

# Chinese Research Progress Of Blood Eosinophils As Biomarkers In Chronic Obstructive Pulmonary Disease

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## Abstract

Chronic obstructive pulmonary disease (COPD) is a common chronic airway inflammatory disease. With its heterogeneity in clinical manifestations, treatment responses and prognosis, biomarkers that can predict treatment benefits and risk stratification of deterioration are very important. In recent years, many studies have reported that eosinophils are highly involved in the development of airway inflammation in COPD. The baseline blood eosinophil count (EOS) is related to the therapeutic effect of inhaled corticosteroids (ICS) and the risk of acute exacerbation in patients. The level of EOS may be affected by many factors such as geography, race, etc. In domestic clinical work, the actual reference data of EOS may not be consistent with the recommended reference threshold value in GOLD. Since there is no uniform and accurate epidemiological data on EOS in COPD patients in China, this review focuses on the research progress and controversy in the areas of EOS and COPD airway inflammation, development as biomarkers, and the role of guiding the clinical application of ICS, to discuss the setting of the critical value of EOS of Chinese COPD patients.

**Key words:** Chronic obstructive pulmonary disease, blood eosinophil count, inhaled corticosteroids, cut-off value

## Introduction

### I. Peripheral blood eosinophils and airway inflammation

Airway inflammation mediated by different inflammatory cells may be a manifestation of heterogeneity and may be the reason why different COPD patients have different therapeutic responses to ICS. Although macrophages and neutrophils are mainly concentrated locally, recent studies on airway microorganisms in COPD patients suggest that *Haemophilus* bacteria and other microorganisms may

participate in the conversion process of airway neutrophilic and eosinophilic inflammation in COPD patients, and airway microorganisms are related to clinical classification, severity and prognosis of COPD [8]. A cohort study on COPD in 2020 suggested reduced eosinophilic inflammation in some COPD patients with long-term airway colonization of *Haemophilus* [9]. The study of Dicker, A.J. et al. further proved that EOS was positively correlated with Firmicutes and *Streptococcus pneumoniae*, and negatively correlated with *Proteus* and *Haemophilus* [10]. The above studies indicated from the pathophysiological level that EOS could be regulated by airway-colonizing microorganisms, thus reflecting airway inflammation.

Many early studies have revealed that some stable COPD patients have increased sputum and EOS elevated, while these patients have a better therapeutic effect on corticosteroids [11-14]. Increased airway EOS may be associated with lower COPD severity and some functional "asthma-like" features, which may explain the better response to ICS in this subgroup of patients [15]. Zanini A et al. confirmed that about 1/3 of COPD patients had increased EOS in induced sputum, and sputum EOS was related to airway hyperreactivity [16]. Meanwhile, Barnes, P.J. et al found that some stable patients had increased EOS in the airway and alveolar lavage fluid, and such patients also responded better to corticosteroid therapy [17]. Local EOS increase is associated with corticosteroid reactivity and reduced acute COPD exacerbation [18]. However, whether sputum or alveolar lavage fluid, local EOS test requires high patient cooperation and high sampling and cytological classification techniques in medical institutions, which challenges clinical repeatability and generality [5,19,20], and peripheral blood EOS sampling is simple. Recently, a large number of high-level studies have shown that blood EOS is related to lung EOS [21-23], and blood EOS can be used as a substitute for sputum EOS to predict the risk of acute exacerbation in COPD patients and the therapeutic effect of ICS [3, 19, 24-26]. Since 2017, GOLD has continued to recommend blood EOS as a biomarker to guide clinical practice. However, the SPIROMICS cohort study [47] suggests that blood EOS alone is not a reliable biomarker for predicting increased EOS in sputum.

## II. Development of blood eosinophil counts as biomarkers

GOLD2017 included the first post-hoc analysis of some trials [19,26], suggesting that blood EOS may be a biomarker for predicting ICS in preventing therapeutic response and predicting the risk of acute exacerbations in COPD patients, but this contention lacks prospective clinical studies. GOLD2019[27] included a large number of high-quality studies [28-31] that reinforced the role of blood EOS as a biomarker to predict the benefit of ICS and delineated recommended cutoff values for predicting the benefit of inhaled corticosteroids in patients and for stratified assessments of the risk of acute exacerbations in stable patients. GOLD2020 for the first time juxtaposed EOS with a history of acute exacerbation, history of asthma, history of recurrent pneumonia, and history of tuberculosis infection as the reference index for initiating the inhaled corticosteroids (ICS) regimen [32]. GOLD2022 continues GOLD2020's recommendations: In the case of the standard use of long-acting bronchodilators in stable COPD patients, ICS therapy is strongly recommended for patients with peripheral blood EOS > 300/ $\mu$ L. The 2020 European Respiratory Society (ERS) guidelines on ICS

withdrawal strongly recommend that ICS should not be withdrawn from COPD patients whose blood EOS count is  $\geq 300/\mu\text{L}$ . However, the 2020 AMERICAN THORACIC SOCIETY (ATS) medication guidelines on COPD state that ICS is not recommended as a long-acting bronchodilator supplement in COPD patients, and discontinuation of ICS is independent of EOS levels. Combined with Chinese national conditions, in 2021, the Chronic obstructive pulmonary Disease Group of the Respiratory Branch of the Chinese Medical Association released the revised chronic obstructive pulmonary disease guidelines [33], pointing out that EOS can be used to guide the selection of ICS. Based on the use of one or two long-acting bronchodilators, ICS therapy can be considered according to patient symptoms and clinical characteristics, acute exacerbation risk, EOS, and complications.

### III. Blood eosinophils predict the risk of acute exacerbation in COPD patients

acute exacerbation of chronic obstructive pulmonary disease (AECPOD) refers to exacerbation of respiratory symptoms, leading to the need for additional treatment [33]. Studies suggest that patients with elevated EOS have an increased risk of acute COPD exacerbation [26]. In 2015, a large cohort study showed that EOS levels higher than  $0.34 \cdot 10^9 /\text{L}$  in COPD patients were associated with a 1.76-fold increased risk of severe exacerbations [34], while another analysis of the ECLIPSE cohort did not provide conclusive evidence of a link between EOS and acute exacerbations [2]. Pascoe S et al. conducted a secondary analysis of two parallel randomized controlled trials and proposed that EOS could stratify the risk of acute exacerbations in patients, and the proportion of patients with acute exacerbations gradually increased with the increase of EOS level in the case of Verantol alone [19]. Zysman M et al. suggested that COPD patients with elevated EOS had no special characteristics in terms of symptoms, lung function, exacerbation rate, and prognosis, which does not support the promotion of EOS as a biomarker of COPD phenotype [35]. Casanova C et al. followed up 799 subjects and concluded that EOS count  $\geq 300$  cells  $/\mu\text{L}$  was not a risk factor for acute COPD exacerbation [36]. In contrast, the COPD Gene study showed an increased risk of acute exacerbations in patients with a blood EOS count  $\geq 300$  cells  $/\mu\text{L}$  [37]. In conclusion, the relationship between EOS and the risk of acute exacerbation of COPD is still controversial.

### IV. discussion of cut-off value of EOS for clinical application

The epidemiological studies on EOS in COPD patients at home and abroad have different data, which may be related to the lack of uniform EOS cutoff value, and whether the use of counting or proportion is controversial. The most commonly used clinical cutoff is 2% of the total number of white blood cells. A study by Bafadhel M et al showed that the benefit of oral prednisolone in patients with acute exacerbation of COPD was limited to patients with an EOS higher than 2% [38].

Both the ECLIPSE study [2] and the ISOLDE study [39] used 2% as the cut-off point, suggesting that ICS therapy can significantly delay the decline of lung function in COPD patients with an EOS percentage  $> 2\%$ . Zeng Q et al. [40] included 559 COPD patients in a clinical study, and divided the

patients into two groups for analysis according to two criteria: EOS increase in peripheral blood was defined as EOS percentage  $\geq 2\%$  and EOS percentage  $\geq 3\%$ . In the study of Cheng et al. [41], 3% was used as the cut-off value of EOS to group COPD patients and concluded that lung function, quality of life, and frequency of acute exacerbation were significantly improved in COPD patients with a percentage greater than 3% after inhaling high doses of ICS. Currently, GOLD2022 uses 2% and absolute counts of 100-300/ $\mu\text{L}$  as nodes to guide clinicians using the ICS. Many studies have been conducted abroad to discuss the EOS cutoff values[28,34,42]. In 2000, the Lancet published a randomized controlled trial in which more than 40% of patients with COPD had a sputum count  $\geq 3\%$ [14]. Bafadhel M et al published research results in 2011, which used unbiased cluster analysis to demonstrate that 2% as the cut-off value of EOS has higher sensitivity and specificity than 3% [3, 28]. The following year, Bafadhel M again led his team to conduct a randomized controlled trial in which approximately 60% of COPD patients had an EOS ratio of more than 2%[25].

According to the guidelines for the diagnosis and treatment of COPD in China, domestic studies were mainly grouped by EOS accounting for 2% of the total leukocyte count or by the absolute value of blood EOS ranging from 150 to 400 / $\mu\text{L}$ . The author collected statistics on COPD patients included in many domestic studies. The percentage of EOS  $> 2\%$  was mostly  $< 50\%$ [43-45], which was lower than foreign research data [19]. Considering that the EOS level of the Chinese COPD population has not been released by domestic mainstream academic groups, it is hypothesized that the EOS level of the Chinese COPD population might be lower than that of foreign countries and that continuing to use international data in current diagnosis and treatment guidelines may lead to a bias in the estimation of ICS benefit groups, and the selection bias of cutoff value will limit the use of EOS as guidance data. The overall progress of COPD disease control lags behind. This may indicate that the current cut-off value selection in China is controversial, and more large-scale epidemiological survey data need to be clarified.

### Summary and Prospect:

The burden of COPD is heavy, the treatment rate of COPD is low and the treatment process is not standard in China [46]. The correct use of biomarkers is conducive to accurate treatment and improves the prognosis of COPD patients, so reliable biomarkers are worthy of active exploration. EOS has exploratory value in predicting the risk of acute exacerbation and the treatment response to ICS in stable COPD patients. The cutoff values of peripheral blood EOS for clinical use need to be further explored in large clinical studies and stratified according to different races and regions.

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