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# Blood eosinophil phenotypes in non-cystic fibrosis bronchiectasis: a protocol for a systematic review and meta-analysis

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## ADMINISTRATIVE INFORMATION

**Support -** No specific funding.

**Review Stage at time of this submission -** The review has not yet started.

**Conflicts of interest -** None declared.

**INPLASY registration number:** INPLASY202690122

**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 September 2026 and was last updated on 28 September 2026.

## INTRODUCTION

**Review question / Objective** The primary objectives are:
1.To estimate the prevalence of different blood eosinophil count (BEC) phenotypes among patients with non-cystic fibrosis bronchiectasis (NCFB), based on available data.
2.To evaluate the potential associations between these BEC phenotypes and clinical outcomes, such as exacerbations and mortality.
3.To explore the hypothesis that a non-linear (e.g., U-shaped) relationship may exist, aiming to assess whether both low BEC (eosinopenia) and high BEC (eosinophilia) are associated with worse clinical outcomes compared to an intermediate reference range.

**Rationale** While type-2 inflammation is increasingly recognized in NCFB, the interpretation of BEC remains inconsistent. Existing literature often dichotomizes BEC, which may inadvertently merge patients with eosinopenia and those with normal/intermediate levels into a single category. We hypothesize that both very low and elevated BEC might represent distinct clinical phenotypes with elevated risks. If feasible, this review aims to move beyond simple dichotomization by evaluating the clinical significance of low, intermediate, and high BEC groups, providing a more nuanced understanding of eosinophilic phenotypes in NCFB.

**Condition being studied** Non-cystic fibrosis bronchiectasis.
Bronchiectasis is a chronic respiratory disease characterized by permanent bronchial dilatation associated with chronic airway inflammation, recurrent infection, sputum production, and acute exacerbations.
The exposure of interest is peripheral blood eosinophil count or blood eosinophil percentage measured in patients with bronchiectasis.
Stable-state, repeated/persistent, and acute-exacerbation eosinophil measurements will be distinguished because eosinophil levels may vary

according to infection, corticosteroid exposure, and clinical state.

## METHODS

**Search strategy** A comprehensive literature search will be conducted across the following electronic databases from their inception to the date of the final search:
MEDLINE (via PubMed)
Embase
Web of Science Core Collection
Scopus
A draft search strategy developed for MEDLINE (via PubMed) is as follows:
("Bronchiectasis"[Mesh] OR bronchiectas*[Title/Abstract] OR "non-cystic fibrosis bronchiectasis"[Title/Abstract] OR "non-CF bronchiectasis"[Title/Abstract] OR NCFB[Title/Abstract])
AND
("Eosinophils"[Mesh] OR eosinophil*[Title/Abstract] OR eosinopen*[Title/Abstract] OR eosinophilia[Title/Abstract] OR "blood eosinophil count"[Title/Abstract] OR "blood eosinophil counts"[Title/Abstract] OR BEC[Title/Abstract] OR "type 2 inflammation"[Title/Abstract] OR "T2 inflammation"[Title/Abstract])
No publication date, language, or outcome-related search filters will be applied to maximize search sensitivity. The search syntax will be adapted appropriately for Embase, Web of Science, Scopus using their respective controlled vocabularies and field tags.
In addition to the database searches, we plan to:
Manually screen the reference lists of all included primary studies and relevant review articles.
Perform forward citation searching of key eligible articles to identify further relevant literature.
Update the search prior to the final analysis to ensure all recent publications are captured.

**Participant or population** Eligible participants will be patients with clinically and/or radiologically confirmed non-cystic fibrosis bronchiectasis.
Studies of adult populations will be eligible. Studies including mixed age groups will be considered if bronchiectasis-specific data can be extracted.
Studies including patients with asthma, COPD, or allergic bronchopulmonary aspergillosis (ABPA) will not automatically be excluded, but the management of these potentially eosinophil-associated conditions will be recorded.
Studies consisting exclusively of cystic fibrosis bronchiectasis will be excluded.

**Intervention** The exposure of interest is peripheral blood eosinophil level.
Where data permit, we plan to categorize the BEC phenotypes into three tiers for analysis:
1.Eosinopenia (e.g., less than 100 cells/μL)
2.Intermediate/Reference (e.g., 100 to 299 cells/μL)
3.Eosinophilia (e.g., 300 cells/μL or greater)
However, we will also extract and accommodate alternative thresholds or percentage-based definitions as originally reported by the primary study authors.

**Comparator** For prognostic analyses, the preferred reference group will ideally be the intermediate BEC phenotype (e.g., 100 to 299 cells/μL). Comparisons of interest include eosinopenia vs. intermediate, and eosinophilia vs. intermediate. If studies use different reference groups, they will be analyzed according to their original design.

**Study designs to be included** Eligible designs will include:1.prospective cohort studies;2.retrospective cohort studies;3.registry-based observational studies;4.cross-sectional analytical studies;5.case-control studies where appropriate;6.secondary or post-hoc analyses of clinical trials providing relevant BEC data.Randomized controlled trials evaluating eosinophil-directed therapies may be included in a separate treatment-related section where they provide information relevant to BEC phenotype or treatment-effect modification.Case reports and very small uncontrolled case series will be excluded from quanti.

**Eligibility criteria** Inclusion criteria
Studies will be eligible if they:
1. Include patients with non-cystic fibrosis bronchiectasis;
2. Report peripheral blood eosinophil count or percentage;
3. Report at least one relevant measure of:
o prevalence;
o exacerbation;
o severe exacerbation;
o hospitalization;
o mortality;
o disease severity;
o lung function;
o microbiology;
o healthcare utilization;
o treatment response;
4. Provide sufficient data for qualitative synthesis or quantitative extraction.
Exclusion criteria
Studies will be excluded if:

1. The population consists exclusively of cystic fibrosis;
2. Bronchiectasis-specific results cannot be separated from another disease population;
3. Blood eosinophils are not measured or reported;
4. Only airway or sputum eosinophils are reported without blood eosinophil data;
5. The publication is a narrative review, editorial, commentary, guideline, protocol, or case report without usable primary data;
6. The same patient population is duplicated in another publication reporting the same exposure and outcome.

When multiple publications originate from overlapping cohorts, the most informative report will be selected for each exposure-outcome analysis according to sample size, follow-up completeness, appropriateness of exposure definition, availability of adjusted estimates, and reporting quality.

Different publications from the same cohort may contribute to different outcomes but will not be counted twice within the same pooled estimate.

**Information sources** The following sources will be searched:
• MEDLINE/PubMed;
• Embase;
• Web of Science Core Collection;
• Scopus, where accessible;
• reference lists of eligible studies;
• reference lists of relevant reviews;
• forward citation searching;
• related-article searches.

Relevant trial registries may be searched for ongoing or completed studies of eosinophil-targeted therapies in bronchiectasis.

Study authors may be contacted when essential numerical outcome or exposure information is unavailable or internally inconsistent.

**Main outcome(s)** The principal outcomes will be:
1. Prevalence of eosinophilic bronchiectasis

The principal quantitative definition will be stable-state BEC ≥300 cells/μL.

Prevalence using alternative thresholds will be summarized separately.
2. Bronchiectasis exacerbation

Including:
• occurrence of exacerbation;
• exacerbation frequency or annualized rate;
• time to first exacerbation.

Rate-based outcomes and time-to-event outcomes will not automatically be combined.
3. Severe exacerbation / hospitalization

Including:
• hospitalization for bronchiectasis exacerbation;
• severe exacerbation as defined by individual studies;
• time to first hospitalization.
4. All-cause mortality

Where possible, longitudinal studies evaluating baseline BEC and subsequent mortality will be distinguished from concurrent or cross-sectional associations.

Effect measures may include hazard ratios, risk ratios, incidence rate ratios, or odds ratios.

Different effect measures will not be assumed to be interchangeable.

**Additional outcome(s)** Secondary outcomes will include:
• Bronchiectasis Severity Index (BSI);
• FACED or E-FACED score;
• FEV1 or FEV1 % predicted;
• radiological severity;
• Pseudomonas aeruginosa infection or chronic colonization;
• other microbiological characteristics;
• length of hospital stay;
• healthcare utilization;
• quality of life;
• persistent or repeated eosinophil phenotypes;
• eosinophil variability over time.

Treatment-related outcomes, including potential interaction between baseline BEC and inhaled corticosteroids or eosinophil-directed biological therapies, will be analysed separately from natural-history associations.

**Data management** Search results will be imported into reference-management software and deduplicated before screening.

Titles and abstracts will be assessed against predefined eligibility criteria. Potentially eligible reports will undergo full-text assessment.

Two reviewers will independently assess eligibility wherever feasible, with disagreements resolved through discussion and, when required, consultation with a third reviewer.

A standardized Microsoft Excel data-extraction form will be used.

The following information will be collected:
• author and publication year;
• country and participating centres;
• study design;
• cohort or registry name;
• recruitment period;
• sample size;
• clinical state at BEC measurement;
• BEC measurement timing;
• single versus repeated measurement;
• BEC thresholds and group sizes;
• asthma, ABPA, COPD, and other relevant exclusions;

• outcomes and their definitions;
• follow-up duration;
• number of events;
• effect estimate;
• 95% confidence interval;
• crude versus adjusted estimate;
• adjustment covariates;
• potential cohort overlap.

Multiple reports from the same cohort will be linked to prevent double counting.

Where discrepancies occur between the abstract, main text, tables, or supplementary material, the discrepancy will be documented rather than resolved by unsupported inference.

**Quality assessment / Risk of bias analysis** Risk of bias will be assessed using design-appropriate tools.

For prevalence studies, the Joanna Briggs Institute Critical Appraisal Checklist for Studies Reporting Prevalence Data will be used.

For longitudinal prognostic-factor studies, the Quality In Prognosis Studies (QUIPS) tool will be used.

For randomized trials included in the treatment-related section, the Cochrane Risk of Bias 2 (RoB 2) tool will be used where applicable.

Non-randomized treatment-effect studies will be appraised using an appropriate observational-study risk-of-bias framework.

Assessment will be performed independently by two reviewers where feasible, with disagreements resolved by consensus.

Risk-of-bias judgments will be considered in sensitivity analyses and interpretation of the evidence.

**Strategy of data synthesis** Analyses will be performed using R software.

Prevalence: If clinically appropriate and data are sufficient, prevalence estimates will be pooled using a generalized linear mixed model (GLMM) or other appropriate models for proportions.

Prognosis/Associations: We anticipate pooling hazard ratios, risk ratios, and odds ratios separately using random-effects models. Adjusted effect estimates will be prioritized.

Non-linear relationship evaluation: Where data allow (e.g., if sufficient studies report multiple categories or spline analyses), we will explore potential non-linear relationships. If formal quantitative meta-analysis is precluded by significant methodological or clinical heterogeneity, findings will be summarized descriptively using a structured narrative synthesis.

**Subgroup analysis** Where sufficient independent studies are available, subgroup analyses may be conducted to explore heterogeneity, including factors such as:

Timing of measurement (stable state vs. acute exacerbation).

Geographic region.

Inclusion or exclusion of comorbid asthma/COPD.

**Sensitivity analysis** Planned sensitivity analyses (subject to data availability) include:

Excluding studies deemed at high risk of bias.

Restricting prognostic analyses to studies reporting adjusted effect estimates.

**Language restriction** No language restrictions will be applied to the literature search.

**Country(ies) involved** China.

**Keywords** Bronchiectasis; blood eosinophil count; eosinopenia; eosinophilia; clinical phenotype; prognosis; systematic review; meta-analysis.

**Dissemination plans** We plan to submit the findings of this systematic review and meta-analysis for publication in a peer-reviewed academic journal specializing in respiratory medicine. Additionally, the results may be presented at relevant national or international scientific conferences. The final manuscript will be reported in strict accordance with the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Any necessary amendments made to this protocol during the course of the review will be transparently documented and reported in the final publication.

**Contributions of each author**

Author 1 - Xiong Gao - Conceptualization, Methodology, and Project administration. Planned roles include conducting the literature search, screening, data extraction, statistical analysis, and writing the original draft.
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Author 2 - Xin Yan - Planned roles include acting as the independent second reviewer for literature screening, data extraction, and risk-of-bias assessment, as well as reviewing the final manuscript.
Email: 244913260@qq.com
Author 3 - Yihan Meng - Planned roles include developing the statistical framework for non-linear (U-shaped) associations, conducting advanced data synthesis (e.g., GLMM models), and creating data visualizations.
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Author 4 - Yuanjie Qiu - Planned roles include developing, adapting, and executing the

comprehensive literature search strategies across all target databases (PubMed, Embase, Scopus, Web of Science), and managing reference deduplication.
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Author 5 - Huizhong Hu - Planned roles include providing clinical expertise on non-cystic fibrosis bronchiectasis, defining outcome variables, and interpreting the clinical relevance of different eosinophil phenotypes.
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Author 6 - Xinming Xie - Planned roles include conducting cross-verification of extracted data and identifying/managing overlapping multi-center cohorts to prevent double-counting.
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Author 8 - Zhuxuan Han - Planned roles include assisting in the planned subgroup and sensitivity analyses, and reviewing the manuscript for critical intellectual content.
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