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

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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 inception to March 2023. Randomized 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. 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 initial assessment. Relative risks (RR) with their 95% confidence interval (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 vs no systematic search of PE and localization 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 (PRISMA) statement.

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

PROSPERO registration number: CRD42023459429

Strengths and limitations of the study

- This will be the first systematic review with meta-analysis evaluating the association between the risk of pulmonary embolism (PE) and the acute exacerbation of chronic obstructive pulmonary disease (AECOPD) purulence status.
- The AECOPD purulence status may not be homogenous across studies, which may make it more challenging to pool some data.
- This study has the potential to improve PE diagnostic management 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 5-fold 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 were used[4]. In addition, negative effects are seen with computed tomography 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.

Thus, the aim of this systematic review with meta-analysis is to evaluate whether purulence status in AECOPD is associated with PE. We hypothesize that the risk of PE will be lower in purulent AECOPD compared to non-purulent or unknown purulent status AECOPD, since the etiology of

the exacerbation is unknown in up to 30% of the AECOPD[7] and PE could thus be an explanation in those cases.

STUDY OBJECTIVES

Primary objective

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

Secondary objective

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

METHODS AND ANALYSIS

Eligibility criteria

Randomized 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 categorized 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 March 2023. 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 March 2023. There will be no restriction on language. The search strategy will be reviewed by a research librarian with expertise in knowledge synthesis and translation, and will be included in the supplemental file.

Study records

Two reviewers (V.M. and L.G.) 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 (G.L.G.). 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 (V.M. and L.G.) will extract the data from included papers by using a standardized collection form. Collected data will include study characteristics (study ID, reference, study design), patients' characteristics [number of patients, age, sex, BMI, mean forced expiratory volume in 1 second (FEV1), Global Initiative for Chronic Obstructive Lung Disease (GOLD) 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), number of previous AECOPD in the last year, pre-test 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) was undertaken, localization of PE, clinical setting (inpatients vs outpatients) and 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 segmental 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)[8] and incidental PE found fortuitously on imaging and fatal PE. If the localization 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 (V.M. and L.G.) by using the ROBINS-E tool[9]. Publication bias will be assessed by conducting and evaluating the funnel plot for the primary outcome. A symmetrical funnel plot indicates absence of publication bias.

Data synthesis

The prevalence of PE, VTE and DVT, respectively, at initial assessment will be calculated with its 95% confidence interval (CI) by using the binomial exact method[10]. Data will be pooled using Review Manager version 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 categorized in the definitive purulent AECOPD group if it was mentioned purulent AECOPD or the sputum was described as purulent. Events will be categorized in the possible purulent AECOPD group if there was 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. 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 (randomized 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 localization 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 (PRISMA) statement.

Patient and public involvement

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

DISCUSSSION

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 to 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 being 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.

Limitations and challenges

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 homogenous across studies which could make it more challenging to pool the data. Finally, although we will analyze all patients with AECOPD, there might be some heterogeneity within this population (e.g. patients admitted vs treated as an outpatient).

CONCLUSION

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 minimize 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.

ETHICS AND DISSEMINATION

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

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AUTHORS' CONTRIBUTIONS

VM, FC and GLG conceived the idea and design of this systematic review. VM, LG, KdW, LC, SA, FC, DF 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, DF and GLG for important intellectual content. All authors read and approved the final version of the manuscript.

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COMPETING INTERESTS STATEMENT

VM, LG, KdW, SA, FC and DF 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 co-investigator for a clinical trial from Pfizer and one from Bristol-Myers Squibb and GLG received honoraria from Pfizer, Sanofi and Aspen Pharma.

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Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Cardiovascular medicine, Epidemiology, Haematology (incl blood transfusion)
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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. Randomized 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 initial assessment. Relative risks (RR) with their 95% confidence interval (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 vs no systematic search of PE and localization 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 (PRISMA) statement.

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

Study registration: PROSPERO, CRD42023459429.

Strengths and limitations of this study

- An experienced patient partner from the Canadian Venous Thromboembolism Research Network (CanVECTOR) patient partner platform was involved in the protocol elaboration.
- The acute exacerbation of chronic obstructive pulmonary disease (AECOPD) purulence status may not be homogenous 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 5-fold 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 were used[4]. In addition, negative effects are seen with computed tomography 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 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 hypothesize that the risk of PE will be lower in purulent AECOPD compared to non-purulent or unknown purulent status AECOPD, since the

etiology 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 venous thromboembolism (VTE) [deep venous thrombosis (DVT) of the lower extremity and PE] and the risk of DVT, respectively. We hypothesize that the risk of VTE and DVT, respectively, will be lower in patients with purulent AECOPD compared to 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 to 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 to non-purulent or unknown purulent status AECOPD.

METHODS AND ANALYSIS

Eligibility criteria

Randomized 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 categorized 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 (**Appendix 1**) will be reviewed by a research librarian with expertise in knowledge synthesis and translation.

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Data items

Two independent reviewers (V.M. and L.G.) will extract the data from included papers by using a standardized collection form. Collected data will include study characteristics (study ID, reference, study design), patients' characteristics [number of patients, age, sex, BMI, mean forced expiratory volume in 1 second (FEV1), Global Initiative for Chronic Obstructive Lung Disease (GOLD) 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), number of previous AECOPD in the last year, pre-test 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) was undertaken, localization of PE, clinical setting (inpatients vs outpatients) and 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 localization 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 (V.M. and L.G.) 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 absence of publication bias.

Data synthesis

The prevalence of PE, VTE and DVT, respectively, at initial assessment will be calculated with its 95% confidence interval (CI) by using the binomial exact method[13] for each study. Data will be pooled using Review Manager version 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 categorized in the definitive purulent AECOPD group if it was mentioned purulent AECOPD or the sputum was described as purulent. Events will be categorized in the possible purulent AECOPD group if there was 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 (randomized 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 localization 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 (PRISMA) statement.

Patient and public involvement

An experienced patient partner from the Canadian Venous Thromboembolism Research Network (CanVECTOR) 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 to 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 being 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 homogenous across studies which could make it more challenging to pool the data. Finally, although we will analyze 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 minimize 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.

ACKNOWLEDGMENTS

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, DF 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, DF and GLG for important intellectual content. All authors read and approved the final version of the manuscript.

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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 DF 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 co-investigator for a clinical trial from Pfizer and one from Bristol-Myers Squibb and GLG received honoraria from Pfizer, Sanofi and Aspen Pharma.

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

Supplemental file

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APPENDIX 1

Search strategy MEDLINE

1. "Chronic obstructive pulmonary disease".ab,kw,ti.
2. Pulmonary disease, Chronic obstructive/
3. "Chronic obstructive lung disease".ab,kw,ti.
4. "Chronic obstructive airway disease".ab,kw,ti.
5. "Chronic airflow obstruction".ab,kw,ti.
6. COPD.ab,kw,ti.
7. "Chronic bronchitis".ab,kw,ti.
8. Bronchitis, Chronic/
9. "Pulmonary emphysema".ab,kw,ti.
10. Pulmonary emphysema/
11. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12. "Venous thrombos*".ab,kw,ti.
13. Venous thrombosis/
14. "Vein thrombosis".ab,kw,ti.
15. "Vein thromboembolism".ab,kw,ti.
16. "Pulmonary embolism".ab,kw,ti.
17. Pulmonary embolism/
18. "Pulmonary embolisms".ab,kw,ti.
19. "Pulmonary thromboembolism".ab,kw,ti.
20. "Lung embolism".ab,kw,ti.
21. "Lung embolisms".ab,kw,ti.

22. “Lung thromboembolism”.ab,kw,ti.
23. “Venous thromboembolism”.ab,kw,ti.
24. Venous thromboembolism/
25. #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24

#11 AND #25

Search strategy Embase

1. “Chronic obstructive pulmonary disease”.ab,ti,kw
2. “Chronic obstructive pulmonary disease”/
3. “Chronic obstructive lung disease”.ab,ti,kw
4. “Chronic obstructive airway disease”.ab,ti,kw
5. “Chronic airflow obstruction”.ab,ti,kw
6. COPD.ab,ti,kw
7. “Chronic bronchitis”.ab,ti,kw
8. “Chronic bronchitis”/
9. “Pulmonary emphysema”.ab,ti,kw
10. “Pulmonary emphysema”/
11. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12. “Venous Thrombos*”.ti,ab,kw
13. “Venous thromboembolism”.ti,ab,kw
14. “Vein Thrombos*”.ti,ab,kw
15. “Vein thromboembolism”.ti,ab,kw

16. “Vein thrombosis”/
17. “Pulmonary embolism”.ti,ab,kw
18. “Pulmonary embolisms”.ti,ab,kw
19. “Pulmonary thromboembolism”.ti,ab,kw
20. “Lung embolism”.ti,ab,kw
21. “Lung embolisms”.ti,ab,kw
22. “Lung thromboembolism”.ti,ab,kw
23. “Lung embolism”/
24. #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23

#11 AND #24

Search strategy CENTRAL

1. “Chronic obstructive pulmonary disease”.ab,kw,ti.
2. Pulmonary disease, Chronic obstructive/
3. “Chronic obstructive lung disease”.ab,kw,ti.
4. “Chronic obstructive airway disease”.ab,kw,ti.
5. “Chronic airflow obstruction”.ab,kw,ti.
6. COPD.ab,kw,ti.
7. “Chronic bronchitis”.ab,kw,ti.
8. Bronchitis, Chronic/
9. “Pulmonary emphysema”.ab,kw,ti.
10. Pulmonary emphysema/

11. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

12. “Venous thrombos*”.ab,kw,ti.

13. Venous thrombosis/

14. “Vein thrombosis”.ab,kw,ti.

15. “Vein thromboembolism”.ab,kw,ti.

16. “Pulmonary embolism”.ab,kw,ti.

17. Pulmonary embolism/

18. “Pulmonary embolisms”.ab,kw,ti.

19. “Pulmonary thromboembolism”.ab,kw,ti.

20. “Lung embolism”.ab,kw,ti.

21. “Lung embolisms”.ab,kw,ti.

22. “Lung thromboembolism”.ab,kw,ti.

23. “Venous thromboembolism”.ab,kw,ti.

24. Venous thromboembolism/

25. #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24

#11 AND #25

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review p.1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number p.3
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author p.1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review p.11
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments NA
Support:		
Sources	5a	Indicate sources of financial or other support for the review p.11
Sponsor	5b	Provide name for the review funder and/or sponsor NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol NA
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known p.4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) p.5
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review p.5-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage p.6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated p.6 and supplemental file
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review p.6

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) p.6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators p.6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications p.6-7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale p.7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis p.8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised p.8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) p.8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) p.8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned p.8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) p.8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) NA

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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