of PE according to AECOPD purulence status and pooled proportions of PE with their 95% confidence intervals were calculated according to AECOPD purulence status.

Results From 7059 citations identified, 14 studies (5056 participants) were included. The prevalence of PE varied between 0.4% and 33.2% across studies. The relative risk of PE was not statistically significantly lower in patients with purulent AECOPD compared to patients with nonpurulent/unknown aetiology AECOPD (relative risk 0.64, 95% CI 0.26–1.55; I^2=88.0%). The pooled proportion of PE was 7.3% (95% CI 2.4–14.7%; I^2=94.7%) and 13.3% (95% CI 8.0–19.7%; I^2=96.0%) in studies including patients with purulent AECOPD and nonpurulent/unknown aetiology AECOPD, respectively.

Conclusion The relative risk of PE was lower, but not statistically significant, in patients with purulent AECOPD compared to patients with nonpurulent/unknown aetiology AECOPD. Further studies are needed to confirm the association between PE and AECOPD purulence status and to assess its potential role in predicting PE.

Introduction

Acute exacerbation of COPD (AECOPD) is a risk factor for pulmonary embolism (PE) [1]. Patients with COPD have chronic inflammation, either systemic and/or affecting the airways, and this inflammation increases in the context of AECOPD [2], which contributes to the increased risk of thrombosis. Moreover, it has been suggested that PE might be a cause of AECOPD, especially when the cause of the exacerbation is unknown [3]. As the severity of COPD progresses, the risk of AECOPD also increases, with an estimated rate of 0.5–3.5 exacerbations per person per year [4, 5]. With a five-fold increase in mortality when PE is diagnosed in patients with AECOPD [6], it is critical to diagnose PE in these patients.

However, diagnosing PE in patients with AECOPD is challenging since the two diseases have a similar clinical presentation. Moreover, it is unclear when PE should be suspected or when imaging should be performed to rule out PE in patients with COPD presenting with increased respiratory symptoms. Given

the higher prevalence of PE in patients with AECOPD, it may not be safe to exclude PE based on history and clinical exam alone [7, 8]. When standard PE diagnostic strategies, (such as the revised Geneva or Wells PE scores combined with D-dimer at a fixed cut-off), are applied, a high proportion of patients need imaging to rule out PE [7, 9]. Computed tomography pulmonary angiography (CTPA) is the diagnostic modality most frequently used to rule out PE, but this radiological test comes with radiation (important given most COPD patients have repeated exacerbations), cost, possible contrast-induced allergy or nephropathy as well as incidental findings.

Therefore, identifying predictors of PE diagnosis could help improve diagnostic management of patients with AECOPD. Some studies showed a lower rate of PE or venous thromboembolism (VTE) in patients with purulent AECOPD as compared with patients with nonpurulent or unknown aetiology AECOPD [10–12]. Since the cause of nonpurulent and unknown aetiology AECOPD is most often unclear, PE could account for those types of exacerbations. Thus, the aim of this systematic review with meta-analysis was to evaluate the association between the AECOPD purulence status and the presence of PE.

Methods

Protocol and registration

The protocol of this systematic review with meta-analysis has been published previously [13] and was also registered in PROSPERO (CRD42023459429). Since this study is a systematic review with meta-analysis, institutional review board approval was not required.

Eligibility criteria

Inclusion criteria were randomised trials, cohort studies (retrospective or prospective) or cross-sectional studies that reported on the prevalence of PE according to the AECOPD purulence status. AECOPD purulence status was categorised as 1) definitive purulent AECOPD (purulent AECOPD or purulent sputum), 2) possible purulent AECOPD (clinical and/or radiological evidence of tracheobronchial infection or pneumonia), 3) nonpurulent AECOPD or unknown aetiology AECOPD. The term unknown aetiology AECOPD was used instead of unknown purulence status (as published in the protocol) to reflect more precisely this group of patients with AECOPD. There was no restriction on language. Published manuscripts and conference abstracts were included. Studies were excluded if the prevalence of PE according to the AECOPD purulence status was not provided in the paper or by the authors.

Information sources and search strategy

From inception to 1 April 2024, Medline, Embase and CENTRAL (Cochrane Central Register of Controlled Trials) were searched. Conference abstracts from the American Thoracic Society, the American College of Chest Physicians, the European Respiratory Society, the British Thoracic Society, the American Society of Hematology and the International Society on Thrombosis and Haemostasis were hand searched from January 2000 to April 2024. Studies were translated when needed. The search strategy was reviewed by a research librarian with expertise in knowledge synthesis and translation. The search strategy can be found in the supplemental file (appendix 1).

Study selection

Screening of citations was conducted using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). All titles and abstracts for potential inclusion in this study were screened by two independent reviewers (V. Mai and L. Girardi). Full texts of potentially eligible studies were screened independently by two reviewers (V. Mai and L. Girardi). Disagreements were resolved by consensus or by consulting a third reviewer (G. Le Gal). If the same cohort was published in multiple articles, the article with the largest cohort reporting on the information needed was included. For two studies [7, 8] where the prevalence of PE was described but not available according to the AECOPD purulence status, the corresponding authors were contacted for the data since we knew they were available.

Data extraction

A standardised collection form was used by two reviewers (V. Mai and L. Girardi) for independent data extraction. Disagreements were resolved with a discussion between the two reviewers (V. Mai and L. Girardi) or with the third reviewer's (G. Le Gal) input. Data on baseline characteristics of the studies and outcomes in each study were extracted.

Outcome measures

The primary outcome was PE at initial assessment. PE was defined as either symptomatic, incidental or fatal and was involving subsegmental branches or more proximal arteries on CTPA, high probability on a planar ventilation/perfusion (V'/Q') scan or at least one segmental mismatch or two subsegmental

mismatches on *V′/Q′* single photon emission computed tomography (European Association of Nuclear Medicine criteria) [14], when available. Studies in which the localisation of PE was not specified in the text were included, and subgroup analyses were performed. Secondary outcomes included VTE (*i.e.* deep venous thrombosis (DVT) (either proximal or distal) and/or PE) and DVT (either proximal or distal), respectively, at initial assessment. Distal and proximal DVT were not presented separately as planned in the protocol since many included studies did not specify the localisation of the DVT. DVT could be either symptomatic or incidental and was localised in the lower extremity. Initial assessment was defined as the first 48 h from hospital admission or initial medical evaluation if the patient was admitted or managed as an outpatient, respectively, or as defined by individual studies.

Risk of bias

The risk of bias of each included study was assessed independently by two reviewers (V. Mai and L. Girardi) by using the ROBINS-E tool [15]. The risk of bias of each study was evaluated by using AECOPD purulence status as the exposure. Publication bias was assessed visually with a funnel plot for the primary outcome. Absence of publication bias was considered if the funnel plot was symmetrical.

Data synthesis and statistical analysis

The prevalence of PE, DVT and VTE at initial assessment for each study was calculated with 95% confidence intervals by using the binomial exact method (https://sample-size.net/confidence-interval-proportion/). For the prevalence of VTE, if PE and DVT were diagnosed in a same patient, only one thromboembolic event was counted. The association between the risk of PE and the AECOPD purulence status was assessed by calculating relative risks with 95% confidence intervals using a Mantel–Haenszel random-effects model. Events were categorised in the definitive purulent AECOPD group if it was mentioned purulent AECOPD or the sputum was described as purulent. Events were categorised in the possible purulent AECOPD group if there was clinical and/or radiological evidence of tracheobronchial infection or pneumonia. If two definitions were found in a same study, the definitive purulent AECOPD definition was used for the main analysis and sensitivity analyses were conducted by using alternative definitions of purulent AECOPD. Since some studies could not be pooled in the evaluation of the relative risk evaluating the association between PE and AECOPD purulence status, pooled proportions of PE according to the type of AECOPD (purulent AECOPD and nonpurulent/unknown aetiology AECOPD) were calculated using random-effects model using StatsDirect statistical software. To evaluate heterogeneity, I^2 was calculated. Significant heterogeneity was considered if I^2>50%. Subgroup analyses were conducted for type of study (randomised trials *versus* prospective cohort studies *versus* retrospective cohort studies *versus* cross-sectional studies), systematic search of PE *versus* no systematic search of PE and localisation of PE (segmental and more proximal PE *versus* subsegmental and more proximal PE *versus* unknown). Since the definition of purulent AECOPD was heterogenous across studies and some studies included various definitions of purulent AECOPD, *post hoc* sensitivity analyses were conducted according to the definition of purulent AECOPD (possible purulent AECOPD definition was used primarily instead of the definitive purulent AECOPD definition and clinical purulent AECOPD definition was used in combination with possible purulent AECOPD definition used primarily) and by using a fixed-effects model. Sensitivity analyses according to the risk of bias were planned. Similar analyses for DVT and VTE, respectively, were planned. The manuscript was drafted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.

Results

Studies selection

The systematic search identified 7059 citations, of which 191 full texts were evaluated for eligibility and 14 studies [7, 8, 10, 11, 16–25], representing 5056 participants, were included. The reasons of exclusion can be found in figure 1.

Characteristics of the studies

Out of the 14 included studies [7, 8, 10, 11, 16–25], nine studies [7, 8, 10, 11, 16–20] included patients with purulent and nonpurulent/unknown aetiology AECOPD, whereas five studies [21–25] included only patients with nonpurulent/unknown aetiology AECOPD (table 1). The definition of the AECOPD purulence status can be found in table S1. We identified one randomised controlled trial, eight prospective cohort studies, four retrospective cohort studies and one cross-sectional study (table 1). The proportion of purulent AECOPD varied from 0.0% to 65.4% across studies. The prevalence of PE per study varied between 0.4% and 33.2%. More precisely, the prevalence of PE varied between 0.4% and 17.6% in studies including patients with purulent AECOPD and nonpurulent/unknown aetiology AECOPD, whereas the prevalence of PE varied between 14.0% and 33.2% in studies including only patients with nonpurulent/unknown aetiology AECOPD. The prevalence of DVT per study varied between 0.1% and 20.7% (table 2).

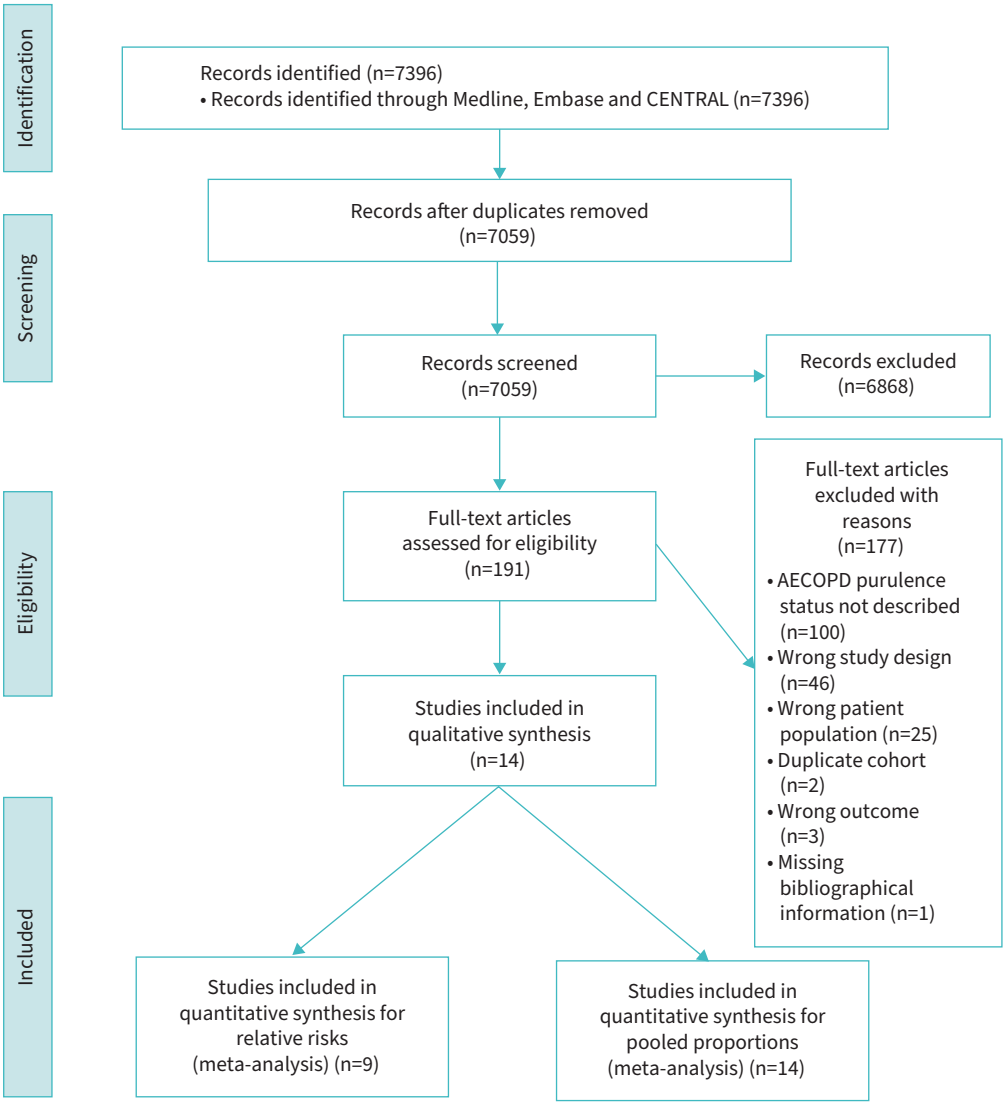

FIGURE 1 Flow chart of the study process. AECOPD: acute exacerbation of COPD; CENTRAL: Cochrane Central Register of Controlled Trials.

Risk of bias of included studies

When using the ROBINS-E tool [15], three studies were considered as having some concerns, nine studies were considered at high risk and two studies were considered at very high risk of bias (table S2). Publication bias was not present for the analysis on the relative risk of PE and AECOPD purulence status (figure S1), whereas publication bias was present for the analysis on pooled proportions of PE (figure S2).

Association between the prevalence of PE and the AECOPD purulence status

Among the nine studies [7, 8, 10, 11, 16–20] including patients with purulent and nonpurulent/unknown aetiology AECOPD, PE occurred in 76/1568 (4.8%) in patients with purulent AECOPD and in 238/2786 (8.5%) in patients with nonpurulent/unknown aetiology AECOPD. Although the risk of PE was lower in patients with purulent AECOPD compared to patients with nonpurulent/unknown aetiology AECOPD, it was not statistically significant (relative risk 0.64, 95% CI 0.26–1.55; p=0.32; I^2=88.0%) (figure 2). No difference was seen in subgroup analyses according to study design, systematic search for PE and localisation of PE (figures S3–S5). *Post hoc* sensitivity analyses based on the definition of purulent AECOPD showed no difference when the possible purulent AECOPD was used as the primary definition instead of the definitive purulent AECOPD definition (relative risk 0.58, 95% CI 0.23–1.43; p=0.23; I^2=88.0%). However, there was a reduction in PE in patients with purulent AECOPD compared to

TABLE 1 Baseline characteristics of the studies

First author, reference, year	Design	Number of patients	Age (mean ±SD)	Female (n)	Prior VTE (n)	Active cancer (n)	Clinical pre-test probability assessment	Proportion of patients who had imaging to rule out PE	Systematic search of PE with imaging regardless of the clinical probability or clinical suspicion	Diagnostic modality	Localisation of PE	Clinical setting
Studies including patients with purulent AECOPD and nonpurulent/unknown aetiology AECOPD												
Bahloul [16] 2015	Retrospective cohort study	131	69±9	13	0	NA	NA	51/131	No	CTPA ±echocardiography	Pulmonary artery or its branches	Inpatient (ICU)
Choi [10] 2013	Prospective cohort study	103	71±6	33	NA	4	Wells score and revised Geneva score	103/103	Yes	CTPA	Interlobar, lobar or main pulmonary arteries	Inpatient
Couturaud [7] 2021	Prospective cohort study	740	68±11	274	55	59[#]	Revised Geneva score	506/740	No	CTPA (six patients had *V′/Q′* scan)	Sub-segmental PE and more proximal	Inpatient
Dentali [11] 2020	Retrospective cohort study	1043	76±10	360	94	208	NA	1043/1043	No[¶]	CTPA	NA	Inpatient
Hassen [17] 2019	Prospective cohort study	131	68±13	27	NA	NA	Wells score	60/131	No	CTPA	44% segmental PE	Inpatient (ICU)
Jiménez [17] 2021	Randomised controlled trial	370[+]	70±10	86	10	12	Wells score	192/370	No	CTPA	Sub-segmental PE and more proximal	Inpatient
Li [18] 2016	Retrospective cohort study	522	74 (PE) 71 (non-PE)	8 (PE) 54 (non-PE)	13	24	NA	522/522	No[¶]	CTPA	NA	Outpatient
Mai [19] 2023	Retrospective cohort study	1158	70±12	620	37	143	NA	185/1158	No	CTPA, chest computed tomography with *i.v.* contrast, *V′/Q′* scan	Segmental and more proximal PE	Inpatient and outpatient
Meitei [20] 2021	Prospective cohort study	156	63±10	35	NA	0	Modified Wells score and revised Geneva score	NA	No	CTPA or clinically diagnosed[§]	Bilateral subsegmental or more proximal arteries	Inpatient

Continued

TABLE 1 Continued

First author, reference, year	Design	Number of patients	Age (mean ±SD)	Female (n)	Prior VTE (n)	Active cancer (n)	Clinical pre-test probability assessment	Proportion of patients who had imaging to rule out PE	Systematic search of PE with imaging regardless of the clinical probability or clinical suspicion	Diagnostic modality	Localisation of PE	Clinical setting
Studies including patients with nonpurulent/unknown aetiology AECOPD only												
Andrejak [21] 2012	Prospective cohort study - Abstract	87	67	16	NA	NA	Wells score	87/87	No[¶]	CTPA	NA	Inpatient
Chaudhary [22] 2021	Prospective cohort study	100	66±14	43	16	14	Simplified Geneva score	99/100	Yes	CTPA (clinical diagnosis for one patient)	Sub-segmental and more proximal PE	Inpatient
Jindal [23] 2020	Cross-sectional study	110	64±12	33	2	4	Wells score	110/110	Yes	CTPA	Lobar and more proximal PE	Inpatient
Tillie-Leblond [24] 2006	Prospective cohort study	197	61±12	32	23	57	Geneva score and modified Geneva score	197/197	Yes	CTPA	Sub-segmental and more proximal PE	Inpatient
Wang [25] 2013	Prospective cohort study	208	62±12	50	18	NA	NA	208/208	Yes	CTPA	NA	Inpatient

AECOPD: acute exacerbation of COPD; CTPA: computed tomography pulmonary angiography; ICU: intensive care unit; *i.v.*: *intravenous*; NA: not available; PE: pulmonary embolism; *V′*/*Q′*: ventilation/perfusion ratio; VTE: venous thromboembolism. [#]: Cancer in the past 2 years. [¶]: All included patients had a CTPA for a suspicion of PE. [+]: Only randomised in the intervention group were included. [§]: Clinical picture, echocardiography and D-dimer positivity.

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TABLE 2 Prevalence of pulmonary embolism, deep venous thrombosis and venous thromboembolism per study

First author, reference, year	Prevalence of PE, n/total (% (95% CI))	Prevalence of DVT, n/total (% (95% CI))	Prevalence of VTE, n/total (% (95% CI))
Studies including patients with purulent AECOPD and nonpurulent/unknown aetiology AECOPD			
Bahloul [16] 2015	23/131 (17.6 (11.5–25.2))	NA	NA
Choi [10] 2013	5/103 (4.9 (1.6–11.0))	6/103 (5.8 (2.2–12.3))	8/103 (7.8 (3.4–14.7))
Couturaud [7] 2021	44/740 (6.0 (4.4–7.9))	27/740 (3.7 (2.4–5.3))	54/740 (7.3 (5.5–9.4))
Dentali [11] 2020	132/1043 (12.7 (10.7–14.8))	67/1043 (6.4 (5.0–8.1))	160/1043 (15.3 (13.2–17.7))
Hassen [17] 2019	18/131 (13.7 (8.4–20.8))	1/131 (0.8 (0.0–4.2))	18/131 (13.7 (8.4–20.8))
Jiménez [17] 2021	17/370 (4.6 (2.7–7.3))	NA	NA
Li [18] 2016	54/522 (10.3 (7.9–13.3))	33/522 (6.3 (4.4–8.8))	75/522 (14.4 (11.5–17.7))
Mai [19] 2023	5/1158 (0.4 (0.1–1.0))	1/1158 (0.1 (0.0–0.5))	5/1158 (0.4 (0.1–1.0))
Meitei [20] 2021	16/156 (10.3 (6.0–16.1))	1/156 (0.6 (0.0–3.5))	16/156 (10.3 (6.0–16.1))
Studies including patients with nonpurulent/unknown aetiology AECOPD only			
Andrejak [21] 2012	13/87 (14.9 (8.2–24.2))	NA	NA
Chaudhary [22] 2021	14/100 (14.0 (7.9–22.4))	10/100 (10.0 (4.9–17.6))	14/100 (14.0 (7.9–22.4))
Jindal [23] 2020	20/110 (18.2 (11.5–26.7))	NA	NA
Tillie-Leblond [24] 2006	43/197 (21.8 (16.3–28.3))	25/197 (12.7 (8.4–18.2))	49/197 (24.9 (19.0–31.5))
Wang [25] 2013	69/208 (33.2 (26.8–40.0))	43/208 (20.7 (15.4–26.8))	86/208 (41.4 (34.6–48.4))

AECOPD: acute exacerbation of COPD; DVT: deep venous thrombosis; NA: not available; PE: pulmonary embolism; VTE: venous thromboembolism.

nonpurulent/unknown aetiology AECOPD when the clinical purulent AECOPD definition was used in combination with possible purulent AECOPD as the primary definition (relative risk 0.44, 95% CI 0.20–0.97; p=0.04; I^2<0.01) (figures S6–S7). Moreover, the risk of PE was also lower in patients with purulent AECOPD compared to patients with nonpurulent/unknown aetiology AECOPD when using a fixed-effects model (relative risk 0.57, 95% CI 0.45–0.72; p<0.01; I^2=88.0%) (figure S8). Sensitivity analyses according to the risk of bias could not be conducted since no study was considered at low risk of bias. These analyses were not conducted for DVT and VTE, respectively, since data on DVT in the included studies was not available to allow the evaluation of the association between the relative risk of DVT and the AECOPD purulence status.

Pooled proportion of PE according to the AECOPD purulent status

In the nine studies [7, 8, 10, 11, 16–20] including patients with purulent AECOPD, the pooled proportion of PE was 7.3% (95% CI 2.4–14.7%; I^2=94.7%) and in the 14 studies [7, 8, 10, 11, 16–25] including

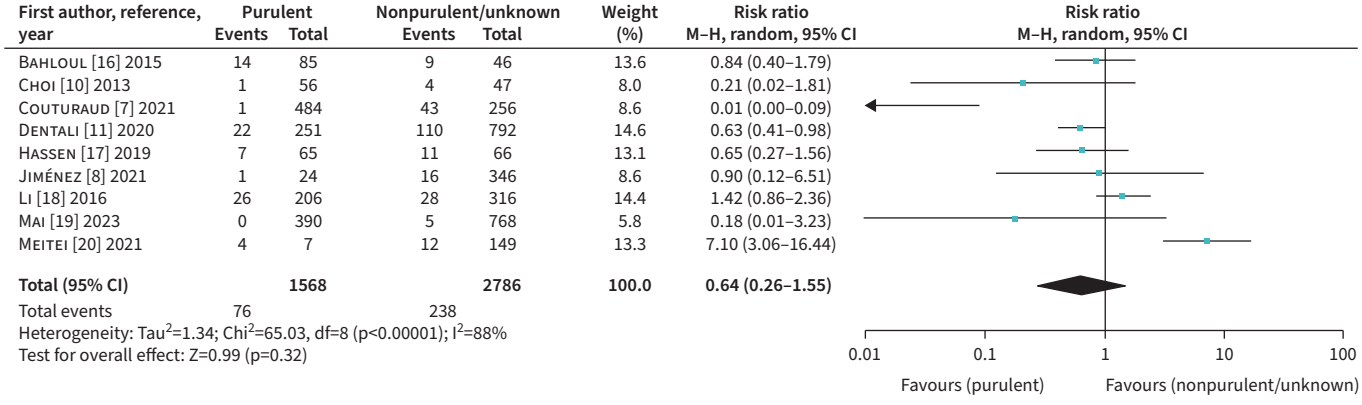

FIGURE 2 Forest plot and relative risk for the association between the risk of pulmonary embolism and the acute exacerbation of chronic obstructive pulmonary disease purulence status. M–H: Mantel–Haenszel.

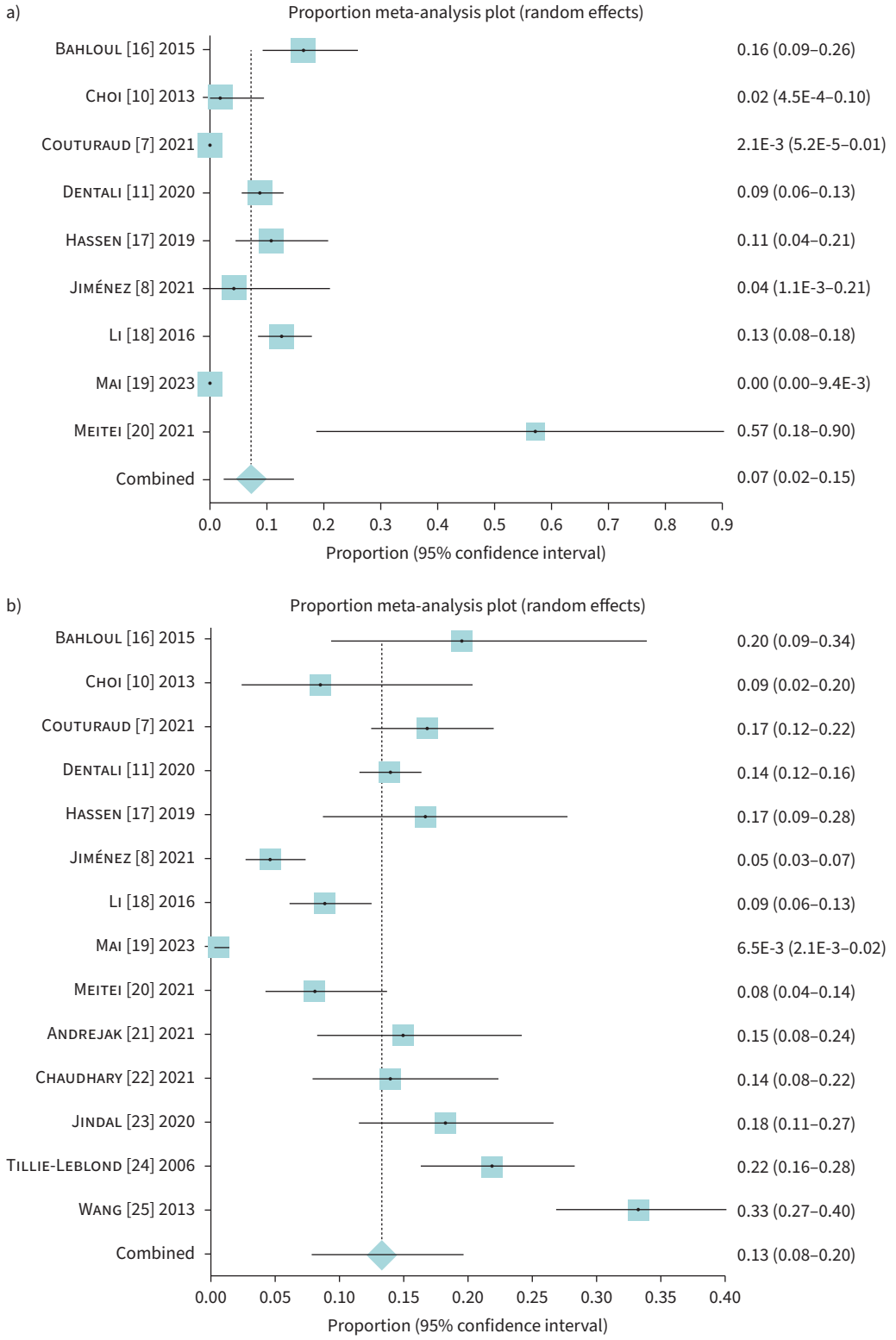

FIGURE 3 Pooled proportions of pulmonary embolism in patients with a) purulent acute exacerbation of COPD (AECOPD) and b) nonpurulent/unknown aetiology AECOPD.

patients with nonpurulent/unknown aetiology AECOPD, the pooled proportion of PE was 13.3% (95% CI 8.0–19.7%; I^2=96.0%) (figure 3). Subgroup analyses according to study design, systematic search for PE and localisation of PE did not show any significant differences (table S3).

Discussion

In this systematic review of 5056 participants, the relative risk of PE was found to be lower in patients with purulent AECOPD compared to patients with nonpurulent/unknown aetiology AECOPD, although it was not statistically significant. Importantly, the prevalence of PE is not low enough to rule out PE based on clinical evaluation only in patients with purulent AECOPD and nonpurulent/unknown aetiology AECOPD, respectively.

These findings are a step forward in improving PE diagnostic management in patients with AECOPD. The relative risk of PE seems to be lower in patients with purulent AECOPD compared to patients with nonpurulent/unknown aetiology AECOPD. AECOPD purulence status could be further evaluated as a potential predictor of PE and, if possible, be integrated in PE diagnostic strategy specifically for patients with AECOPD. This may reduce the need for imaging to rule out PE and, consequently, reduce the negative effects of CTPA. Although purulent AECOPD exacerbation could be considered as an alternative diagnosis of PE, it should probably not be viewed as a strong alternative diagnosis of PE since the relative risk of PE according to the AECOPD purulence status found in this study was not as low as the relative risk usually observed for the alternative diagnosis of PE item of the Wells criteria [26, 27]. Moreover, even if the relative risk of PE seems lower in patients with purulent AECOPD, the pooled proportion of PE of 7.3% in this group of patients may be considered too high to safely exclude PE without further investigations [28]. In the general population, PE is generally deemed to be ruled out when imaging is negative for PE or D-dimer is negative in patients with nonhigh clinical pre-test probability. Hence, in patients with COPD, purulent AECOPD could not exclude by itself the presence of PE but could rather be a predictor and help in the PE diagnostic algorithm. Although the most frequent cause of AECOPD is infection, in up to 30% of the cases the aetiology of the exacerbation is unknown [3]. Among these patients, a proportion may have not experienced an actual AECOPD, with symptoms of PE that could have been misattributed to symptoms related to the exacerbation, whereas others could have had their exacerbation triggered by a PE. The prevalence of PE was higher in patients with nonpurulent/unknown aetiology AECOPD compared to patients with purulent AECOPD. Thus, PE should still be kept in the mind of clinicians, no matter the type of AECOPD.

The definition of purulent AECOPD was highly variable across and within studies. This may explain why the main analysis and the subgroup analyses evaluating the relative risk of PE according to the AECOPD purulent status were not always statistically significant, although they were clinically significant, possibly due statistical power. To our knowledge, there is no standardised AECOPD purulent status definition that can explain this heterogeneity in the definition of purulent AECOPD. Moreover, the diagnosis of AECOPD can be difficult with potential misclassification [29]. These elements support the need in clarifying which patients with COPD and symptoms compatible with AECOPD should be targeted for further investigations to rule out PE. Finding the subgroup of patients at higher risk of PE will help reduce unnecessary radiological testing and associated risks.

Given the clinical and methodological heterogeneity and potential bias, caution in the interpretation of findings is warranted and should be considered hypothesis generating. We acknowledge that this study has limitations. First, the definition of purulent AECOPD was highly heterogenous across studies, which made it more challenging to pool data. Sensitivity analyses were conducted to further explore this element and did not show any difference in the clinical significance although some results were statistically significant according to the definition used, but this might rather be explained by the power and not necessarily by the definition of purulent AECOPD used. Second, most of the studies were at high risk of bias. In the majority of the studies, presence of detection bias could have partly explained a higher prevalence of PE among patients with nonpurulent/unknown aetiology AECOPD compared to patients with purulent AECOPD. Third, there was presence of publication bias for the analysis on pooled proportions of PE. This could be explained by studies on the prevalence of PE including only patients with nonpurulent/unknown aetiology AECOPD that tend to be more frequently published since the origin of the AECOPD is unknown. Fourth, heterogeneity was high and subgroup analyses were not able to explain it. Finally, only a small proportion of studies evaluating the prevalence of PE in patients with AECOPD reported this outcome according to the AECOPD purulence status. The main strength of this study is that to our knowledge, this is the first systematic review with meta-analysis evaluating the association between PE and AECOPD purulence status.

Conclusion

This systematic review shows that the relative risk of PE is lower, but not statistically significant, in patients with purulent AECOPD compared to patients with nonpurulent/unknown aetiology AECOPD but it was not statistically significant. Further studies are needed to confirm the association between the prevalence of PE and AECOPD purulence status to improve PE diagnostic management in this special population.

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Author contributions: V. Mai, F. Couturaud and G. Le Gal conceived the idea and design of this systematic review. V. Mai, L. Girardi, K. de Wit, L.A. Castellucci, S. Aaron, F. Couturaud, D.A. Fergusson and G. Le Gal contributed to the analysis and interpretation of the results of this study. V. Mai drafted the initial work, which was critically revised for intellectual content by L. Girardi, K. de Wit, L.A. Castellucci, S. Aaron, F. Couturaud, D.A. Fergusson and G. Le Gal. All authors read and approved the final version of the manuscript.

Conflict of interest: V. Mai, L. Girardi, K. de Wit, S. Aaron, F. Couturaud and D.A. Fergusson do not have conflicts of interest. L.A. Castellucci's research institution has received honoraria from Bayer, BMS–Pfizer Alliance, The Academy for Continued Advancement in Healthcare Education, Amag Pharmaceutical, LEO Pharma, Sanofi, Valeo Pharma and Servier. G. Le Gal is a co-investigator for a clinical trial from Pfizer and one from Bristol-Myers Squibb, and G. Le Gal received honoraria from Pfizer, Sanofi and Aspen Pharma.

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