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Clinical and biomarker significance of interleukin-4 and interleukin-13 in acute exacerbations and the frequent exacerbator phenotype of chronic obstructive pulmonary disease: a systematic review

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Abstract

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are one of the major causes of morbidity, mortality, and hospitalization; reliable inflammatory biomarkers predicting exacerbation risk and guiding emerging interleukin (IL)-targeted therapies are still undefined. IL-4 and IL-13 are key T-helper 2 cytokines implicated in eosinophilic airway inflammation and remodeling, but their clinical and prognostic relevance in COPD is still controversial.

MEDLINE and EMBASE databases were manually searched from inception to December 2025, including observational studies reporting quantitative IL-4 and/or IL-13 levels in adults with COPD and healthy controls, with measurements in serum by enzyme-linked immunosorbent assay or V-PLEX immunoassay. Study selection, data extraction, and quality assessment (Newcastle-Ottawa Scale) were performed independently by three reviewers, following PRISMA recommendations.

Of 1147 records screened, 5 cohort studies (total patient number: 1168) met inclusion criteria. Across studies, serum IL-4 was consistently higher in AECOPD than in healthy controls, with IL-13 also frequently elevated during exacerbations. Comparisons between AECOPD and stable COPD yielded non-significant results. Two studies reported higher serum IL-4 in frequent versus infrequent exacerbators, whereas IL-13 was not as significantly high as IL-4. In stable COPD, IL-4 and IL-13 showed only modest, often non-significant increases versus controls. Available evidence suggests that IL-4 and IL-13 are variably upregulated in COPD, with more pronounced elevations during AECOPD and a possible association between higher IL-4 and frequent exacerbations. However, small sample sizes, methodological heterogeneity, and limited longitudinal data can't lead to definitive conclusions, requiring the need for larger, well-designed studies to validate IL-4/IL-13 as prognostic biomarkers and therapeutic targets in COPD.

Key words: COPD, acute exacerbation, IL-4, IL-13, systematic review, frequent exacerbator phenotype, Th2 inflammation, biomarker.

Introduction

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) represent the fourth leading cause of hospitalization worldwide, carrying a heavy burden of disease progression, impaired quality of life, prolonged hospital stays, escalating healthcare costs, and high mortality rates [1,2]. Despite this clinical impact, the prognostic assessment of patients hospitalized with AECOPD remains highly challenging and widely debated.

While multiple studies have linked elevated and persistently high serum inflammatory biomarkers to clinical deterioration, functional decline, and comorbidities in COPD patients [2-5], the precise role of specific inflammatory pathways remains to be fully elucidated. Specifically, although the involvement of T-helper 2 (Th2) cytokines—namely interleukin-4 (IL-4) and interleukin-13 (IL-13)—in airway inflammation is well-documented [6-8], and despite growing interest in IL-targeted therapies for AECOPD [9,10], the exact expression profile and biological functions of these cytokines in COPD remain unclear. Clarifying the relationship between systemic IL-4/IL-13 levels and AECOPD is therefore crucial to identify which patient subgroups are most likely to benefit from these novel targeted interventions.

To address this gap, we conducted a systematic review to evaluate the clinical impact of serum IL-4 and IL-13 on the occurrence and frequency of COPD exacerbations, a topic that remains controversial in current literature.

Methods

A protocol for this systematic review of the literature was prospectively developed, detailing specific objectives, criteria for study selection, approach to assess study quality, outcomes and statistical methods. This study received no financial support. The authors deny conflict of interest. The study was registered on PROSPERO (CRD420261453224).

Aim of the study

The aim of the study was to investigate the association between serum IL-4 and IL-13 levels and the frequent exacerbator phenotype in COPD patients (defined as ≥2 exacerbations during the observation period), and to compare these levels with those observed in healthy control subjects.

We consider control group patients with stable COPD, which is defined as the chronic state of the disease, characterized by the absence of an exacerbation, where respiratory symptoms have returned to their baseline level and the patient does not require any change in their

regular pharmacological treatment or the reduction of symptoms after 10 days of medical therapy, or patients without COPD [1].

Data source and search strategy

MEDLINE and EMBASE databases were manually searched from inception up to December 2025 screening titles, abstracts and full text. The search strategy was developed using a combination of controlled vocabulary terms—Medical Subject Headings (MeSH) in MEDLINE and Emtree terms in EMBASE—and free-text terms, synonyms, spelling variations, truncations (using wildcards where appropriate), and Boolean operators (AND, OR) to maximize sensitivity. No filters for study design or publication year were applied, but the search was restricted to articles published in the English language.

We used these MESH terms: "Pulmonary Disease, Chronic Obstructive" OR "chronic obstructive pulmonary disease" OR "COPD" OR "chronic obstructive airway disease" OR "chronic obstructive lung disease" OR "airflow obstruction" OR "bronchitis, chronic" OR "emphysema" AND "Interleukin-4"OR "Interleukin-13"OR "IL-4" OR "IL4" OR "interleukin 4" OR "interleukin-4" OR "IL-13" OR "IL13" OR "interleukin 13 OR "interleukin-13".

Research included all the sampling methods (ELISA or V-PLEX immunoassay con serum).

Eligibility criteria

Studies were considered potentially eligible for this systematic review if they met the following criteria: describe the relationship between IL-4 and/or IL-13 and AECOPD or relationship with exacerbation frequency; give specific serum concentrations of IL-4 and/or IL-13; provide control of IL-4 and/or IL-13 levels in control patients. COPD patients were diagnosed according to the criteria of the American Thoracic Association [11], or the Global Chronic Obstructive Pulmonary Disease Initiative based on exposure history (e.g., smoking, occupational dust, air pollution), symptoms (chronic cough, sputum production, and/or dyspnea), spirometry [1]. Control group included stable COPD, considered patients with 4 weeks of absence of symptoms, or patients without COPD.

Exclusion criteria

Conference abstracts, editorials, case series, letters, reviews, meta-analyses; studies without a control group; studies on patients younger than 18 years; patients with a history or diagnosis

of respiratory disease other than COPD; patients with immune system disorders; animal experiments or in vitro culture models; articles published in a different language from English.

Data extraction and quality assessment

Screening information was independently performed by three investigators from the original study. If relevant, the full article is retrieved. In these articles, references citing relevant reviews or original studies were also accessed to identify other eligible studies.

Any disagreements between reviewers were resolved by a fourth researcher. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of included studies [12]. The NOS is a semi-quantitative instrument comprising three domains: selection (4 items), comparability (1 item), and exposure assessment (3 items), designed to evaluate case-control and cohort studies. An evaluative "star system" (scale 0–9) was implemented for scoring. Studies with total scores ≤3 were classified as low quality, those scoring 4–6 as moderate quality, and those scoring 7–9 as high quality [12].

From each study, we collected the following data: authors, year of publication, design of the study, the total number of included patients, IL-4 and/or IL-13 value and clinical phenotype (AECOPD, stable COPD, frequent exacerbator, non frequent exacerbator). The methodology used was in accordance with the PRISMA guidelines [13].

Results

Due to the heterogeneity of study populations, a quantitative meta-analysis was not feasible and results were synthesized qualitatively**.**

Description of included studies

The initial search revealed a total of 1845 citations (709 from Medline and 1136 from Embase) were identified by our systematic search; 698 studies were in both databases. In total we considered 1147 studies. 944 were excluded after title screening or because clinical cases or animal studies or in languages other than English or because full text wasn't available. 203 studies' abstracts were evaluated and 137 were excluded after abstract evaluation. 61 were excluded after full-text revision because they did not provide information about the value of blood IL-4 or because they did not address the outcome of interest in our study.

Thus, a total of 5 studies [14-18] were included in the systematic review. All the studies were written in English and were observational (prospective or retrospective cohorts).

A flow chart diagram of the search strategy and study selection is provided in figure 1. The study population included 1168 adult patients ranging from 60 to 488 patients. In 3 studies serum biomarkers (IL-13 and/or IL-4) were analyzed with V-PLEX immunoassay kit; two studies evaluated the biomarkers with ELISA technique. In two studies IL-4 and/or IL-13 were evaluated in AECOPD patients. In 3 studies IL-4 and/or IL-13 were evaluated in stable COPD patients with 4 weeks of absence of symptoms. Two studies also considered patients in remission from AECOPD (10 days after recovery). One study didn't specify the selection criteria of stable COPD patients. All 5 studies were considered of high quality according to NOS [12]. Table 1 reported studies characteristics [14-18].

Non-frequent exacerbators vs. frequent exacerbators

Two studies stratified patients based on exacerbation frequency [14,16]. Lin et al evaluated both IL-4 and IL-13 as markers of systemic inflammation finding increased levels of IL-4 in frequent exacerbators ($p=0.001$) and a non-significant increased level of IL-13 in non-frequent exacerbators ($p=0.3$) [14]. Zhao et al considered serum concentration of IL-4 between the two groups, finding greater value in patients who experienced two or more exacerbations in the previous year in comparison with non-frequent exacerbators [16]. These results show a correlation between IL-4 and the phenotype of frequent exacerbators with stable COPD, suggesting a link between elevated IL-4 and susceptibility to recurrent exacerbations.

AECOPD vs. stable COPD vs. control

Three studies evaluate IL-4 and/or IL-13 in patients with AECOPD or with stable COPD (or in remission stage) or without COPD [15,17,18]. Sun et al found significant increased levels of IL-4 compared with the controls without COPD ($p < 0.05$) [15]. However they didn't find a significant difference in IL-4 between AECOPD and remission group or between remission and control. It was also evaluated IL-13, finding significance in the elevations in AECOPD vs control; similarly to IL-4 there was no difference between AECOPD and remission group or remission and control.

Jiang et al found greater levels of IL-4 in peripheral blood in the AECOPD group compared to healthy control. It was not found a significant difference between AECOPD and stable COPD or between stable COPD and healthy control [17]. Wei et al found that serum IL-4 levels were significantly higher in patients experiencing an acute exacerbation compared to patients with stable COPD or healthy controls [18]. This study also highlighted a Th1/Th2 imbalance

towards Th2 during exacerbations, suggesting increased production of Th2 cells and associated cytokines, including IL-4.

Discussion

As highlighted by recent trials on IL-target therapies such as Dupilumab [9,10], IL-4 and IL-13 are emerging as potential biomarkers and possible therapeutic targets in COPD management. The cytokines IL-4 and IL-13 have gained attention for their potential role to mark or drive eosinophilic inflammation, remodeling, and exacerbation risk. Data from the five studies under review indicate that systemic IL-4 and IL-13 have different levels depending on disease state, and these patterns align with the wide COPD literature [14-18]. Our analysis demonstrated that IL-4 is elevated in patients with acute exacerbation and in patients with a frequent exacerbation phenotype. This suggests that exacerbations trigger or amplify systemic T2 responses, possibly via activation of adaptive immunity. The role of IL-4 in COPD exacerbations is linked to type 2 inflammation, present in 20-40% of COPD patients. IL-4, together with IL-13, promotes the infiltration of type 2 inflammatory cells into the lung, contributing to pathological processes such as bronchial hyperresponsiveness, airway remodeling, goblet cell hyperplasia, and mucus hypersecretion. [9]. Indeed, exacerbations may be driven by triggers (viral, bacterial, allergen) that provoke a T-cell mediated response, recruiting eosinophils and other effector cells via IL-4/IL-13 pathways. In fact in recent transcriptomic analyses of COPD lung samples show that IL-13–induced gene signatures (e.g., POSTN, CCL26) are strongly enriched in patients with elevated tissue eosinophils, suggesting that local T2 activation is biologically relevant [19]. Phenotype-specific analyses further reinforce the importance of IL-13. Two of the reviewed studies reported increased serum IL-4 in stable COPD [15,17], but these changes did not uniformly achieve statistical significance, while serum IL-13 likewise showed only non-significant elevations in other cohorts. This limited systemic expression during stable disease suggests that robust Th2 activation is not a universal feature of COPD, aligning with prior findings that the dominant inflammation in many patients is neutrophilic and macrophage-driven (e.g., IL-8, TNF-α), rather than classical Th2 [20]. Indeed, a large cross-sectional cohort study found that plasma IL-13 correlated inversely with FEV_1 in stable patients, implying that higher IL-13 may track with airflow limitation severity, though not necessarily with overt Th2-dominant inflammation [21].

However, challenges remain considering the small size of the population included and heterogeneity of the review studies in terms of patients included, timing of specimen collection

and laboratory technique. In the literature there aren't studies that show a clear prognostic role of interleukins in AECOPD and our review has clinical relevance in order to define the frequent exacerbators phenotype and a relationship between IL-4 and IL-13 and AECOPD, although the small size and heterogeneity of the population included. Further studies can confirm our results and find a prognostic role with the aim of a better patient selection for IL target therapy.

When evaluating the translational potential of systemic IL-4 and IL-13, their relationship with eosinophilic inflammation and COPD severity must be carefully considered in its full context. Although a direct, quantitative correlation between serum Th2 cytokines and blood eosinophil counts was not reported across all included cohorts, a clear link can be assumed. IL-4 and IL-13 act as primary drivers for eosinophil recruitment and tissue infiltration. The observed cytokine elevations during AECOPD—primarily documented in hospitalized inpatients (e.g., Sun et al. [15], Jiang et al. [17], and Wei et al. [18])—strongly suggest that Th2 upregulation tracks with severe, acute clinical events requiring inpatient care. There isn't enough data about milder, outpatient-managed exacerbations. This inpatient-outpatient setting imbalance and the lack of standardized stratification by baseline FEV1% and concomitant blood eosinophil thresholds, make it difficult to define precise clinical cut-offs for routine practice.

The lack of longitudinal studies with standardized sampling during the acute, recovery, and stable phases of an exacerbation prevents us from defining the optimal timing for biomarker assessment, as it affects cytokine serum levels. In order to address the lack of longitudinal timing data in literature, we propose a standardized, prospective sampling protocol: T0 (ED admission/before steroid-therapy) to get the native, drug-unbiased systemic type 2 peak and avoid corticosteroid-induced cytokine suppression; T1 (Day 3) to evaluate early cytokine clearance kinetics and responsiveness to steroid; T2 (Day 10/clinical recovery) to assess inflammatory resolution and identify patients with unresolved, high-risk biological activity prone to early recurrence; and T3 (stable state at Day 30–90) to establish the patient's constitutional baseline. A transient, pathogen-induced cytokine spike can be differentiated from a true, persistent T2-high endotype with this systematic approach.

Limits of the study

Our study has several limitations, and the results should be interpreted with caution. The first limitation is the small number of included studies with potential selection bias.

Despite a broad search, only five studies met the inclusion criteria, limiting statistical power. The small sample size increases the likelihood that observed associations are unstable and

susceptible to random error, especially given heterogeneity across studies. It also raises the risk of publication bias, as studies without significant results may be underrepresented in literature. Another limitation is related to the heterogeneity of the studies. The included studies are observational designs (prospective or retrospective cohorts) with varying patient populations (stable COPD, AECOPD) and different settings (inpatient vs outpatient). Differences in disease state at sampling (acute exacerbation versus remission), in the definition of "stable" COPD, and in the criteria used to classify eosinophilic phenotypes introduce substantial clinical and methodological heterogeneity, complicating cross-study synthesis. Marked variations in comparator group characteristics, clinical heterogeneity in patient disease states, and the utilization of diverse assay platforms introduced substantial methodological and clinical inconsistency. Furthermore, incomplete reporting of key statistical parameters across the included studies limited data extraction, ultimately preventing a robust pooling of effect sizes.

Another limit is related to the lack of data about inhaled and/or systemic corticosteroids. It is well known that patients with stable COPD and AECOPD frequently receive inhaled and/or systemic corticosteroids, but the clinical effect on IL-4 and IL-13 is not clear. IL-4 and IL-13 levels may be influenced by steroid treatment, but in the analyzed studies this kind of data was not reported.

A further limitation due to different biomarkers measurements. IL-4 and IL-13 were measured using different platforms (ELISA, V-PLEX). Assay sensitivity, specificity, and calibration, as well as pre-analytical factors (sample handling, timing relative to exacerbation, comedications), vary across studies and may account for inconsistent findings. Such methodological diversity reduces comparability and the precision of pooled estimates.

Finally, although the primary aim was to relate IL-4 and/or IL-13 to AECOPD risk and exacerbation frequency, several studies did not stratify cohorts by exacerbation phenotype, did not report pre-specified cut-offs, or failed to provide absolute values or confidence intervals for biomarker levels. This incomplete reporting reduces the ability to perform robust meta-analyses and to draw firm conclusions about prognostic utility. While elevated IL-4/IL-13 may mark a Th2-driven phenotype or eosinophilic inflammation, extrapolating these findings to guide IL-targeted therapies requires caution. Without standardized thresholds, prospective validation, and demonstration of incremental prognostic value beyond established clinical predictors, the utility of these biomarkers in routine care remains uncertain.

Conclusions

In conclusion, our systematic review underlines a relation between IL-13 and IL-4 and AECOPD or the frequency of exacerbation. Thus, the clinical role of evaluation of blood IL-13 and IL-4 is still unknown. Due to the limitations present in existing literature, there is a clear need for large, high-quality prospective studies to further evaluate the prognostic role of IL-13 and IL-4 in AECOPD. These future studies will be crucial in establishing more definitive conclusions and improving our understanding of the clinical significance of these interleukins to a more accurate use of biological treatment.

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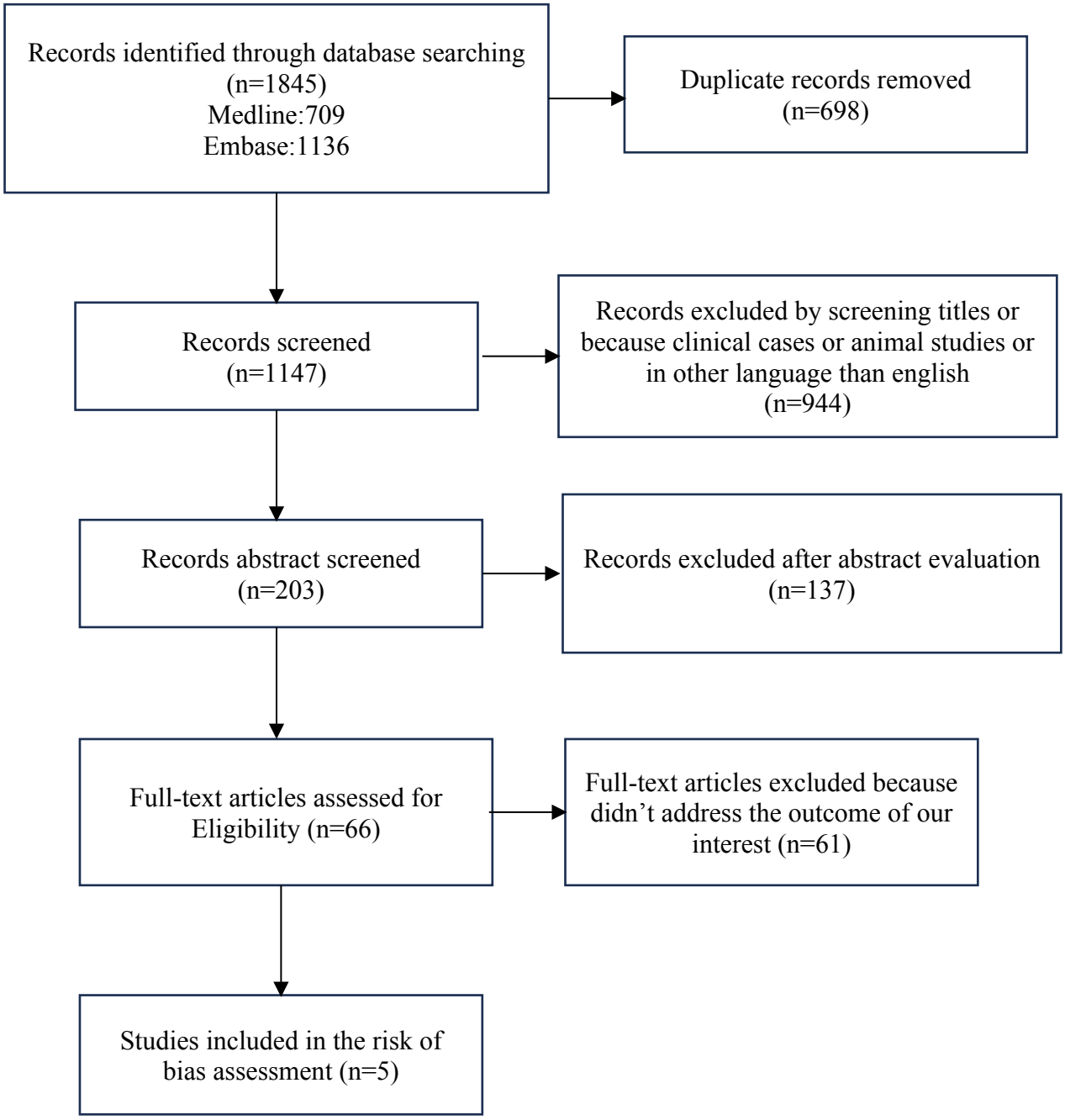


Figure 1. PRISMA flow diagram of study selection.

Table 1. Characteristics study population.

First author	Yiqi Lin	J. Sun	D. Zhao	M. Jiang	B. Wei
Year	2023	2018	2020	2019	2018
Pts	212	60	88	320	488
Study design	Cross-sectional	Observational	Cross-sectional	Observational	Observational
Interleukin evaluated	IL-4, IL-13	IL-4, IL-13	IL-4	IL-4	IL-4
Control population	Non-frequent exacerbator	Stable COPD and non-COPD	Non-frequent exacerbator	Stable COPD and non-COPD	Stable COPD and non-COPD
Outcomes	Exacerbation frequency	AECOPD	Exacerbation frequency	AECOPD	AECOPD
NOS	7	7	7	7	7
Assay platform used	V-PLEX immunoassay kit	ELISA	V-PLEX immunoassay kit	ELISA	ELISA
Biological sample type	Serum	Serum	Serum	Serum	Serum
Key reported IL-4/IL-13 values (pg/mL)	IL-4: Non frequent exacerbator 3,7, Freqeunt exacerbator 4,5 IL-13: Non freqeunt 27, Frequent 25	IL-4: Control 44, AECOPD 75 IL-13: Control 3, AECOPD	Non frequent exacerbator 0.03, non frequent exacerbator 0,12	Control 30, Stable COPD 37, AECOPD 55	Control 186, Stable COPD 310, AECOPD 354