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Investigating fractional exhaled nitric oxide (FeNO) in chronic obstructive pulmonary disease (COPD) and asthma–COPD overlap (ACO): a scoping review protocol

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ABSTRACT

Introduction During the last decade, many articles have been published, including reviews on fractional exhaled nitric oxide (FeNO) use and utility in clinical practice and for monitoring and identifying eosinophilic airway inflammation, especially in asthma, and evaluating corticosteroid responsiveness. However, the exact role of FeNO in patients with chronic obstructive pulmonary disease (COPD) and its ability to distinguish patients with COPD and those having concomitant asthma, that is, asthma–COPD overlap (ACO) is still unclear and needs to be defined. Due to the broad topics of FeNO in chronic airway disease, we undertook a scoping review. The present article describes the protocol of a scoping review of peer-reviewed published literature specific to FeNO in COPD/ACO over the last decade.

Methods and analysis We used Joanna Briggs Institute Reviewers' Manual scoping review methodology as well as Levac *et al*'s and Arksey *et al*'s framework as guides. We searched a variety of databases, including Medline, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library, Web of Science, and BioSciences Information Service (BIOSIS) on 29 June 2016. Additional studies will be recognised by exploring the reference list of identified eligible studies. Screening of eligible studies will be independently performed by two reviewers and any disagreement will be solved by the third reviewer. We will analyse the gathered data from article bibliographies and abstracts.

Ethics and dissemination To investigate the body of published studies regarding the role of FeNO in patients with COPD and its usefulness in the clinical setting, a scoping review can be used as a modern and pioneer model, which does not need ethics approval. By this review, new insights for conducting new research specific to FeNO in COPD/ACO population will emerge. The results of this study will be reported in the scientific meetings and conferences, which aim to provide information to the clinicians, primary care providers and basic science researchers.

Strengths and limitations of this study

- To the best of our knowledge, this will be the first scoping review undertaken on patients with fractional exhaled nitric oxide (FeNO) and chronic obstructive pulmonary disease (COPD); the intent of our scoping review will be to present an overview of the existing literature in a field of interest, that is, FeNO in COPD and also to synthesise and aggregate findings from different studies.
- The strength of this review is the use of an established scoping review methodology, a systematic approach and a multidisciplinary search strategy developed strongly in consultation with a professional medical librarian.
- This scoping review will include all languages, but it will be limited to the year 2005 onwards, as this was the year that the first American Thoracic Society/European Respiratory Society guideline regarding FeNO measurement was published.
- The possibility of missing potentially relevant articles as well as excluding grey literature, conference and meeting (non-peer-reviewed) abstracts can be considered as limitations of this review. However, the reference lists of eligible articles will be exploring to identify articles missed by the search strategy.
- Due to the nature of this review, that is, a scoping review, it will not involve a formal assessment of the quality of the primary studies.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common obstructive pulmonary disease, which is characterised by airflow limitation.[1 2] Asthma–COPD overlap (ACO)[3] syndrome (ACOS)[4] is a distinct clinical phenotype that represents a subset of patients with COPD who share features of asthma.[5] Initiation of pharmacotherapy for the treatment of these two diseases is different,[6] patients with COPD alone should usually be started on bronchodilators as monotherapy or combined therapy and those recognised with ACO should have combined bronchodilators

and inhaled corticosteroids.[3 7] Therefore, differentiating patients with COPD alone from those who show asthma-like symptoms is clinically relevant, especially for the need of ensuring close monitoring of patients with ACO who have worse outcomes and also in guiding treatment decision.

There is a lack of gold standard for the diagnosis of ACO,[2 8] and diagnostic criteria have often been established primarily based on consensus opinion. Fractional exhaled nitric oxide (FeNO) is one of the inflammatory biomarkers that have recently attracted the attention of clinicians as well as researchers. FeNO can be measured non-invasively, fast, reproducibly and in an easy way in close to real time.[9 10] It is suggested using FeNO for the management of asthma and also for monitoring airway inflammation, identifying eosinophilic and T-helper cell 2 (Th2)-mediated airway inflammation and evaluating corticosteroid responsiveness during asthma follow-up.[11 12] The exact role of FeNO in COPD and more specifically for monitoring ACO and patients undergoing inhaled corticosteroid therapy is still unclear and needs to be defined.[13 14] Moreover, literature defining the role of FeNO and the practical cut-off value in patients with ACO and established COPD is minimal.[15]

Our preliminary search showed no comprehensive review, neither a scoping nor a systematic review with a view of the role of FeNO measurement in patients with COPD and/or ACO.

As this topic of FeNO and COPD covers a wide range of potential questions and because of its exploratory nature, a scoping review will be conducted. The intent of our scoping review is to present an overview of the existing literature in a field of interest, that is, FeNO in COPD, and also to synthesise and aggregate findings from different studies. We are considering specific questions/objectives to guide our review but through our search of the literature, we may have opportunities to refine some of these questions. The objectives of this scoping review will be (1) to investigate patients' with COPD factors that can modify FeNO measurements including but not limited to age, cigarette smoking, sex, glucocorticoids (inhaled corticosteroid (ICS)/glucocorticoids (GCS)), bronchodilators and exacerbations; (2) to evaluate the FeNO role and if a useful cut-off value can be used in differentiating patients with COPD from healthy individuals; (3) to determine the relationship of FeNO with disease severity and/or progression (lung function, health status and exacerbations); (4) to assess the role of FeNO and if a useful cut-off value can be used to differentiate patients with COPD-only from those with concomitant asthma (ACO); (5) to determine the relationship of FeNO with inflammatory markers (immunoglobulin E (IgE), blood/sputum eosinophils) and (6) to assess the use of FeNO measurement in treatment response of patients with COPD/ACO, especially ICS/glucocorticoids therapy with or without inhaled bronchodilators.

METHODS

Different types of systematic approaches available for reviewing published literature have been taken into account, and eventually, a scoping review of peer-reviewed published articles was selected as the most appropriate method. This scoping review will provide the readers and researchers with an overview of the topic, determining key concepts and exploring gaps within a developing field of research.[16] Compared with a systematic review, the research questions defined for a scoping review are broader than for a systematic review.[16] A scoping review is appropriate for the topic of FeNO in COPD because the purpose of this study is to have a comprehensive review in an area that is relatively complex. However, there are limitations regarding scoping reviews. These limitations include missing some relevant studies,[17] which is related to the database search, exclusion of grey literature,[17] lack of critical quality appraisal of included studies and therefore difficulty in addressing the gaps in the evidence base[17 18] and limitation of depth of analysis.[19 20] It would be a huge challenge to assess quality among the wide range of study designs and a large volume of literature that will be included in the scoping review. The balance between breadth and depth of analysis is

Table 1 Inclusion and exclusion criteria for selecting eligible studies of the scoping review

Inclusion criteria	Exclusion criteria
Type of study	
Randomised clinical trials (RCT), cohorts, longitudinal studies, cross-sectional studies	Reviews, letters, reports, comments, opinions, editorials, case studies and case series, conference and meeting abstracts as well as other non-peer-reviewed abstracts/articles, grey literature
Participants	
COPD and/or asthma–COPD overlap	Other pulmonary diseases such as asthma
Outcomes	
Clinical usefulness and reproducibility of FeNO alone or combined with other inflammatory biomarkers	Without any focus on FeNO

COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide.

also a challenge.[17] To minimise this, we are planning to aggregate findings from different studies under themes and synthesise the data under each of these themes.

This study will be conducted as per the methodology outlined in the Joanna Briggs Institute Reviewers' Manual[21] and reported as per the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement.[22] It is also according to Levac *et al*'s[23] and Arksey *et al*'s[16] framework for a scoping review.

Eligibility criteria

To be eligible, studies of all languages, from 2005 onwards and including n >10will be considered. Patients diagnosed with COPD/ACO according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[24] and GOLD-Global Initiative for Asthma (GINA),[7] respectively, will be included. Any intervention will be taken into consideration, except the ones that have no focus on FeNO measurement. Table 1 shows inclusion and exclusion criteria for selecting eligible studies, that is, types of study, participants and outcomes.

Information source (databases), literature search and search strategy

A structured comprehensive literature search was conducted in major databases including Medline (via OvidSP), Embase (via OvidSP), Cumulative Index to Nursing and Allied Health Literature (via EBSCO host), Cochrane Library (via Wiley Online), Web of Science, BIOSIS Previews, BIOSIS Previews Archives on 26 June 2016 and an updated search was performed on 29 June 2017. Additional studies will be recognised by exploring the reference list of identified eligible studies. The first inception of database searches was conducted without date limitation, but it will be limited to the year 2005 onwards as this was the year when the American Thoracic Society/European Respiratory Society guideline[25] concerning FeNO and its measurement was published. There is no limitation regarding language in this search strategy. We used a variety of keywords/text words and database subject heading such as [COPD OR Chronic Obstructive Lung Disease OR Emphysema OR Chronic Bronchitis OR ACOS OR Asthma-COPD Overlap Syndrome OR Concomitant asthma] AND [FeNO OR Fractional Exhaled Nitric

Table 2 Search strategy on Medline via OvidSP

#	Searches	Results
1	('10712994' or '10907593' or '11296168' or '11413349' or '15817806' or '15939243' or '16289590' or '16646959' or '17426212' or '18460522' or '18547853' or '19124359' or '19401794' or '19820080' or '19881162' or '20210889' or '21143751' or '21530214' or '23445725' or '23509896' or '23681903' or '23989961' or '24013942' or '24719850' or '24929061' or '25053884' or '26252571' or '26372312' or '26491283' or '26496331' or '26497109' or '26814886' or '26916083' or '26952317' or '27142135' or '27209003').ui.	36
2	exp Pulmonary Disease, Chronic Obstructive/	43308
3	Lung Diseases, Obstructive/	18072
4	exp Pulmonary Emphysema/	14866
5	(obstructive adj2 (pulmonary or (obstructive adj2 (pulmonary or lung$ or respirat$ or air$)).tw,kf.	44058
6	(chronic air$ adj2 (obstruction$ or limitation$ or occlusion$)).tw,kf.	1428
7	(chronic bronch$ adj2 (obstruction$ or limitation$ or occlusion$)).tw,kf.	95
8	(chronic$ adj2 bronch$).tw,kf.	12908
9	COPD.tw,kf.	32628
10	COAD.tw,kf.	222
11	emphysema$.tw,kf.	24011
12	(acos and asthm*).tw,kf.	86
13	or/2–12	99543
14	Nitric Oxide/	78284
15	(feno and (fraction* or exhal* or nitric)).tw,kf.	1099
16	(fe no and (fraction* or exhal* or nitric)).tw,kf.	401
17	nitric oxid*.tw,kf.	126245
18	or/14–17	140975
19	13 and 18	750
20	1 and 19	32
21	1 not 20	4

Table 3 Data extraction framework of the scoping review

Bibliometrics	Comments
Author(s)	First author *et al*
Title	Full title
Year	Year of publication
Country	Country of conducted study
Data extraction	
Aim of study	Full aim, regardless of our research questions
Design of study, if applicable	Type of study
Intervention, if applicable	
Methods	
Setting/Sample of study	Outpatient or inpatient or as described by the author(s)/ population number (N) in analysis (including N in total/ COPD if it is different from N in analysis)
COPD population characteristic, if applicable	Number of patients with COPD, mean/median age or range of age, gender, BMI, smoke pack-year, exacerbation
Results	Overall results and specific ones in regard to our study
Conclusions/Key findings	Overall and specific to our study
Research gaps	As identified by author(s)
Future recommended studies/research	As suggested by the author(s)

BMI, body mass index; COPD, chronic obstructive pulmonary disease.

Oxide]. Table 2 shows search strategy on Medline. The updated search strategy on this database can be found in the online supplementary file.

Study selection

Two reviewers (S-M-YM-P-M and NN) will independently review the title and abstract of retrieved articles from the database searches for the purpose of screening. Then, the full text of potential articles, which will be retrieved from first screening, will be investigated as the second screening. Discrepancies will be solved by reaching the consensus between two reviewers according to the criteria eligibility. If the two reviewers could not reach the consensus concerning the specific article(s) or both were suspicious about including/excluding the articles, these papers will be reviewed by the third reviewer (JB) and the issue will be solved.

Data extraction

Data collection/extraction will be done by using a designated data extraction form and gathered electronically. We will use PICOS[22 26] approach for designing the form and extracting data as well, which will be developed from our research questions. The form will be reviewed and revised again by the reviewers after completing to reach the consensus among reviewers. Data extraction will be independently done by two reviewers (S-M-YM-P-M and NN). The data will include study title, first author's name, publication year, the name of the journal, sample size, sample description, setting description and outcomes. Concerning outcomes, the data will be as follows but not limited to FeNO values, eosinophil level/IgE in sputum and/or in blood, pulmonary function tests, CT scan findings and exacerbations (symptoms based or evidence based, ie, requiring antibiotics or non-inhaled/systemic corticosteroids, emergency or hospital admission). The information from the studies will be summarised by producing descriptive summary tables. Table 3 shows the data extraction framework.

Then the findings will be given in an explanatory and a narrative review and briefed in a table to make the comparisons of different studies easy. The replication of studies' results and their differences will be considered and reported. The results classification will be performed according to the studies' findings and other relevant indicators of interest. This scoping review will provide a comprehensive overview of FeNO use, utility, and validity in describing patients with COPD and/or ACO. In addition, it will provide a new practical model to combine a variety of research articles specific to FeNO in COPD/ACO. We expect to report the results in early 2018. Reviewing and analysing this large amount of peer-reviewed published literature as a scoping review may expose new needs and directions for FeNO research in COPD/ACO.

Quality assessment of included studies

In accordance with scoping review guidance,[21] we will not appraise methodological quality or risk of bias of the included articles. This approach is consistent with scoping reviews of clinical topics.[27]

Contributors All authors have made substantive intellectual contributions to the development of this protocol. All authors were involved in developing the review questions and the review design. S-M-YM-P-M and JB were involved in writing this manuscript. NN, MB and AD commented critically on several drafts of the manuscript. S-M-YM-P-M, NN and JB were involved in conceptualising this scoping review protocol. All authors approve the final version of the protocol manuscript.

Competing interests None declared.

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