BMJ Open

Chronic obstructive pulmonary disease exacerbation purulence status and its association with pulmonary embolism: protocol for a systematic review with meta-analysis

Vicky Mai ,[1] Laura Girardi,[1,2] Kerstin de Wit,[3] Lana Castellucci,[1] Shawn Aaron,[4] Francis Couturaud,[5] Dean A Fergusson ,[6] Grégoire Le Gal[1]

To cite: Mai V, Girardi L, de Wit K, *et al*. Chronic obstructive pulmonary disease exacerbation purulence status and its association with pulmonary embolism: protocol for a systematic review with meta-analysis. *BMJ Open* 2024;**14**:e085328. doi:10.1136/bmjopen-2024-085328

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-085328).

Received 12 February 2024
Accepted 11 June 2024

For numbered affiliations see end of article.

Correspondence to
Professor Grégoire Le Gal; glegal@toh.ca

ABSTRACT

Introduction Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) increases the risk of pulmonary embolism (PE). AECOPD and PE have similar symptoms which results in a high proportion of patients with AECOPD undergoing imaging to rule out PE. Finding predictors and explanatory factors of PE in AECOPD, such as purulence status, could help reduce the need for imaging. This systematic review with meta-analysis aims to evaluate if there is an association between purulence status in AECOPD and PE diagnosis.

Methods and analysis MEDLINE, EMBASE and CENTRAL will be searched from database inception to April 2024. Randomised trials, cohort studies and cross-sectional studies on the prevalence of PE in patients with AECOPD will be included if the prevalence of PE based on the AECOPD purulence status is available. There will be no restriction on language. The primary outcome will be PE at the initial assessment and secondary outcomes will be all venous thromboembolism (deep venous thrombosis (DVT) and PE) and DVT, respectively, diagnosed at the initial assessment. Relative risks with their 95% CI will be calculated by using a Mantel-Haenszel random-effect model to compare the association between the risk of PE and the AECOPD purulence status (purulent vs non-purulent/unknown). Subgroup analyses will be performed based on the type of study, systematic search of PE versus no systematic search of PE and localisation of PE. Risk of bias will be evaluated by the ROBINS-E tool, publication bias will be evaluated with the funnel plot. The manuscript will be drafted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.

Ethics and dissemination This study does not require ethics approval. This work will be submitted for presentation at an international conference and for publication in a peer-reviewed journal.

PROSPERO registration number CRD42023459429.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ An experienced patient partner from the Canadian Venous Thromboembolism Research Network patient partner platform was involved in the protocol elaboration.
⇒ The acute exacerbation of chronic obstructive pulmonary disease (AECOPD) purulence status may not be homogeneous across studies, which may make it more challenging to pool some data.
⇒ Not all studies report on the prevalence of pulmonary embolism (PE) according to the AECOPD purulence status; consequently, the data included in this systematic review may represent a limited proportion of all the data available on the prevalence of PE in patients with AECOPD.

INTRODUCTION

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) increases the risk of pulmonary embolism (PE)[1] due to increased systemic inflammation as well as in the airways.[2] Moreover, PE is associated with a fivefold increased risk of mortality in patients with chronic obstructive pulmonary disease (COPD).[3] Diagnosing PE in the context of AECOPD is challenging for several reasons. First, due to confounding symptoms of AECOPD and PE, it is unknown when PE should be suspected in patients with COPD. Second, even when PE is not suspected, or when another diagnosis is more likely, the prevalence of PE [i.e., 4.5% (PEP[4] and SLICE[5])] is not low enough to safely exclude PE on clinical grounds only. Clinical decision rules and D-dimers, when applied to patients with AECOPD and whether PE is suspected or not, have lower clinical utility in AECOPD since >65% of the patients would need imaging to rule out PE if standard diagnostic strategy was used.[4] In addition, negative effects are seen with CT pulmonary angiogram (CTPA) such as cost, radiation exposure, contrast-induced nephropathy and incidental findings. Furthermore, as the

severity of the COPD progresses, AECOPD occurs more frequently[6] and it is expected that the need to rule out PE will become more frequent. Finding predictors and explanatory factors of PE in AECOPD, such as the purulence status, could help reduce the need for imaging. Clinically, it would make sense that if the AECOPD is explained by an infectious process, then the PE would be less likely, and conversely, if the AECOPD is unexplained, it would make sense that PE would be more likely to be the explanation for the AECOPD. As a matter of fact, some studies showed a lower risk of PE or venous thromboembolism (VTE) in patients with purulent AECOPD.[7–9]

Thus, the main aim of this systematic review with meta-analysis is to evaluate whether purulence status in AECOPD is associated with PE. We hypothesise that the risk of PE will be lower in purulent AECOPD compared with non-purulent or unknown purulent status AECOPD since the aetiology of the exacerbation is unknown in up to 30% of the AECOPD[10] and PE could thus be an explanation in those cases. As a secondary aim, we would like to evaluate the association between AECOPD purulence status and the risk of VTE (deep venous thrombosis (DVT) of the lower extremity and PE) and the risk of DVT, respectively. We hypothesise that the risk of VTE and DVT, respectively, will be lower in patients with purulent AECOPD compared with non-purulent or unknown purulent status AECOPD.

Study objectives

Primary objective

The primary objective is to evaluate the risk of PE in patients with purulent AECOPD compared with non-purulent or unknown purulent status AECOPD.

Secondary objective

The secondary objective is to evaluate the risk of VTE (including DVT of the lower extremity and PE) and the risk of DVT, respectively, in patients with purulent AECOPD compared with non-purulent or unknown purulent status AECOPD.

METHODS AND ANALYSIS

Eligibility criteria

Randomised trials, cohort studies (retrospective or prospective) and cross-sectional studies on the prevalence of PE in patients with AECOPD will be included if the prevalence of PE according to the AECOPD purulence status is available. AECOPD purulence status will be categorised as definitive purulent AECOPD (purulent AECOPD or purulent sputum), possible purulent AECOPD (clinical and/or radiological evidence of tracheobronchial infection or pneumonia), non-purulent AECOPD or unknown purulence status AECOPD.

Information sources and search strategy

MEDLINE, EMBASE and CENTRAL will be searched from inception to April 2024. Conference abstracts from the American Thoracic Society, American College of Chest Physicians, European Respiratory Society, British Thoracic Society, American Society of Hematology, International Society on Thrombosis and Haemostasis will be hand searched from January 2000 to April 2024. There will be no restriction on language. The search strategy (online supplemental appendix 1) will be reviewed by a research librarian with expertise in knowledge synthesis and translation.

Study records

Two reviewers (VM and LG) will independently screen all the titles and abstracts for potentially eligible studies. Full texts of potentially eligible studies will be obtained and screened by two reviewers independently. Both levels of screening will be conducted using Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Any disagreements will be resolved by further discussion or by consulting a third reviewer (GLG). If the same cohort was published in multiple papers, the paper with the largest cohort providing the required information needed will be selected.

Data items

Two independent reviewers (VM and LG) will extract the data from included papers by using a standardised collection form. Collected data will include study characteristics (study ID, reference, study design), patients' characteristics (number of patients, age, sex, body mass index, mean forced expiratory volume in 1s, Global Initiative for Chronic Obstructive Lung Disease stage, prior personal or familial venous thromboembolic event, current tobacco use, active cancer (defined as current diagnosis of cancer, receiving treatment for cancer or not receiving treatment for cancer and not in complete response as per the International Society on Thrombosis and Haemostasis Common Data Elements), the number of previous AECOPD in the last year, pretest clinical probability, mean D-dimers level, VTE (PE and/or DVT), AECOPD purulence status), proportion of patients who had imaging to rule out VTE, whether or not all patients systematically had diagnostic imaging searching for PE (or VTE), localisation of PE, clinical setting (inpatients vs outpatients) and the use of independent adjudication. Study authors will be contacted if important information is missing.

Outcome measures

The primary outcome will be PE at the initial assessment. PE will include symptomatic PE involving subsegmental branches or more proximal arteries on CTPA, high probability on a planar ventilation/perfusion (V/Q) scan, at least one segmental mismatch or two subsegmental mismatches on a V/Q SPECT (EANM criteria)[11] and incidental PE found fortuitously on imaging and fatal PE. If the localisation of the PE was not mentioned in the article, the study will still be included, and subgroup analyses will be performed. Secondary outcomes will include

VTE (proximal DVT and/or PE), proximal DVT and distal DVT, respectively, at the initial assessment. DVT will include DVT of the lower extremity, either symptomatic or incidental. In case it was not mentioned if the DVT was proximal or distal, the study will still be included, and subgroup analyses will be performed. The initial assessment will be defined as the first 48 hours from hospital admission if the patient is admitted, as the first 48 hours from the initial medical evaluation if the patient is managed as an outpatient or as defined by individual studies.

Assessment of risk of bias in included studies

The risk of bias of included studies will be evaluated by two independent reviewers (VM and LG) by using the ROBINS-E tool.[12] Publication bias will be assessed by conducting and evaluating the funnel plot for the primary outcome. A symmetrical funnel plot indicates the absence of publication bias.

Data synthesis

The prevalence of PE, VTE and DVT, respectively, at initial assessment will be calculated with its 95% CI by using the binomial exact method[13] for each study. Data will be pooled using Review Manager V.5.3 (The Cochrane Collaboration, Oxford, England). Relative risks (RR) with their 95% CI will be calculated by using a Mantel-Haenszel random-effects model to compare the association between the risk of PE in patients with purulent AECOPD and the risk of PE in patients with non-purulent/unknown purulence status AECOPD. Events will be categorised in the definitive purulent AECOPD group if it was mentioned purulent AECOPD or the sputum was described as purulent. Events will be categorised in the possible purulent AECOPD group if there is clinical and/or radiological evidence of tracheobronchial infection or pneumonia. Similar analyses will be conducted to evaluate the association between the risk of VTE and the risk of DVT, respectively, and the AECOPD purulence status. Forest plots will be presented. If some studies cannot be pooled in the RR analysis evaluating the association between the risk of PE and the type of AECOPD, pooled proportions of PE of patients with purulent AECOPD and with non-purulent/unknown purulence status AECOPD, respectively, will be calculated using StatsDirect statistical software. I^2 will be calculated to evaluate heterogeneity and will be considered significant if I^2 is >50%. Subgroup analyses will be performed based on the type of study (randomised trials vs prospective cohort studies vs retrospective cohort studies vs cross-sectional studies), systematic search of PE (or VTE) vs no systematic search of PE (or VTE) and localisation of PE (or DVT). Sensitivity analyses will be performed by including only studies at low risk of bias. The manuscript will be drafted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.

Patient and public involvement

An experienced patient partner from the Canadian Venous Thromboembolism Research Network patient partner platform revised the protocol and approved the design and conduct of the study, as well as the outcome measures.

Ethics and dissemination

Since this is a systematic review with meta-analysis of published studies, ethics approval and patients' consent will not be required. We aim to submit this work for presentation at an international conference and for publication in a peer-reviewed journal.

DISCUSSION

This systematic review with meta-analysis aims at comparing the association between the risk of PE in patients with purulent AECOPD and the risk of PE in patients with non-purulent/unknown purulence status AECOPD. Finding predictors or explanatory factors for PE in patients with AECOPD, such as AECOPD purulence status, could help reduce the need for imaging. If the risk of PE is shown to be lower in patients with purulent AECOPD compared with non-purulent or unknown status AECOPD, this new information may help improve PE diagnostic algorithm in reducing the need for imaging in ruling out PE and thus, improve the care of patients with AECOPD. Moreover, if the prevalence of PE is shown to be very low in patients with purulent AECOPD and low enough to exclude PE without further investigations, this will certainly reduce the need for imaging in ruling out PE and subsequently, reduce the side effects of CTPA.

We acknowledge that this study may have some limitations and that we may face some challenges when conducting it. First, only a certain number of studies on the prevalence of PE in patients with AECOPD have reported the prevalence of PE based on the AECOPD purulence status. The data included in this systematic review may thus represent a limited proportion of all the data available on the prevalence of PE in patients with AECOPD. Second, the definition of the AECOPD purulence status may not be homogeneous across studies which could make it more challenging to pool the data. Finally, although we will analyse all patients with AECOPD, there might be some heterogeneity within this population (e.g., patients admitted vs treated as an outpatient).

Improving PE diagnostic algorithm for patients with AECOPD is of high importance to reduce the burden of imaging since PE and AECOPD share similar symptoms but also to minimise the proportion of missed PE. This systematic review with meta-analysis aims at evaluating if AECOPD purulence status could be a predictor of PE in order to improve the care of patients with COPD.

Author affiliations
[1]Department of Medicine, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Ontario, Canada
[2]Department of Medicine and Surgery, University of Insubria, Varese, Italy
[3]Department of Emergency Medicine and Medicine, Queens University, Kingston, Ontario, Canada

[4]Department of Medicine, Faculty of Medicine, Division of Respirology, University of Ottawa, Ottawa, Ontario, Canada
[5]INSERM U1304-GETBO, CIC INSERM 1412, Univ_Brest, Département de Médecine Interne et Pneumologie, Centre Hospitalier Universitaire de Brest, Brest, FCRIN INNOVTE, France
[6]Clinical Epidemiology, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

X Vicky Mai @Vicky_Mai_

Acknowledgements We want to thank Danielle Morneault for her contribution to this protocol by revising the protocol and approving the design and conduct of the study.

Contributors VM, FC and GLG conceived the idea and design of this systematic review. VM, LG, KdW, LC, SA, FC, DAF and GLG developed the methodology for the protocol of this systematic review. The content of this manuscript was drafted by VM and GLG with input from all members of the authorship team. The manuscript was reviewed by LG, KdW, LC, SA, FC, DAF and GLG for important intellectual content. All authors read and approved the final version of the manuscript.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. VM is supported by a Professional Postgraduate Training in Research (Fellowship) Award from the Fonds de recherche Santé Québec, a Canadian Institutes of Health Research Fellowship Award and a CanVECTOR fellowship award; CanVECTOR receives grant funding from the Canadian Institutes of Health Research (Funding Reference: CDT-142654). LC is a member of the Canadian Venous Thromboembolism Research Network (CanVECTOR); the Network received grant funding from the Canadian Institutes of Health Research (Funding Reference: CDT-142654). LC holds a Tier 2 research Chair in Thrombosis and Anticoagulation Safety from the University of Ottawa. GLG holds the Chair on Diagnosis of Venous Thromboembolism at the Department of Medicine, University of Ottawa and a Clinician-Scientist Award from the Heart and Stroke Foundation of Canada.

Competing interests VM, LG, KdW, SA, FC and DAF do not have conflicts of interest. LC'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. GLG is a coinvestigator for a clinical trial from Pfizer and one from Bristol-Myers Squibb and GLG received honoraria from Pfizer, Sanofi and Aspen Pharma.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Vicky Mai http://orcid.org/0000-0001-6874-7109
Dean A Fergusson http://orcid.org/0000-0002-3389-2485

REFERENCES

1 Konstantinides SV, Meyer G. The 2019 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2019;40:3453–5.
2 Hurst JR, Perera WR, Wilkinson TMA, *et al*. Systemic and upper and lower airway inflammation at exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006;173:71–8.
3 Sato R, Hasegawa D, Nishida K, *et al*. Prevalence of pulmonary embolism in patients with acute exacerbations of COPD: a systematic review and meta-analysis. *Am J Emerg Med* 2021;50:606–17.
4 Couturaud F, Bertoletti L, Pastre J, *et al*. Prevalence of pulmonary embolism among patients with COPD hospitalized with acutely worsening respiratory symptoms. *JAMA* 2021;325:59–68.
5 Jiménez D, Agustí A, Tabernero E, *et al*. Effect of a pulmonary embolism diagnostic strategy on clinical outcomes in patients hospitalized for COPD exacerbation: a randomized clinical trial. *JAMA* 2021;326:1277–85.
6 Hurst JR, Vestbo J, Anzueto A, *et al*. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010;363:1128–38.
7 Choi K-J, Cha S-I, Shin K-M, *et al*. Prevalence and predictors of pulmonary embolism in Korean patients with exacerbation of chronic obstructive pulmonary disease. *Respiration* 2013;85:203–9.
8 Dentali F, Pomero F, Micco PD, *et al*. Prevalence and risk factors for pulmonary embolism in patients with suspected acute exacerbation of COPD: a multi-center study. *Eur J Intern Med* 2020;80:54–9.
9 Liu X, Jiao X, Gong X, *et al*. Prevalence, risk factor and clinical characteristics of venous thrombus embolism in patients with acute exacerbation of COPD: a prospective multicenter study. *Int J Chron Obstruct Pulmon Dis* 2023;18:907–17.
10 Connors AF Jr, Dawson NV, Thomas C, *et al*. Outcomes following acute exacerbation of severe chronic obstructive lung disease. the SUPPORT investigators (study to understand prognoses and preferences for outcomes and risks of treatments). *Am J Respir Crit Care Med* 1996;154:959–67.
11 Bajc M, Schümichen C, Grüning T, *et al*. EANM guideline for ventilation/perfusion single-photon emission computed tomography (SPECT) for diagnosis of pulmonary embolism and beyond. *Eur J Nucl Med Mol Imaging* 2019;46:2429–51.
12 Higgins J, Morgan R, Rooney A, *et al*. Risk of bias in non-randomized studies - of exposure (ROBINS-E). 2022.
13 Kohn MA, Senyak J. Sample size calculators (Website). UCSF CTSI; 2021.