



# Effectiveness of inhaled corticosteroids on COPD exacerbation rates based on serum eosinophil count; a prospective cohort study

Amir Behnam Kharazmi<sup>1</sup>, Zeinab Taabzadeh<sup>2</sup>, Atefeh Abedini<sup>3</sup>, Parisa Delkash<sup>4</sup>, Seyed Amir Sheikholeslami<sup>5</sup>, Alireza Kashefzadeh<sup>6</sup>

<sup>1</sup>Department of Pulmonology, Imam Hossein Hospital, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>2</sup>Department of Internal Medicine, Imam Hossein Hospital, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>3</sup>Chronic Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Disease, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>4</sup>Department of Adult Rheumatology, Imam Hossein Hospital, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>5</sup>Department of Hematology-Oncology, Imam Hossein Hospital, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>6</sup>Department of Pulmonology, Shahid Labbafinejad Hospital, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

## \*Correspondence to

Alireza Kashefzadeh, Email: alikashefzadeh@hotmail.com

Received 7 Apr. 2025

Revised: 29 May 2025

Accepted 25 Jul. 2025

ePublished 29 Jul. 2025

**Keywords:** Chronic obstructive pulmonary disease, COPD exacerbation, Inhaled corticosteroids, Eosinophil count

## Abstract

**Introduction:** Chronic obstructive pulmonary disease (COPD) is a heterogeneous respiratory condition characterized by chronic inflammation and exacerbations. Inhaled corticosteroids (ICS) are commonly prescribed to reduce exacerbation risk, yet their efficacy varies among patients. Emerging evidence suggests that blood eosinophil count may serve as a biomarker to predict ICS responsiveness in COPD patients.

**Objectives:** This study investigates the relationship between serum eosinophil counts and the effectiveness of ICS in reducing COPD exacerbation rates.

**Patients and Methods:** This prospective cohort study enrolled 430 COPD patients from two major pulmonology centers in Tehran, Iran, between May 2021 and November 2022. After obtaining written informed consent, demographic data and spirometry measurements were collected to classify COPD severity according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. Venous blood samples were analyzed for eosinophil counts, categorizing patients into groups with counts below or above 300 cells/ $\mu$ L. Participants were followed for six months to record clinical outcomes, including mortality, hospitalizations, and outpatient visits related to COPD exacerbations. The study's primary focus was to assess the impact of ICS on exacerbation rates stratified by eosinophil levels, aiming to evaluate eosinophil count as a biomarker for treatment responsiveness and to inform personalized COPD management.

**Results:** In a population of COPD patients who underwent ICS, the results indicated that patients with eosinophil counts higher than 300 cells/ $\mu$ L, compared to those with lower counts, demonstrated significantly fewer hospitalization rates (unadjusted B: -0.52 and adjusted B: -0.55). Similarly, the relationship between elevated eosinophil counts and outpatient visit frequency showed significant negative associations (unadjusted B: -1.82 and adjusted B: 1.88). However, in terms of six-month outcomes (recovery versus death), no statistically significant differences were observed between the two groups.

**Conclusion:** These findings suggest that blood eosinophil counts  $\geq 300$  cells/ $\mu$ L are associated with a pronounced reduction in severe COPD exacerbations among patients treated with ICS. This supports the use of eosinophil levels as a practical biomarker to guide ICS therapy, enabling more targeted, personalized treatment strategies that optimize clinical outcomes in COPD management.



**Citation:** Kharazmi AB, Taabzadeh Z, Abedini A, Delkash P, Sheikholeslami SA, Kashefzadeh A. Effectiveness of inhaled corticosteroids on COPD exacerbation rates based on serum eosinophil count; a prospective cohort study. Immunopathol Persa. 2026;12(1):e43926. DOI:10.34172/ipp.2025.43926.

## Introduction

Chronic obstructive pulmonary disease (COPD) exacerbations represent acute worsening of respiratory symptoms that accelerate lung function decline, increase mortality risk, and impose substantial healthcare burdens (1,2). These events exhibit heterogeneous triggers ranging from viral infections to environmental pollutants, with variable clinical presentations complicating standardized definitions (2,3). Current

diagnostic criteria combine symptom-based assessments with healthcare utilization metrics, yet this approach lacks precision in identifying patients most likely to benefit from specific therapies (2,4). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines emphasize exacerbation prevention as a key treatment target, necessitating biomarkers to optimize therapeutic strategies (5,6).

Inhaled corticosteroids (ICS) remain

**Key point**

In our prospective cohort study of chronic obstructive pulmonary disease (COPD) patients receiving inhaled corticosteroids (ICS), we observed that individuals with peripheral blood eosinophil counts greater than 300 cells/ $\mu$ L experienced less severe COPD exacerbations compared to those with lower eosinophil counts.

controversial in COPD management due to their variable efficacy and well-documented risks of pneumonia (5,7). While ICS/long-acting bronchodilator combinations reduce exacerbation frequency in select populations, indiscriminate use exposes many patients to adverse effects without clinical benefit (6,7). This therapeutic paradox has driven research into predictive biomarkers, with blood eosinophil counts emerging as the most promising candidate for personalizing ICS therapy (5,6,8). Mechanistically, eosinophils reflect type 2 airway inflammation responsive to corticosteroid modulation, though their predictive value appears threshold-dependent and influenced by comorbidities (5,8).

Recent evidence suggests serum eosinophil levels may stratify ICS responsiveness, with thresholds  $\geq 300$  cells/ $\mu$ L consistently associated with greater exacerbation reduction (5,6,8). However, conflicting data indicate elevated eosinophils might paradoxically predict higher baseline exacerbation risk, creating clinical uncertainty about their role in treatment algorithms (8). This dichotomy underscores the need for rigorous evaluation of eosinophil-guided ICS strategies, particularly given evolving definitions of COPD exacerbations and growing recognition of phenotype-specific therapeutic responses (3,4). The current study investigates these relationships through a systematic analysis of eosinophil thresholds and ICS efficacy across diverse.

**Objectives**

The objective of this prospective cohort study is to evaluate the effectiveness of ICS in reducing the rate of COPD exacerbations, with a particular focus on how this effect varies according to patients' serum eosinophil counts. Specifically, the study aims to determine whether patients with higher blood eosinophil levels ( $\geq 300$  cells/ $\mu$ L) experience a differential benefit from ICS therapy compared to those with lower eosinophil counts, by analyzing exacerbation rates, hospitalizations, outpatient visits, and outcomes (recovery or death) over the follow-up period. By stratifying outcomes based on eosinophil thresholds, this research seeks to clarify the utility of blood eosinophil count as a predictive biomarker for ICS responsiveness and to inform more personalized treatment strategies for COPD management.

**Patients and Methods****Study design and participants**

This longitudinal, prospective cohort study was conducted

on 430 patients diagnosed with COPD who were referred to two major pulmonology centers in Tehran, Iran, Imam Hossein and Masih Daneshvari hospitals-over 18 months spanning from May 2021 to November 2022.

**Inclusion and exclusion criteria**

The inclusion criteria encompassed patients with confirmed COPD classified as GOLD categories C and D (9,10), who provided written informed consent to participate in the study. Eligible participants were adults over 18 years of age with forced expiratory volume in one second (FEV1) values below 50% of predicted, who were initiating ICS (Symbicort spray) for the first time and continued during a six-month follow-up. The study protocol excluded patients with incomplete documentation during the six-month follow-up period, as well as those who died from causes unrelated to COPD complications.

**Definition of COPD exacerbation**

The COPD exacerbation is defined as an acute worsening of respiratory symptoms necessitating additional medical intervention (11,12). In this study, to operationalize this definition, we assessed exacerbations based on the frequency of hospitalizations and outpatient visits attributable to COPD, as well as patient outcomes, specifically, recovery or death, over a six-month follow-up period.

**Data collection**

At the start of the study, written informed consent was obtained from all participants. Demographic information, including age and gender, was collected through participant interviews. Each participant underwent spirometry testing to determine their FEV1 values, and COPD severity was classified as either class C or class D based on GOLD criteria. Venous blood samples were drawn and analyzed for complete blood count (CBC) and eosinophil levels, with patients subsequently grouped according to whether their eosinophil count was below or above 300 cells/ $\mu$ L. Participants were then followed for six months, during which key outcomes, including mortality rates, number of hospitalizations, and outpatient visits-were recorded. These outcomes were compared between the two eosinophil-level groups to assess potential differences related to eosinophil counts.

**Outcomes**

The primary outcome of this prospective cohort study is assessing outcomes, including the number of hospitalizations and outpatient visits attributable to COPD exacerbations, as well as patient outcomes measured by mortality and recovery rates during the follow-up period. Secondary outcomes are the rate of COPD exacerbations over a six-month follow-up period, stratified by patients' serum eosinophil counts ( $\geq 300$  cells/ $\mu$ L versus  $< 300$  cells/ $\mu$ L), to evaluate the effectiveness of ICS in reducing

exacerbation frequency. These outcomes collectively assess the clinical impact of ICS therapy concerning eosinophil levels, aiming to clarify the predictive value of blood eosinophil count for treatment responsiveness and to inform personalized COPD management strategies.

### Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics version 27 (IBM Corp., USA). The normality of quantitative variables was assessed with the Kolmogorov-Smirnov test. Group comparisons for continuous variables were performed using independent t-tests, while categorical variables were analyzed using chi-square tests. To evaluate the association between the eosinophil count threshold of 300 cells/ $\mu$ L and COPD exacerbations, both univariate and multivariate linear logistic regression models were employed.

### Results

The study population included 430 COPD patients (259 males and 171 females), with a mean age of  $59.79 \pm 17.98$  years. A higher proportion of patients were classified as COPD class D than class C according to the GOLD criteria. Following the six-month observation period, the vast majority of patients demonstrated recovery, while a small fraction experienced mortality. Notably, the distribution of peripheral blood eosinophil counts showed that approximately three-quarters of the participants exhibited counts exceeding 300 cells/ $\mu$ L, with the remainder falling below this threshold. The number of hospitalizations was  $2.44 \pm 1.95$  times, and the number of outpatient visits was  $10.29 \pm 6.91$  times (Table 1).

The frequency distribution analysis of demographic and clinical characteristics between two groups of COPD patients stratified by peripheral blood eosinophil count, lower and higher than 300 cells/ $\mu$ L, revealed several noteworthy patterns. When examining gender distribution, COPD classification (class C versus class D), and six-month outcomes (recovery versus death), no statistically significant differences were observed between the two groups. Similarly, age and forced expiratory volume in one second (FEV1) showed comparable distributions across both eosinophil groups without reaching statistical significance. However, healthcare utilization metrics, which were considered as the criteria for COPD exacerbation, demonstrated significant differences between the groups, with patients having higher eosinophil counts ( $>300$  cells/ $\mu$ L) experiencing significantly lower hospitalizations and outpatient visits compared to those with lower eosinophil counts ( $<300$  cells/ $\mu$ L) (Table 2).

The linear logistic regression analysis examining the relationship between peripheral blood eosinophil counts and COPD exacerbations revealed significant negative correlations between eosinophil counts and COPD exacerbations. Using patients with eosinophil counts below 300 cells/ $\mu$ L as the reference group, those with elevated

**Table 1.** Baseline characteristics of all participating patients

Variables	N	Percent
Gender		
Male	259	60.2
Female	171	39.8
COPD classification		
Class C	191	44.4
Class D	239	55.6
Outcomes after 6 months of follow-up		
Recovery	406	94.4
Death	24	5.6
Eosinophil count (cells/ $\mu$ L)		
$<300$	116	27
$>300$	314	73
Quantitative variable		
Age (year)	59.79	17.98
FEV1 (%)	34.10	9.24
Number of hospitalizations	2.44	1.95
Number of outpatient visits	10.29	6.91

N: Number; SD: Standard deviation; COPD: Chronic obstructive pulmonary disease; FEV1: Forced expiratory volume in 1 second.

counts demonstrated significantly fewer hospitalizations, as evidenced by negative B coefficients in both unadjusted ( $B = -0.52$ ) and adjusted ( $B = -0.55$ ) models. Similarly, the relationship between elevated eosinophil counts and outpatient visit frequency showed significant negative associations in both unadjusted ( $B = -1.82$ ) and adjusted ( $B = -1.88$ ) analyses. These findings suggest that patients with eosinophil counts exceeding 300 cells/ $\mu$ L experienced fewer COPD-related healthcare encounters compared to those with lower counts, potentially indicating a lower severity of COPD exacerbation in these patients (Table 3).

### Discussion

In this study, we studied COPD patients using ICS and found that those with higher eosinophil levels in their blood (above 300 cells/ $\mu$ L) had less severe COPD flare-ups than those with lower eosinophil levels. Our finding that COPD patients with higher blood eosinophil levels (above 300 cells/ $\mu$ L) experienced fewer severe exacerbations when using ICS aligns with multiple studies in the current literature. This relationship between elevated eosinophil counts and improved ICS response represents an important area for precision medicine in COPD management. Our result is consistent with multiple systematic reviews and clinical trials. A 2020 systematic review and meta-analysis by Harries et al demonstrated that ICS therapy provides greater benefit in preventing COPD exacerbations as blood eosinophil counts increase (13). Similarly, Oshagbemi et al in a systematic review and meta-analysis study found

**Table 2.** Frequency distribution of demographic and clinical characteristics of COPD patients stratified by peripheral blood eosinophil count threshold (300 cells/ $\mu$ L)

Variable	Sub-variable	Eosinophil count (cells/ $\mu$ L)				P value
		< 300 (N = 116)		> 300 (N = 314)		
		N	%	N	%	
Gender	Male (n = 259)	73	28.2	186	71.8	0.487*
	Female (n = 171)	43	25.1	128	74.9	
COPD classification	Class C (n = 191)	47	24.6	144	75.4	0.322*
	Class D (n = 239)	69	28.9	170	71.1	
Outcomes after 6 months of follow-up	Recovery (n = 406)	112	27.6	294	72.4	0.242*
	Death (n = 24)	4	16.7	20	83.3	
Variable		Mean	SD	Mean	SD	P value
Age (year)		61.01	17.04	59.34	18.32	0.393**
FEV1 (%)		34.78	7.36	33.85	9.85	0.293**
Number of hospitalizations		2.82	2.17	2.30	1.85	0.023**
Number of outpatient visits		11.62	7.67	9.80	6.55	0.024**

N: Number; SD: standard deviation; COPD: Chronic obstructive pulmonary disease; FEV1: Forced expiratory volume in 1 second.

\*Chi-square; \*\*Independent T-test.

**Table 3.** The correlation between the eosinophil count threshold at 300 cells/ $\mu$ L and COPD exacerbations using univariate and multivariate linear logistic regression

Variable		Number of hospitalizations							
		Unadjusted				Adjusted			
		P-value	B	95% CI		P value	B	95% CI	
				Lower	Upper			Lower	Upper
Eosinophil count (cells/μL)	<300	Reference (1)							
	>300	0.014	- 0.52	- 0.93	- 0.10	0.007	- 0.55	- 0.96	- 0.15

Variable		Number of outpatient visits							
		Unadjusted				Adjusted			
		P value	B	95% CI		P value	B	95% CI	
				Lower	Upper			Lower	Upper
Eosinophil count (cells/μL)	<300	Reference (1)							
	>300	0.015	- 1.82	- 3.28	- 0.35	0.012	- 1.88	- 3.34	- 0.42

B, Unstandardized coefficients; CI, Confidence interval.

a significant reduction in the risk of moderate or severe exacerbations in patients with absolute blood eosinophil thresholds ranging from  $\geq 100$  to  $\geq 340$  cells/ $\mu$ L who escalated to ICS therapy. The threshold of 300 cells/ $\mu$ L appears particularly significant, as their analysis showed that de-escalation of ICS in patients with counts  $\geq 300$  to  $\geq 340$  cells/ $\mu$ L resulted in an increased risk of exacerbations (6). Post-hoc analysis of a study by Bafadhel et al, further supports our findings, showing that budesonide/glycopyrronium/formoterol fumarate dihydrate (BGF) triple therapy reduced moderate/severe exacerbation rates compared to dual therapy without ICS, with treatment differences increasing as eosinophil counts rose (14). This dose-response relationship between eosinophil counts and ICS effectiveness provides additional validation for our results.

In contrast with our study, Chen and colleagues' meta-analysis presents an interesting counterpoint, suggesting that high blood eosinophils ( $\geq 300$  cells/ $\mu$ L) are associated with an increased risk of COPD exacerbation (8). This

apparent contradiction may indicate that while patients with higher eosinophil counts are at greater baseline risk for exacerbations, they also derive greater benefit from ICS therapy. Indeed, Cheng et al meta-analysis study demonstrated a 17% reduction in exacerbations among patients with  $\geq 2\%$  blood eosinophils who received ICS therapy compared to control groups (5).

In comparison of the exacerbation history with the eosinophil count as a predictor of future COPD exacerbations, some research suggests exacerbation history may be more predictive than blood eosinophils alone. Worth et al found that in real-world COPD patients, exacerbation history was a more reliable predictor of future exacerbations than eosinophil counts (15). The study by Calverley et al indicated that withdrawal of ICS only increased exacerbation rates in patients with both raised eosinophils ( $\geq 400$  cells/ $\mu$ L) and a history of frequent exacerbations (16). These findings suggest that optimal treatment decisions might require considering both biomarkers and clinical history.



Overall, our finding that COPD patients with blood eosinophil counts above 300 cells/ $\mu$ L experience fewer exacerbations when using ICS aligns with the growing consensus that eosinophil counts can help identify patients most likely to benefit from ICS therapy. The research demonstrates a relationship between higher eosinophil counts and greater ICS efficacy for exacerbation prevention, though the interplay with exacerbation history merits consideration in clinical decision-making. This personalized approach to COPD management may help optimize treatment outcomes while minimizing unnecessary ICS exposure in patients unlikely to benefit.

## Conclusion

This prospective cohort study provides compelling evidence that blood eosinophil count may serve as a valuable biomarker for predicting response to ICS therapy in COPD patients. Our findings demonstrate that patients with peripheral blood eosinophil counts exceeding 300 cells/ $\mu$ L who received ICS therapy experienced significantly fewer severe COPD exacerbations compared to those with lower eosinophil counts. These findings suggest that blood eosinophil count could guide more targeted therapeutic approaches, with clinicians potentially prioritizing ICS therapy in COPD patients with eosinophil counts above 300 cells/ $\mu$ L while exploring alternative treatment strategies for those with lower counts. Future research should focus on validating these findings in larger, more diverse populations and investigating the underlying mechanisms by which elevated eosinophil counts may predict enhanced ICS responsiveness.

## Limitations of the study

First, as a prospective cohort study conducted at only two hospitals in Tehran, the results may have limited generalizability to broader or more diverse populations. Second, the reliance on a single baseline measurement of eosinophil count may not fully capture fluctuations over time, potentially affecting the accuracy of patient classification. Third, potential confounding factors such as variations in adherence to ICS therapy, comorbidities, and environmental exposures were not fully controlled, which could influence exacerbation rates and outcomes. Additionally, the six-month follow-up period may be insufficient to observe long-term effects of treatment or disease progression.

## Acknowledgments

We gratefully acknowledge the invaluable support and cooperation of the staff, clinicians, and administrative teams at Imam Hossein and Masih Daneshvari hospitals affiliated with Shahid Beheshti University of Medical Sciences, Tehran, Iran, for their assistance in patient recruitment and data collection throughout this study. We also extend our sincere appreciation to all the patients who participated and contributed their time to this research.

## Authors' contribution

**Conceptualization:** Amir Behnam Kharazmi and Zeinab Taabzadeh.

**Data curation:** Alireza Kashefzadeh and Zeinab Taabzadeh.

**Formal analysis:** Atefeh Abedini.

**Investigation:** Amir Behnam Kharazmi and Seyed Amir Sheikholeslami.

**Methodology:** Atefeh Abedini and Parisa Delkash.

**Resources:** All authors.

**Supervision:** Amir Behnam Kharazmi.

**Validation:** Parisa Delkash and Seyed Amir Sheikholeslami.

**Project management:** Alireza Kashefzadeh.

**Writing—original draft:** All authors.

**Writing—review and editing:** All authors.

## Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (Ethical code No: IR.SBMU.MSP.REC.1400.071; <https://ethics.research.ac.ir/EthicsProposalView.php?id=196305>). Prior to any intervention, all participants provided written informed consent. The study was extracted from Zeinab Taabzadeh internal medicine residency thesis at this university (Thesis #28418). The authors have fully complied with ethical issues, such as plagiarism, data fabrication, and double publication.

## Declaration of generative artificial intelligence (AI) and AI-assisted technologies in the writing process

While preparing this work, the authors utilized AI ([Perplexity.ai](https://www.perplexity.ai) and [Grammarly.com](https://www.grammarly.com)) to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

## Conflicts of interest

The authors declare that they have no competing interests.

## Funding/Support

The funding was supported by the Shahid Beheshti University of Medical Sciences, Tehran, Iran (Grant #28418).

## References

1. Gayle AV, Quint JK, Fuertes EI. Understanding the relationships between environmental factors and exacerbations of COPD. *Expert Rev Respir Med.* 2021;15:39–50. doi: 10.1080/17476348.2020.1801426.
2. Montes de Oca M, Lauchó-Contreras ME. Is It Time to Change the Definition of Acute Exacerbation of Chronic Obstructive Pulmonary Disease? What Do We Need to Add? *Med Sci (Basel).* 2018;6. doi: 10.3390/medsci6020050.
3. Mathioudakis AG, Möberg M, Janner J, Alonso-Coello P, Vestbo J. Outcomes reported on the management of COPD exacerbations: a systematic survey of randomised controlled trials. *ERJ Open Res.* 2019;5. doi: 10.1183/23120541.00072-2019.
4. Althobiani MA, Shah AJ, Khan B, Hurst JR. Clinicians' and Researchers' Perspectives on a New Chronic Obstructive Pulmonary Disease Exacerbation Definition: Rome Wasn't Built in a Day. *Am J Respir Crit Care Med.* 2023;207:1095–7. doi: 10.1164/rccm.202210-1949LE.
5. Cheng SL. Blood eosinophils and inhaled corticosteroids in patients with COPD: systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis.* 2018;13:2775–84. doi: 10.2147/copd.S175017.
6. Oshagbemi OA, Odiba JO, Daniel A, Yunusa I. Absolute Blood Eosinophil Counts to Guide Inhaled Corticosteroids Therapy

- Among Patients with COPD: Systematic Review and Meta-analysis. *Curr Drug Targets*. 2019;20:1670–9. doi: 10.2174/1389450120666190808141625.
7. Zhang Q, Li S, Zhou W, Yang X, Li J, Cao J. Risk of Pneumonia with Different Inhaled Corticosteroids in COPD Patients: A Meta-Analysis. *Copd*. 2020;17:462–9. doi: 10.1080/15412555.2020.1787369.
  8. Chen F, Yang M, Wang H, Liu L, Shen Y, Chen L. High blood eosinophils predict the risk of COPD exacerbation: A systematic review and meta-analysis. *PLoS One*. 2024;19:e0302318. doi: 10.1371/journal.pone.0302318.
  9. Rieger-Reyes C, García-Tirado FJ, Rubio-Galán FJ, Marín-Trigo JM. Classification of chronic obstructive pulmonary disease severity according to the new Global Initiative for Chronic Obstructive Lung Disease 2011 guidelines: COPD assessment test versus modified Medical Research Council scale. *Arch Bronconeumol*. 2014;50:129–34. doi: 10.1016/j.arbres.2013.09.014.
  10. Bhatta L, Leivseth L, Mai XM, Henriksen AH, Carslake D, Chen Y, et al. Spirometric Classifications of Chronic Obstructive Pulmonary Disease Severity as Predictive Markers for Clinical Outcomes: The HUNT Study. *Am J Respir Crit Care Med*. 2021;203:1033–7. doi: 10.1164/rccm.202011-4174LE.
- Celli BR, Fabbri LM, Aaron SD, Agusti A, Brook R, Criner GJ, et al. An Updated Definition and Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbations: The Rome Proposal. *Am J Respir Crit Care Med*. 2021;204:1251–8. doi: 10.1164/rccm.202108-1819PP.
- Oh YM. Definition of Chronic Obstructive Pulmonary Disease Exacerbation: The Essentials of the Rome Proposal. *Tuberc Respir Dis (Seoul)*. 2023;86:61–2. doi: 10.4046/trd.2022.0119.
- Harries TH, Rowland V, Corrigan CJ, Marshall IJ, McDonnell L, Prasad V, et al. Blood eosinophil count, a marker of inhaled corticosteroid effectiveness in preventing COPD exacerbations in post-hoc RCT and observational studies: systematic review and meta-analysis. *Respir Res*. 2020;21:3. doi: 10.1186/s12931-019-1268-7.
- Bafadhel M, Rabe KF, Martinez FJ, Singh D, Darken P, Jenkins M, et al. Benefits of Budesonide/Glycopyrronium/Formoterol Fumarate Dihydrate on COPD Exacerbations, Lung Function, Symptoms, and Quality of Life Across Blood Eosinophil Ranges: A Post-Hoc Analysis of Data from ETHOS. *Int J Chron Obstruct Pulmon Dis*. 2022;17:3061–73. doi: 10.2147/copd.S374670.
- Worth H, Buhl R, Criée CP, Kardos P, Gückel E, Vogelmeier CF. In ‘real world’ patients with COPD, exacerbation history, and not blood eosinophils, is the most reliable predictor of future exacerbations. *Respir Res*. 2023;24:2. doi: 10.1186/s12931-023-02311-x.
- Calverley PM, Tetzlaff K, Vogelmeier C, Fabbri LM, Magnussen H, Wouters EF, et al. Evaluating blood eosinophils and exacerbation history to predict ICS response in COPD. *Pneumologie*. 2017;71:P251. doi: 10.1183/13993003.CONGRESS-2016.OA1973.