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# Clinical Indicators for Asthma-COPD Overlap: A Systematic Review and Meta-Analysis

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**Background:** Some clinical indicators have been reported to be useful in differentiating asthma-chronic obstructive pulmonary disease (COPD) overlap (ACO) from pure asthma/COPD, but the results were inconsistent. This study aims to evaluate the diagnostic value of these indicators for ACO.

**Methods:** Databases of PubMed, EMBASE, Ovid and Web of Science were retrieved. Pooled standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated in random-effects models.

**Results:** 48 eligible studies were included. The pooled results indicated, compared with pure asthma, ACO patients had lower levels of forced expiratory volume in the first second ($FEV_1$)% predicted (pred) (SMD=−1.09, 95% CI −1.3 to −0.87), diffusion lung capacity for carbon monoxide (DLCO)% pred (SMD=−0.83, 95% CI −1.24 to −0.42), fractional exhaled nitric oxide (FeNO) (SMD=−0.23, 95% CI −0.36 to −0.11), and higher levels of induced sputum neutrophil (SMD = 0.51, 95% CI 0.21 to 0.81), circulating YKL-40 (SMD = 0.96, 95% CI 0.27 to 1.64). However, relative to COPD alone, ACO patients had higher levels of $FEV_1$% pred (SMD = 0.15, 95% CI 0.05 to 0.26), DLCO% pred (SMD = 0.38, 95% CI 0.16 to 0.6), FeNO (SMD = 0.59, 95% CI 0.40 to 0.78), serum total immunoglobulin (Ig)E (SMD = 0.42, 95% CI 0.1 to 0.75), blood eosinophil (SMD = 0.44, 95% CI 0.29 to 0.59), induced sputum eosinophil (SMD = 0.62, 95% CI 0.42 to 0.83), and lower levels of induced sputum neutrophil (SMD=−0.48, 95% CI −0.7 to −0.27), circulating YKL-40 (SMD=−1.09, 95% CI −1.92 to −0.26).

**Conclusion:** Compared with pure asthma/COPD, ACO patients have different levels of $FEV_1$% pred, DLCO% pred, FeNO, serum total IgE, blood eosinophil, induced sputum eosinophil/neutrophil, and circulating YKL-40, which could be helpful to establish a clinical diagnosis of ACO.

**Keywords:** asthma, asthma-COPD overlap, COPD, indicators, meta-analysis

## Introduction

Asthma-chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS) is a term to describe patients with both features of asthma and COPD, firstly proposed by a joint section of the Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) in 2014, and revised to "ACO" in GINA 2017.[1] ACO is epidemiologically considered in 2% of the general population, 29.6% of asthmatic patients and 26.5% of COPD patients.[2] Patients with ACO have a greater burden of symptoms, frequent exacerbations, poor quality of life, a more rapid decline in lung function and greater use of healthcare resources compared to patients with asthma or COPD alone, but global diagnostic criteria for ACO are inconclusive.[3,4]

To date, asthma and COPD are considered as two different types of chronic airway inflammation.[5,6] T-helper (Th) 2 inflammatory pattern plays an important role in the development and progression of asthma, which is indicated by blood/sputum eosinophil, serum total immunoglobulin (Ig) E, circulating periostin and fractional exhaled nitric oxide (FeNO).[1,5] However, COPD is often characterized by Th1 inflammation, dominated by macrophages and neutrophils.[6] ACO shares some

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inflammatory characteristics between asthma and COPD, and in the past few years, some clinical indicators were reported to be useful in differentiating ACO from pure asthma or COPD, but the results were inconsistent.[7–10]

Therefore, we performed a systematic review and meta-analysis to evaluate the potential diagnostic value of these clinical indicators, including post-bronchodilator forced expiratory volume in the first second ($FEV_1$)% predicted (pred), diffusing capacity of the lungs for carbon monoxide (DLCO)% pred, FeNO, serum total IgE, blood/induced sputum eosinophil, induced sputum neutrophil, and circulating YKL-40/periostin/neutrophil gelatinase-associated lipocalin (NGAL).

# Methods

## Searching Strategy

This meta-analysis was reported in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) (Table S1).[11] We systematically retrieved databases of PubMed, EMBASE, Ovid and Web of Science from inception to March 2022, with restrictions of human study and English language only. The search terms were as follows: ((asthma and chronic obstructive pulmonary disease overlap) OR (asthma and COPD overlap) OR (asthma-COPD overlap) OR (ACO and asthma) OR (ACO and COPD)) AND (biomarker OR DLCO OR FeNO OR IgE OR eosinophil OR sputum OR YKL OR periostin OR NGAL). Furthermore, we checked the references of relevant studies to seek out potentially eligible articles. No Ethics approval or patient-informed consent was needed as this meta-analysis was based on the published data.

## Study Selection

To date, no global diagnostic standard for ACO was available. In the present study, referring to criteria of ACO from GOLD, GINA and Spanish consensus,[3,4,12] the inclusion criteria were as follows: 1. Studies evaluated clinical indicators in differentiating ACO from pure asthma or COPD. 2. Studies were limited to cohort, case-control or cross-sectional. 3. In these studies, ACO patients suffered from persistent airflow limitation (post-bronchodilator $FEV_1$/forced vital capacity (FVC) ratio <0.70) and meet at least one of the following principles: 1) a physician-diagnosed asthma with respiratory symptoms (episodic breathlessness, wheezing, cough, and chest tightness worsening at night or in the early morning), or long-term usage of asthma medications; 2) a self-reported asthma or respiratory symptoms, accompanied by variable expiratory airflow limitation that characterized by an increase of $FEV_1$% pred ≥12% post-bronchodilator, or a diurnal variation in peak expiratory flow (PEF) ≥20%, or a decrease in $FEV_1$% pred ≥15% post-bronchial provocation test; 3) an increase of $FEV_1$ ≥400mL and/or an increase of $FEV_1$% pred ≥15% post-bronchodilator. 4. Appropriate data were available for synthesis and calculation of pooled effect sizes. 5. As for duplicated data, only the most up-to-date were included.

## Data Extraction

Two reviewers (JP and MW) independently extracted information from selected studies using a pre-designed excel form. For any inconsistencies, consensus was reached via discussion with a third reviewer (YW). The extracted information included first author, year of publication, sample size, age, sex, body mass index (BMI), smoking history, post-bronchodilator $FEV_1$% pred, DLCO% pred, FeNO, serum total IgE, blood eosinophil counts, percentage of induced sputum eosinophils or neutrophils, circulating YKL-40/periostin/NGAL and study design. Data were combined for meta-analysis only if at least two studies reported the same indicators measured by a similar method. Moreover, if medians and interquartile ranges (IQRs) were offered only in a study, we converted the data into approximate means with standard deviations (SDs) according to the validated statistical method,[13,14] and if there were two or more subgroups in a study, we calculated the combined means and SDs according to the Cochrane Handbook guidelines.[15]

## Quality Evaluation

A scale with 11 items offered by the Agency for Healthcare Research and Quality (AHRQ) was applied to evaluate the quality of cross-sectional study.[16] If an item of the scale met 'Yes', then it got a "1" score, or a "0" if it was "No" or "Unclear". The total score was divided into three levels: low quality = 0-3, moderate quality = 4–7 and high quality = 8–11. The cohort and case–control studies were assessed by the Newcastle-Ottawa Scale (NOS),[16] which contained the aspects of "selection, comparability and exposure" and three levels (low quality = 0–3, moderate quality = 4–6 and high quality = 7–9, respectively).

## Statistical Analysis

The meta-analysis was performed by Review Manager (RevMan) Version 5.4 and Stata/MP version 16.0. Due to differences in testing methods of some indicators, the pooled standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated, with a p-value <0.05 implying a statistically significant difference, and random-effects models were used to evaluate the pooled effects. Heterogeneity was assessed by the I-squared ($I^2$) test, when $I^2$ >50% indicating substantial heterogeneity, in which case multivariate meta-regression and subgroup analyses by year of publication, total sample size (n <200 or ≥200), study type, and quality score were conducted to explore sources of heterogeneity. The leave-one-out sensitivity analyses were performed to evaluate the stability of the pooled results. Funnel plots as well as begg's and egger's tests were adopted to assess publication bias when at least ten studies were included. Since the diagnostic criteria of ACO were not consistent in the included studies, linkage bias analyses based on the different populations in these studies, were conducted to explore the influence of such inconsistency on the pooled results.[17]

# Results

## Study Characteristics

A total of 1191 articles were identified, of which 141 articles were reviewed in full text, and 48[7–10,18–61] eligible studies (35 cross-sectional studies, 10 cohort studies and 3 case–control studies) were finally included (Figure 1). Of the 35 cross-sectional studies, 12 studies were of high quality, and the others were of moderate quality. In the 10 cohort studies, 4 studies were of high quality, and the other 6 studies were of moderate quality. The 3 case–control studies were of moderate quality. Characteristics of the included studies and detailed data of each indicator were listed in Table S2.

## Indicators

Compared to asthma alone, ACO patients had a higher percentage of induced sputum neutrophil and circulating YKL-40 level, but lower levels of $FEV_1$% pred, DLCO% pred and FeNO. There were no statistical differences between patients with asthma and those with ACO in serum total IgE, blood eosinophil counts, percentage of induced sputum eosinophil or circulating periostin. However, compared to pure COPD, ACO patients had higher levels of $FEV_1$% pred, DLCO% pred, FeNO, serum total IgE, blood eosinophil counts and percentage of induced sputum eosinophil, while lower percentage of induced sputum neutrophil and circulating YKL-40 level. There were no statistical differences between ACO and COPD with respect to circulating periostin or NGAL. Detailed results are summarized in Table 1.

## Heterogeneity and Sensitivity

Meta-regression and subgroup analyses did not find out sources of heterogeneity in each indicator (data not shown). However, in the comparison of sputum eosinophils between ACO and pure asthma, the $I^2$ dropped to 0 by excluding the study by Carpagnano et al,[20] with no significant change in the pooled results, which could be attributed to the different inclusion criteria in this study. In addition, sensitivity analyses showed that the pooled results of serum total IgE between ACO and pure asthma/COPD were unstable,[24,30,31,45,47] and the reasons could be the different allergic history of the subjects and various methods in detecting IgE (Figure S1).

## Publication Bias

Visualized funnel plots (Figure S2) and begg's tests (Table 1) indicated no significant publication bias. However, a publication bias was detected in the egger's test (Table 1), when comparing the percentage of induced sputum neutrophil between ACO and pure asthma patients, which could be addressed via excluding the study by Carpagnano et al,[20] without significant alteration in the pooled results.

## Linkage Bias

Only linkage bias analyses with deterministic rules could be achieved due to limited data.[17] By the Linkage Structure Classification Tree provided by Doidge et al,[17] 27 studies with a linkage structure of "nested" and the rest 21 studies with

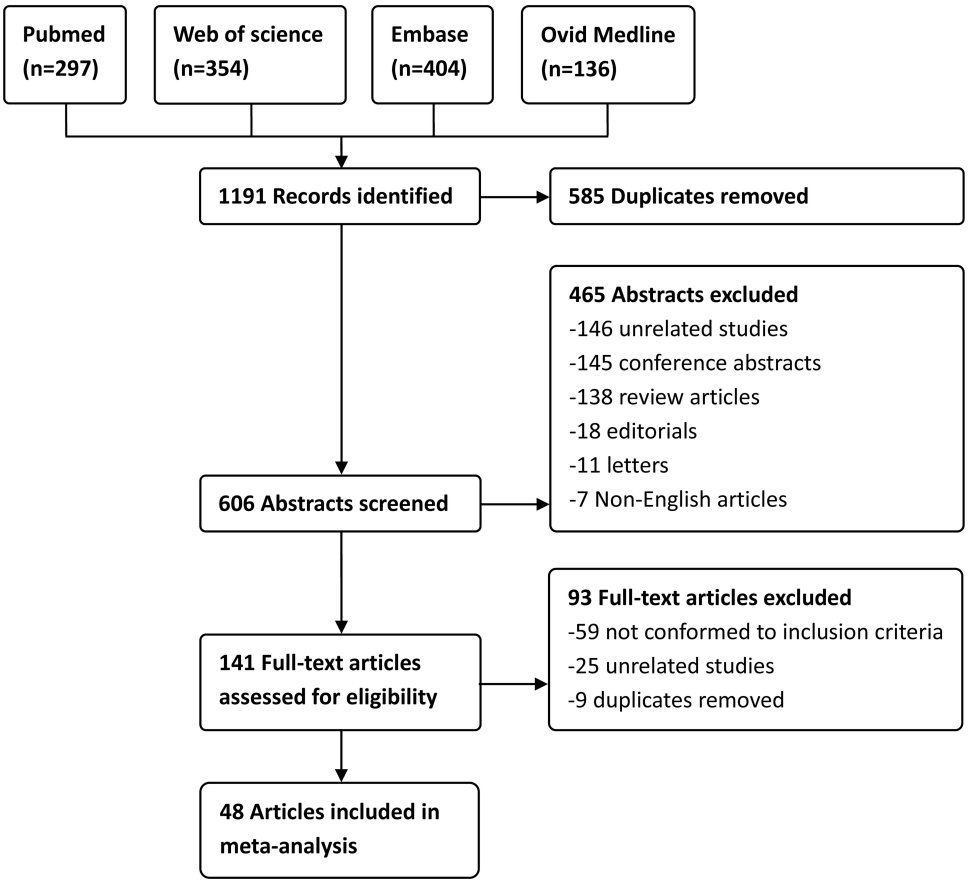


**Figure 1** Flow chart of study selection and exclusion.

a linkage structure of "imperfect nest" were identified, and both of the linkages showed potential misclassification or measurement error associated with the pooled results (Table S3).

## Discussion

In the present study, the percentage of induced sputum neutrophils and circulating YKL-40 level were higher and levels of FEV1% pred, DLCO% pred and FeNO were lower in ACO patients than in pure asthmatic patients, but the opposite was true when compared to patients with COPD alone. In addition, ACO patients had higher levels of serum total IgE, blood eosinophil counts and percentage of induced sputum eosinophils than those with pure COPD.

Airflow limitation in COPD is irreversible and progressive, while conversely, it is usually reversible in asthma. $FEV_1$ % pred, as a key indicator of small airway function, is applied in assessing the severity of airflow limitation in COPD and the extent of variation for airflow limitation in asthma.[3,12] DLCO% pred is another indicator of lung function, reflecting gas exchange between alveoli and capillaries. Physiologically, carbon monoxide (CO) in lung units will diffuse across the alveolar cell, the basement membrane, the interstitial space, the capillary endothelium, the plasma, and the red blood cell membrane to combine with the hemoglobin.[62] This physiological process can be disturbed by small airway remodeling and lung parenchyma destruction in COPD patients, while patients with asthma often preserve CO diffusing capacity, which may be explained by the improved ventilation–perfusion relationships in the apices of lungs.[6,62] It was reported that adult smokers with normal DLCO% pred were more likely to be asthmatic, whereas those with low DLCO% pred were more likely to be COPD.[63] Our study revealed that $FEV_1$% pred and DLCO% pred in ACO patients were lower than those in patients with pure asthma but higher than in pure COPD.

FeNO, IgE and eosinophil are all biomarkers of Th2 inflammation. Exhaled nitric oxide is synthesized in the airway epithelial cells by inducible nitric oxide synthase (iNOS), which is mainly regulated by Th2 inflammatory molecules like interleukin (IL)-4

**Table 1** Results of Comparisons on Each Indicator Between ACO and Pure Asthma or COPD

| Indicators | Comparisons | Pooled SMDs | 95% Confidence Intervals | | p-value | Heterogeneity | Egger's Test | Begg's Test | Total No. of Studies | Reference No. |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | | $I^2$ | p-value | p-value | | |
| PB-FEV1% pred | ACO vs asthma | −1.09 | −1.3 | −0.87 | <0.001 | 91% | 0.357 | 0.295 | 28 | 7,9,10,18–20,22,24,26,27,29–33,36,37,39,41,44–47,50,51,53,58,61 |
| | ACO vs COPD | 0.15 | 0.05 | 0.26 | 0.004 | 80% | 0.157 | 0.6 | 40 | 7–10,18,20–29,31–36,38–43,47,49–57,59–61 |
| DLCO% pred | ACO vs asthma | −0.83 | −1.24 | −0.42 | <0.001 | 89% | 0.166 | 0.536 | 8 | 19,22,27,30–32,36,47 |
| | ACO vs COPD | 0.38 | 0.16 | 0.6 | 0.001 | 82% | 0.3 | 0.21 | 10 | 21,22,25,27,31,32,36,43,47,55 |
| FeNO | ACO vs asthma | −0.23 | −0.36 | −0.11 | <0.001 | 55% | 0.688 | 0.274 | 14 | 9,10,20,30–33,36,39,44,47,51,58,61 |
| | ACO vs COPD | 0.59 | 0.40 | 0.78 | <0.001 | 82% | 0.345 | 0.529 | 19 | 8–10,20,31–34,36,39,40,42,43,47,51,52,54,59,61 |
| Serum total IgE | ACO vs asthma | 0.16 | −0.03 | 0.35 | 0.096 | 73% | 0.13 | 0.115 | 12 | 9,10,19,24,30,31,44,45,47,48,51,61 |
| | ACO vs COPD | 0.42 | 0.10 | 0.75 | 0.011 | 93% | 0.146 | 0.228 | 14 | 9,10,21,24,25,31,43,47,51,52,55,56,59,61 |
| Blood EOS counts | ACO vs asthma | −0.08 | −0.19 | 0.03 | 0.143 | 55% | 0.164 | 0.363 | 18 | 7,9,10,19,30,31,33,37,39,41,44,45,47,48,50,51,58,61 |
| | ACO vs COPD | 0.44 | 0.29 | 0.59 | <0.001 | 82% | 0.813 | 0.46 | 23 | 7–10,23,31,33,35,39–41,43,47,49–52,54,56,57,59–61 |
| Induced sputum EOS | ACO vs asthma | −0.15 | −0.4 | 0.1 | 0.23 | 74% | 0.147 | 0.087 | 10 | 7,18,20,22,26,30,45,47,51,58 |
| | ACO vs COPD | 0.62 | 0.42 | 0.83 | <0.001 | 49% | 0.36 | 0.602 | 8 | 7,18,20,22,26,34,47,51 |
| Induced sputum NEU | ACO vs asthma | 0.51 | 0.21 | 0.81 | 0.001 | 82% | 0.031 | 0.161 | 10 | 7,18,20,22,26,30,45,47,51,58 |
| | ACO vs COPD | −0.48 | −0.7 | −0.27 | <0.001 | 52% | 0.213 | 0.348 | 8 | 7,18,20,22,26,34,47,51 |
| Circulating YKL-40 | ACO vs asthma | 0.96 | 0.27 | 1.64 | 0.006 | 93% | - | - | 3 | 10,41,50 |
| | ACO vs COPD | −1.09 | −1.92 | −0.26 | 0.01 | 94% | - | - | 3 | 10,41,50 |
| Circulating periostin | ACO vs asthma | −0.01 | −0.18 | 0.17 | 0.95 | 10% | - | - | 3 | 10,31,50 |
| | ACO vs COPD | 0.53 | −0.19 | 1.25 | 0.15 | 92% | - | - | 3 | 10,31,50 |
| Circulating NGAL | ACO vs COPD | 0.28 | −0.54 | 1.09 | 0.51 | 94% | - | - | 3 | 35,41,50 |

**Abbreviations**: ACO, asthma-COPD overlap; COPD, chronic obstructive pulmonary disease; DLCO% pred, diffusion lung capacity for carbon monoxide as a percentage of predicted value; EOS, eosinophil; FeNO, fractional exhaled nitric oxide; PB-FEV1% pred, post-bronchodilator forced expiratory volume in the first second as a percentage of predicted value; IgE, immunoglobulin E; NEU, neutrophil; NGAL, neutrophil gelatinase-associated lipocalin; SMD, standardized mean difference.



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and IL-13, and FeNO testing is a noninvasive method that is widely used in the auxiliary diagnosis of asthma.[5,23,64] Moreover, IgE is commonly associated with allergic inflammation, and specific IgE for inhaled allergens is a risk factor for asthma.[64,65] A cytokine microenvironment consisted of IL-4 and IL-13 is necessary for the maturation of B-lymphocytes and their transformation to specific plasma cells, some of which can synthesize and secrete IgE.[65] It was reported that patients with ACO had higher serum total IgE than those with pure COPD characterized by Th1 inflammation.[6,66] In addition, eosinophils can be recruited to the lungs in response to stimulation of Th2 inflammatory factors such as IL-3 and IL-5, and promote persistent airway inflammation by releasing various inflammatory factors, among which eosinophil-derived neurotoxins are significantly higher in patients with ACO than those with pure COPD or asthma.[64,67] Our study revealed that there were no statistical differences in serum total IgE, blood eosinophil counts and percentage of induced sputum eosinophil between ACO and pure asthma patients, however, patients with asthma alone had a higher FeNO level than those with ACO. When compared with pure COPD, ACO patients had higher levels of FeNO, serum total IgE, blood eosinophil counts and percentage of induced sputum eosinophil, indicating ACO might share more characteristics of Th2 inflammation than COPD.

As a Th1 inflammatory mediator, neutrophils can be identified in patients with COPD as well as in a group of asthmatic patients who express low-Th2 inflammatory cytokines.[5,6,68] COPD is mainly associated with smoking, which can stimulate neutrophil production and recruitment to the lungs by some chemokines such as leukotriene-B4 (C-X-C motif) ligand 1 (CXCL1) and CXCL5 that are released by alveolar epithelial cells, macrophages or Th1 lymphocytes, to secrete inflammatory mediators and participate in a series of inflammatory reactions.[6,68] Our study showed that patients with ACO had a higher percentage of induced sputum neutrophil than those with pure asthma but lower than those with pure COPD. Further, most of the included studies reported higher pack-years of smoking in patients with ACO than those with pure asthma, suggesting more features of cigarette smoke-associated Th1 inflammation in ACO patients than pure asthma. Moreover, Zhou et al reported more current smokers in patients with pure COPD than those with ACO,[69] which implied smoking status could be a potential factor impacting neutrophil counts in patients with ACO and pure asthma/COPD. However, in the present study, due to limited data regarding smoking information, related subgroup analyses were unable to perform.

Moreover, it was reported that patients with both higher levels of circulating YKL-40 and periostin might be possibly diagnosed with ACO,[10] and circulating NGAL level in ACO patients was higher than pure asthma and lower than pure COPD.[41] Based on the limited data, this meta-analysis revealed circulating YKL-40 level in ACO patients was higher than in pure asthma but lower than COPD alone, and no statistical differences were observed in periostin and NGAL between ACO and pure asthma/COPD.

Although no global diagnostic standard for ACO was available, guidelines of ACO from Finnish, Czech and Spanish incorporated several items from the following indicators: age, tobacco exposure, history of atopy, spirometry, FeNO, serum total IgE, and sputum/blood eosinophilia, but the details varied from each other, leading to possible confusion in recognizing ACO.[4] Our study uncovered that, in order to identify ACO, clinicians should pay attention to evaluation of Th2 inflammatory indicators in COPD patients who had some asthmatic features, while assessment of smoking status, $FEV_1$% pred, DLCO% pred and Th1 inflammatory biomarkers in asthma patients with irreversible airflow limitation.

However, some limitations in this study should be considered. First, inconsistent inclusion criteria for ACO patients could lead to potential bias for the pooled results, which could not be well corrected. Second, significant heterogeneity existed in the comparisons, although it was resolved by meta-regression and subgroup analyses. Third, lack of data regarding age, sex, BMI, smoking status, allergic history and disease severity prevented further analyses.

Overall, compared with pure asthma/COPD, ACO patients have different levels of $FEV_1$% pred, DLCO% pred, FeNO, serum total IgE, blood eosinophil, induced sputum eosinophil/neutrophil, and circulating YKL-40, which could be helpful to establish a clinical diagnosis of ACO. Large scale studies are warranted to validate the present findings.

## Abbreviations

ACO, asthma-COPD overlap; AHRQ, Agency for Healthcare Research and Quality; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DLCO, diffusion lung capacity for carbon monoxide; FeNO, fractional exhaled nitric oxide; $FEV_1$, forced expiratory volume in the first second; FVC, forced vital capacity; $I^2$, I-squared; IgE, Immunoglobulin E; IL, interleukin; IQR, interquartile range; NGAL, neutrophil gelatinase-associated

lipocalin; NOS, Newcastle-Ottawa Scale; PEF, peak expiratory flow; SMD, standardized mean difference; SD, standard deviation; Th, T-helper.

## Data Sharing Statement

The datasets used and/or analyzed in this study are available from the corresponding author upon reasonable request.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests.

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