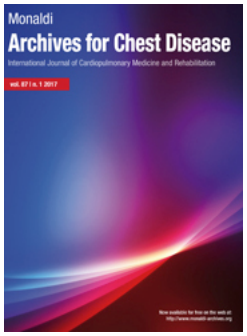

Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2025 [Online ahead of print]

To cite this Article:
Para O, Cassataro G, Fantoni C, et al. **Prognostic role of blood eosinophils in acute exacerbations of chronic obstructive pulmonary disease: systematic review and meta-analysis.** *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2025.3298

Prognostic role of blood eosinophils in acute exacerbations of chronic obstructive pulmonary disease: systematic review and meta-analysis

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Contributions: OP conceived the study; LB, FD, performed statistical analyses; OP, GC, LC, CF, SR, CT, revised literature and collected data; OP, GC, CF, wrote the manuscript; FD, AS, revised manuscript. All the authors contributed to manuscript writing and revision.

Conflict of interest: the authors declare that they have no conflict of interest.

Ethics approval and consent to participate: not applicable.

Informed consent: not applicable.

Patient consent for publication: not applicable.

Availability of data and materials: all data analyzed during this study are included in this published article and supplementary material.

Funding: none.

Acknowledgments: the authors thank everyone involved for their efforts in the writing and critical review of this manuscript.

Abstract

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a major cause of hospitalization and mortality worldwide. While blood eosinophils have been suggested as a prognostic biomarker of COPD, their predictive value in AECOPD remains uncertain. This meta-analysis aims to evaluate the prognostic role of blood eosinophil counts in predicting mortality and hospital readmission in these patients. A systematic review and meta-analysis were conducted according to PRISMA guidelines. We included studies that evaluated the prognostic role of blood eosinophils in AECOPD, with predefined cut-offs. Data on mortality and readmission rates were extracted, and statistical analyses were performed to assess sensitivity, specificity, and likelihood ratios. A total of 14 studies with 23,625 patients were included. High blood eosinophil counts during AECOPD hospitalization had low sensitivity (28.1%) and specificity (66.2%) in predicting 12-month mortality and readmission. Positive and negative likelihood ratios were also suboptimal, with values of 0.8 and 1.1, respectively. Sensitivity analyses, including only high-quality studies, confirmed these findings. The results suggest that blood eosinophil counts have limited prognostic value in predicting mortality and readmission in AECOPD patients. The variability in eosinophil cut-offs and lack of consistent data across studies contribute to this limitation. Further large-scale prospective studies are needed to clarify the role of eosinophils as a prognostic marker in AECOPD. Consequently, routine measurement of blood eosinophils during acute exacerbations may not be warranted for prognostic purposes.

Key words: COPD, acute exacerbations, bronchitis, eosinophils, biomarker.

Introduction

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is the fourth cause of hospitalization worldwide and can lead to negative effects such as disease progression, worsening of quality of life, prolonged hospitalizations, increasing costs and mortality [1]. Determining the prognosis of hospitalized patients with AECOPD is still difficult and debated. Complete blood count (CBC) with leucocyte populations is cheap and easy to acquire. Therefore, this parameter is readily available in almost all hospitalized patients with AECOPD. Compelling evidence suggests a prognostic role of CBC and leucocyte populations in predicting mortality and hospital admission in patients with stable COPD, probably due to an underlying association between airways and systemic inflammation [2]. In several studies, patients with COPD present one or more serum inflammatory parameter increased [3-5] moreover, in COPD patients, the persistent elevation of serum inflammatory markers has been related to the progression of the disease, worsening of clinical and functional parameters and the development of comorbidities [2-5].

A number of observational studies have suggested that blood eosinophil levels may be useful as a biomarker in stable COPD for the optimization of treatments, however evidence of its role as a prognostic marker in AECOPD events remains controversial [6]. Therefore, we conducted an extensive systematic review and meta-analysis of the literature, performed in accordance with the PRISMA guideline [7], to clarify these uncertainties.

Methods

A protocol for this systematic review and meta-analysis 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.

Aim of the study

The primary outcome of our meta-analysis was to analyze the prognostic role of blood eosinophils' count to predict long term (12 months) mortality and severe exacerbation's risk determining hospital readmission after hospital discharge for AECOPD. Subsequently, mortality and hospital readmission were considered separately. The secondary outcome was to analyze the prognostic role of blood eosinophils' count to predict short term (in-hospital or

30-days) mortality and readmission due to severe exacerbation after hospital discharge for AECOPD.

Search strategy

MEDLINE and EMBASE databases were searched from inception up to March 2024 screening titles and abstracts, and, eventually, full texts without any language restriction (search strategy and studies selection flow are available upon request). We identified all published studies that evaluated the prognostic role of blood eosinophil in AECOPD. Search results were reported according to Meta-analysis Of Observational Studies in Epidemiology (MOOSE) reporting guidelines [8].

Study selection

Six investigators, divided into pairs, independently selected studies and extracted data. Studies were considered potentially eligible for this systematic review if they met the following criteria: they included a population of patients with a hospitalization for AECOPD; eosinophil cut-off was clearly specified.

For the study purpose, we considered eligible studies that used a cut off of ≥ 150 cells/μL or ≥200 cells/μL and/or ≥ 2% or ≥300 cells/μL or≥400 cells/μL to define high eosinophil count.

Studies that included patients with stable COPD only, case reports, case series, and studies on patients younger than 18 years. were excluded.

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of included studies [9].

Data extraction

From each study, we collected the following data: authors, year of publication, design of the study, the total number of included patients, blood eosinophil cut-off value and clinical outcomes (death and in-hospital readmission due to a new severe AECOPD during follow-up).

Statistical analysis and risk of bias assessment

A bivariate random-effects regression approach was applied to obtain summary estimates of both weighted mean sensitivity (WMSe) and weighted mean specificity (WMSp) of the eosinophil concentration in predicting primary and secondary outcomes.

The pooled estimates of the likelihood ratios (LRs) are derived from WMSe and WMSp following the approach suggested by Zwinderman and Bossuyt [10]. We used pooled and

weighted mortality/hospital readmission to estimate cut-off eosinophils positive and negative predictive values (PPV and NPV, respectively). By convention, marked changes in predicted pre-test mortality probability can be assumed in positive likelihood ratios exceeding 5 and negative likelihood ratios below 0.2. Results were presented with 95% confidence interval (CI). We used the ROC curve to estimate accuracy in predicting 12-months mortality and in-hospital readmission. Area under the curve (AUC) was calculated. Heterogeneity was considered significant when $p < 0.10$.

Finally, a sensitivity analysis was performed, focusing only on studies that were rated as high quality according to the NOS criteria [9].

Statistical analysis was performed with R software version 4.2.2 and package Meta-Analysis of Diagnostic Accuracy (MA87DA) version 0.5.11. The SAS Glimmix procedure version 9.4. was used to estimate the overall weighted mortality/readmission.

Results

A total of 1348 citations (470 from Medline and 878 from Embase) were identified by our systematic search; 1289 studies were excluded after title and abstract screening, according to the predefined inclusion and exclusion criteria, or because they were duplicates. Subsequently, 45 studies were excluded, after full-text revision, because they did not provide information about the pre-specified cut-off of blood eosinophils or because they did not address the outcome of interest of our study. Thus, a total of 14 studies were included in the meta-analysis [11-24]. All the studies were written in English and were observational (prospective or retrospective cohorts). The study population consisted of 8,430 adult patients (ranging from 123 to 3,084 patients) for the primary outcome and 17,725 adult patients (ranging from 243 to 12,831 patients) for the secondary outcome, all with a confirmed diagnosis of AECOPD. Different eosinophil cut-offs were used in the studies included in our meta-analysis and some studies have considered different eosinophil cut-offs in the same population: two studies [11,12] used a cut off of ≥ 150 cells/μL, nine studies [13-21] used a cut off of ≥200 cells/μL and/or ≥ 2%, five studies [12,20,22-25] used a cut off of ≥300 cells/μL and two studies [12,13] used a cut off of ≥400 cells/μL. Additionally, a minority of studies reported results using more than one cut-off. In such cases, we opted to perform the analysis using the lowest cut-off to maximize sensitivity.

Six studies [11,14,17,18,23,24] were considered of high quality according to NOS[9]. The study characteristics are summarized in Table 1.

Weighted mean sensitivity (WMSe) and weighted mean specificity (WMSp) of the eosinophilia in predicting 12-months mortality and/or in-hospital readmission were sub-optimal (28.1% CI 17.3% to 42.3% and 66.2%, 95% CI 54.4 to 76.2% respectively). Heterogeneity among the studies was significant (I2 99%, chi-square: 39.67; $p < 0.001$). Likewise, Eosinophilia had a low PPV (27.2% 95% CI 25.5% to 29.0%) and NPV (67.1% 95% CI 65.9% to 68.3%) in predicting 12-months mortality and/or in-hospital readmission. Positive and Negative LR were 0.8 (95% CI 0.4-1.4) and 1.1 (95% CI 0.8-1.4) respectively. AUC of eosinophilia in predicting the primary outcome is 0. 48. Figure 1a and 1b showed forest plot of pooled sensibility and pooled specificity of blood eosinophils in predicting primary composite outcome. Analyses considering separately mortality and hospital readmission gave similar results (*Supplementary Material - Appendix 1*)

Sensitivity analyses, considering only high-quality studies according to NOS gave similar results: WMSe and WMSp of the eosinophilia in predicting 12-months mortality and/or in-hospital readmission remained sub-optimal (28.3% CI 13.0% to 51.0% and 6.4%, 95% CI 39.7% to 71.7% respectively); eosinophilia showed a low PPV (32.4% C95% CI 30.4% to 34.4%) and NPV (72.8% C95% CI 71.6% to 74.1%) in predicting 12-months mortality and/or hospital readmission; Positive and Negative LR were 0.6 (95% CI 0.3 to 1.3) and 1.2 (95% CI 0.8 to1.9) respectively. AUC of eosinophilia in predicting the primary outcome is 0. 42. Figure 2a and 2b showed forest plot of pooled sensibility and pooled specificity of analysis considering only high-quality studies.

Regarding the secondary outcome (in-hospital or 30-days mortality or 30-day readmission after a hospital discharge for AECOPD), one study evaluated only 30-day readmission [22], one study evaluated only 30-day mortality [11], one study considered a composite outcome (30-day readmission and 30-day mortality) [12], and four studies considered in-hospital mortality [17,19,21].

High eosinophil count had a low WMSe (11.0%; CI 3.0% to 32.6%) and WMSp (55.2% CI 31.1% to 77.1%) in predicting the secondary outcome. Pooled positive and negative LR were 0.2 (95% CI 0.1-0.7) and 1.6 (1.2-2.2) respectively. AUC of eosinophilia in predicting the secondary outcome is 0.2. Figure 3a and 3b showed forest plot of pooled sensibility and pooled specificity of blood eosinophils in predicting secondary short-term composite outcome.

Discussion

Blood eosinophils have emerged as a significant biomarker in the prognosis and management of stable COPD. Elevated eosinophil levels in COPD patients are associated with an increased risk of exacerbations, making them valuable for predicting clinical outcomes. Studies indicate that higher blood eosinophil counts can help identify patients who may benefit from inhaled corticosteroid (ICS) therapy [26-31]. On the other hand, the prognostic role of blood eosinophils in AECOPD remains controversial.

Our study provided compelling evidence on their potential short and long-term prognostic role in this setting summarizing, with a strict methodology, evidence from 14 studies for a total of more than 23000 patients.

Thus, results of our meta-analysis clearly showed that high blood eosinophil count, measured during a hospitalization for AECOPD, had a low accuracy in predicting short and long -term risk of mortality and hospital readmission with a low sensitivity, specificity and AUC. Furthermore, positive and negative LR for both time end points were inconsistent. Analyses considering separately mortality and hospital readmission and sensitivity analyses including high-quality studies only gave similar findings, reinforcing the results of our primary analyses.

COPD patients have frequent exacerbations. These significantly increase the risk of hospitalization and are associated with a higher mortality rate accelerating the decline in lung function and leading to severe disability. Identification of patients at high risk of a new exacerbation may be crucial to set up the most appropriate therapy to improve the outcomes and reduce mortality.

Blood eosinophilia is a marker for eosinophilic airway inflammation [32]. Several studies suggest that, in a subset of COPD patients, Th2 cytokines could drive eosinophilic airway inflammation and bronchial hyperresponsiveness [33]. Randomized controlled trials have reported that this biomarker can guide use of oral and inhaled corticosteroid therapy in patients with stable COPD [29]. Additionally, anti-interleukin-5 receptor α monoclonal antibody appeared to be effective in reducing exacerbations of COPD only in patients with sputum eosinophil count $\geq$ 3.0% [34].

In a study published in 2016, Hasegawa and Camargo [23] assessed the prevalence of blood eosinophilia (≥300 cells/microL) in a cohort of 3084 patients hospitalized with AECOPD. In this population, blood eosinophilia was extremely common (17% of the whole population) and was associated with a higher frequency of readmission at 1 year-follow up.

In another retrospective study in 2445 patients with acute AECOPD identified among electronic medical records at all Intermountain Healthcare hospitals, Hagewald et al. found that high eosinophil counts (≥300 cells/μL) were not associated with an increased risk of 30-day all-cause readmissions [22]. However, higher eosinophil counts were associated with a greater risk of readmissions at 90 days and 12 months, as well as COPD-related readmissions across all time points up to 12 months.

On the other hand, several retrospective and prospective cohort studies failed to demonstrate an association between the presence of eosinophilia and risk of bad outcome (re-hospitalization and/or death at follow-up).

In a retrospective cohort study on COPD 496 patients published by Belanger et al [14], high blood eosinophil cell count (blood eosinophil count on admission $\geq$ 200 cells/μL and/or $\geq$2% of the total white blood cell count) was associated with an increased risk of 1-year COPD-related readmission and with an increased number of 1-year COPD-related ED visits) but not with an increased risk of all-cause death or readmission.

In patients enrolled in a multicenter randomized controlled trial evaluating health outcomes during severe exacerbations (requiring hospitalization), those with a peripheral blood eosinophil count greater than 200 cells/mL and/or exceeding 2% of the total leukocyte count at admission did not show a significantly higher readmission rate at 12 months compared to patients with normal eosinophil counts [34].

Finally, in a multicenter prospective cohort study on 12,831 AECOPD inpatients [21], the eosinophilic group (EOS $\geq$ 2%) was associated with lower in-hospital mortality than the non-eosinophilic group.

Underlying mechanisms remain unclear. Non-eosinophilic AECOPD patients tend to have higher levels of inflammatory biomarkers and are more prone to infections like pneumonia and sepsis, which may contribute to higher mortality rates [35]. Additionally, these patients were generally older with more comorbidities, suggesting a greater vulnerability to severe infections, potentially explaining the observed higher mortality [21].

Our meta-analysis overcoming some of the limitations of single studies provided compelling evidence on the usefulness of blood eosinophils test during the AECOPD. Given that measurement of blood eosinophils has low sensitivity, specificity, and unsatisfactory likelihood ratios in predicting the prognosis of these patients, eosinophils do not appear to be a reliable biomarker for guiding clinical decisions in this setting and should not be measured during the AECOPD.

Of note, in our meta-analysis, we were unable to gather data on the risk of COPD exacerbations that did not require hospitalization in patients with elevated eosinophil counts and, to assess the potential role of eosinophilia as a marker of response to steroid therapy. Consequently, our meta-analysis could not provide insights into these specific aspects, highlighting the need for further research in this field.

Our meta-analysis has several potential limitations. The populations of patients with COPD exacerbations included in our meta-analysis exhibit some differences in terms of inclusion and exclusion criteria, follow-up periods, and other methodological aspects., and, more importantly, when combining the various studies, these result in a statistically significant heterogeneity. Unfortunately, we were only able to conduct a study-level meta-analysis and it was not possible to adjust for these and other potential confounders. Moreover, for most studies, precise information on the exact timing of blood eosinophil evaluations during hospitalization and detailed data on treatments—particularly inhaled steroid therapy at the time of enrollment—is lacking, making it impossible to adjust our findings for these potential confounders. Additionally, due to the limited information available in the original studies we were unable to clearly determine whether the observed mortality and hospital readmissions were specifically related to an AECOPD event or were caused by other factors. As a result of these limitations, our findings should therefore be interpreted with extreme caution.

Although the number of studies included in our meta-analysis does not allow a realistic graphical assessment of publication bias, we believe that such potential bias is primarily due to the non-publication of studies with non-significant results. Consequently, we are confident that publication bias does not significantly affect our meta-analysis. Finally, the cut-offs used to define eosinophilia were arbitrary and varied across the included studies. As a result, we cannot determine whether the use of different cut-off points might have led to different outcomes.

Conclusions

In conclusion, our meta-analysis underlines the limited prognostic role of eosinophilia measured during hospitalization for an AECOPD. Thus, evaluation of blood eosinophils at this time point should not be recommended. However, due to the limitations present in the existing literature, there is a clear need for large, high-quality prospective studies to further evaluate the prognostic role of blood eosinophils (using various cut-off values) in AECOPD. These future

studies will be crucial in establishing more definitive conclusions and improving our understanding of the prognostic significance of eosinophil counts in this context.

References

1. Zhang HL, Tan M, Qiu AM, et al. Antibiotics for treatment of acute exacerbation of chronic obstructive pulmonary disease: a network meta-analysis. BMC Pulm Med 2017;17:196.
2. Ko FW, Chan KP, Hui DS, et al. Acute exacerbation of COPD. Respirology 2016;21:1152-65.
3. Fermont JM, Masconi KL, Jensen MT, et al. Biomarkers and clinical outcomes in COPD: a systematic review and meta-analysis. Thorax 2019;74:439-46.
4. Brusselle G, Pavord ID, Landis S, et al. Blood eosinophil levels as a biomarker in COPD. Respir Med 2018;138:21-31.
5. Brightling C, Greening N. Airway inflammation in COPD: progress to precision medicine. Eur Respir J 2019;54:1900651.
6. Emami Ardestani M, Alavi-Naeini N. Evaluation of the relationship of neutrophil-to lymphocyte ratio and platelet-to-lymphocyte ratio with in-hospital mortality in patients with acute exacerbation of chronic obstructive pulmonary disease. Clin Respir J 2021;15:382-8.
7. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
8. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. JAMA 2000;283:2008-12.
9. Wells GA, Wells G, Shea B, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2014.
10. Zwinderman AH, Bossuyt PM. We should not pool diagnostic likelihood ratios in systematic reviews. Stat Med 2008;27:687-97.
11. Kostikas K, Papathanasiou E, Papaioannou AI, et al. Blood eosinophils as predictor of outcomes in patients hospitalized for COPD exacerbations: a prospective observational study, Biomarkers 2021;4:354-62.
12. Martínez-Gestoso S, García-Sanz MT, Calvo-Álvarez U, et al. Variability of blood eosinophil count and prognosis of COPD exacerbations. Ann Med 2021;53:1152-8.

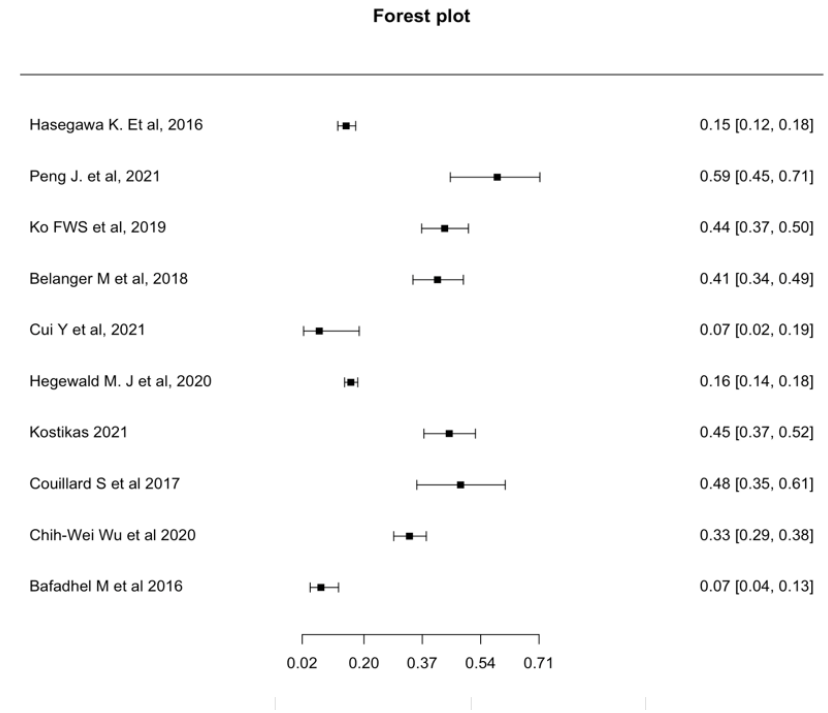
13. Peng J, Yu Q, Fan S, et al. High blood eosinophil and YKL-40 levels, as well as low CXCL9 levels, are associated with increased readmission in patients with acute exacerbation of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2021;16:795-806.
14. Bélanger M, Couillard S, Courteau J, et al. Eosinophil counts in first COPD hospitalizations: a comparison of health service utilization. Int J Chron Obstruct Pulmon Dis 2018;13:3045-54.
15. Couillard S, Larivée P, Courteau J, Vanasse A. Eosinophils in COPD exacerbations are associated with increased readmissions. Chest 2017;151:366-73.
16. Wu CW, Lan CC, Hsieh PC, et al. Role of peripheral eosinophilia in acute exacerbation of chronic obstructive pulmonary disease. World J Clin Cases 2020;8:2727-37.
17. Bafadhel M, Greening NJ, Harvey Dunstan TC, et al. Blood eosinophils and outcomes in severe hospitalized exacerbations of COPD. Chest 2016;150:320-8.
18. Ko FWS, Chan KP, Ngai J, et al. Blood eosinophil count as a predictor of hospital length of stay in COPD exacerbations. Respirology 2020;25:259-66.
19. Russell R, Beer S, Pavord ID, et al. The acute wheezy adult with airways disease in the emergency department: a retrospective case-note review of exacerbations of COPD. Int J Chron Obstruct Pulmon Dis 2019;14:971-7.
20. Ruiying W, Zhaoyun, Jianying X. Clinical features and three-year prognosis of AECOPD patients with different levels of blood eosinophils. Heart Lung 2022;56:29-39.
21. Pu J, Yi Q, Luo Y, et al. Blood eosinophils and clinical outcomes in patients with acute exacerbation of chronic obstructive pulmonary disease: a prospective cohort study. Int J Chron Obstruct Pulmon Dis 2023;18:169-79.
22. Hegewald MJ, Horne BD, Trudo F, et al. Blood eosinophil count and hospital readmission in patients with acute exacerbation of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2020;15:2629-41.
23. Hasegawa K, Camargo CA Jr. Prevalence of blood eosinophilia in hospitalized patients with acute exacerbation of COPD. Respirology 2016;21:761-4.
24. Cui Y, Zhan Z, Zeng Z, et al. Blood eosinophils and clinical outcomes in patients with acute exacerbation of chronic obstructive pulmonary disease: a propensity score matching analysis of real-world data in China. Front Med 2021;8:653777.
25. Yun JH, Lamb A, Chase R, et al. Blood eosinophil count thresholds and exacerbations in patients with chronic obstructive pulmonary disease. J Allergy Clin Immunol 2018;141:2037-47.e10.

26. Kim VL, Coombs NA, Staples KJ, et al. Impact and associations of eosinophilic inflammation in COPD: analysis of the AERIS cohort. Eur Respir J 2017;50:1700853.
27. Vedel-Krogh S, Nielsen SF, Lange P, et al. Blood eosinophils and exacerbations in COPD: the Copenhagen general population study. Am J Respir Crit Care Med 2016;193:965-74.
28. Bafadhel M, McKenna S, Terry S, et al. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. Am J Respir Crit Care Med 2011;184:662-71.
29. Pascoe S, Locantore N, Dransfield MT, et al. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. Lancet Respir Med 2015;3:435-42.
30. Siddiqui SH, Guasconi A, Vestbo J, et al. Blood eosinophils: a biomarker of response to extrafine beclomethasone/formoterol in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2015;192:523-5.
31. Håkansson KEJ, Ulrik CS, Godtfredsen NS, et al. High suPAR and low blood eosinophil count are risk factors for hospital readmission and mortality in patients with COPD. Int J Chron Obstruct Pulmon Dis 2020;15:733-43.
32. Reddel HK, Gerhardsson de Verdier M, Agustí A, et al. Prospective observational study in patients with obstructive lung disease: NOVELTY design. ERJ Open Res 2019;5:00036-2018.
33. Woodruff PG, Agusti A, Roche N, et al. Current concepts in targeting chronic obstructive pulmonary disease pharmacotherapy: making progress towards personalised management. Lancet 2015;385:1789-98.
34. Brightling CE, Bleecker ER, Panettieri RA Jr, et al. Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised, double-blind, placebo-controlled, phase 2a study. Lancet Respir Med 2014;2:891-901.
35. Mao Y, Qian Y, Sun X, Li N, Huang H. Eosinopenia predicting long-term mortality in hospitalized acute exacerbation of COPD patients with community-acquired pneumonia-a retrospective analysis. Int J Chron Obstruct Pulmon Dis 2021;16:3551-9.

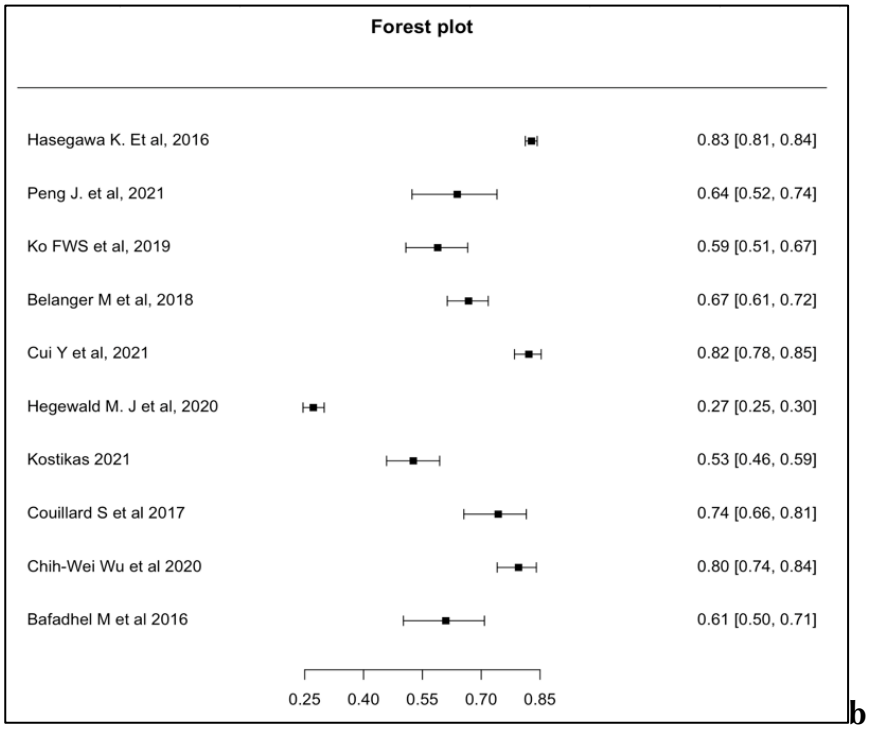
Online supplementary material
Appendix 1. Analyses considering separately mortality and hospital readmission.

Table 1. Studies characteristics.

First author	year	Pts	Study design	Eosinophils cut-off	Outcome
Hasegawa et al.	2016	3084	Retrospective cohort	≥300 cells/μL	12-months mortality/readmission
Peng et al.	2021	123	Prospective observational	≥200 cells/μL or 2% ≥300 cells/μL or 3%	12-months readmission
Ko et al.	2019	346	Prospective observational	≥2%	12-months mortality 12-month readmission
Belanger et al.	2018	479	Observational restrospective	≥200 cells/μL and/or ≥ 2%	12-months mortality 12-month readmission
Russell et al.	2019	423	Retrospective cohort	≥2%	In-hospital mortality
Cui et al.	2021	530	Prospective observational	≥300 cells/μL	12-months mortality 12-month readmission
Hegewald et al.	2020	2445	Retrospective cohort	≥300 cells/μL	12-months readmission 30-days mortality
Kostikas et al.	2021	388	Prospective observational	>150 cells/μL	12-months readmission 30-days mortality
Martinez-Gestoso et al.	2021	411	Prospective observational	≥300 cells/μL >150 cells/μL >400 cells/μL	30-days readmission 30-days mortality
Jang Pu et al.	2023	12831	Prospective observational	≥2%	In-hospital mortality
Wang Ruiying et al.	2022	984	Retrospective cohort	≥2% ≥3%	In-hospital mortality
Couillard et al.	2017	167	Retrospective cohort	≥2%	12-months readmission
Chih-Wei Wu et al.	2020	625	Retrospective cohort	≥2%	12-months readmission
Bafadhel et al.	2016	243	Prospective randomized	≥200 cells/Ml	12-months mortality In-hospital mortality

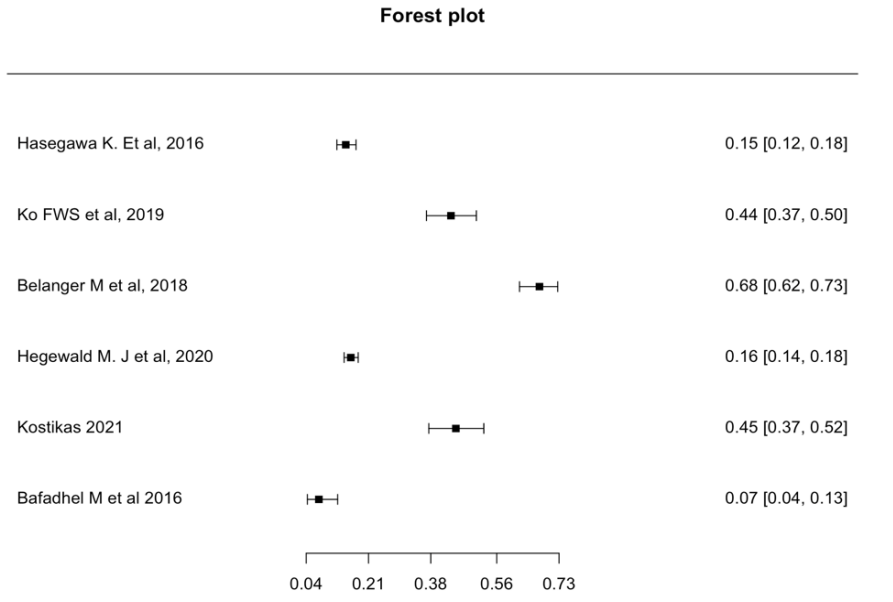


a

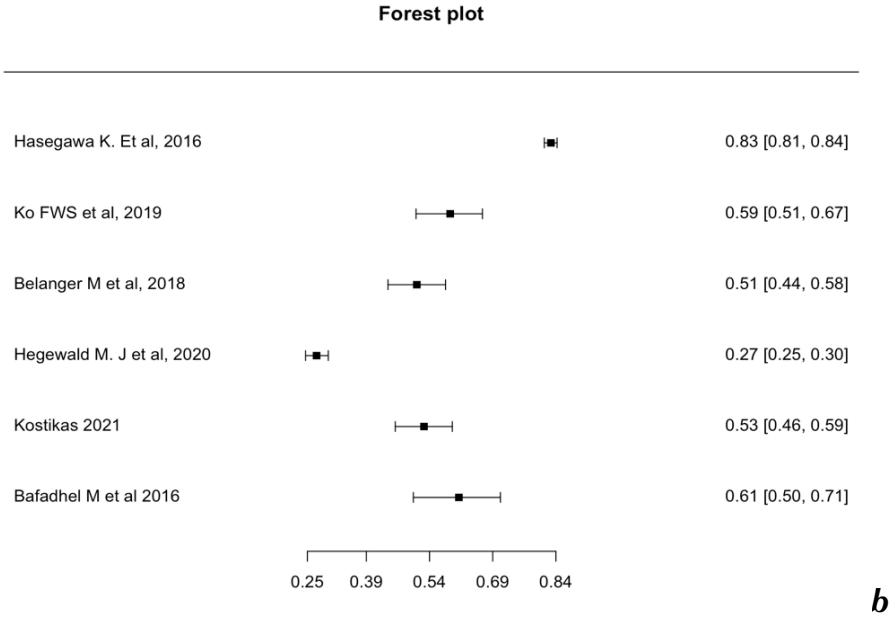


b

Figure 1. Forrest plot evaluating the pooled sensibility (a) and pooled specificity (b) of blood eosinophils in predicting primary composite outcome. CI, confidence interval.



a



b

Figure 2. Forrest plot evaluating the pooled sensibility (a) and pooled specificity (b) in analysis considering only high-quality studies. CI, confidence interval.

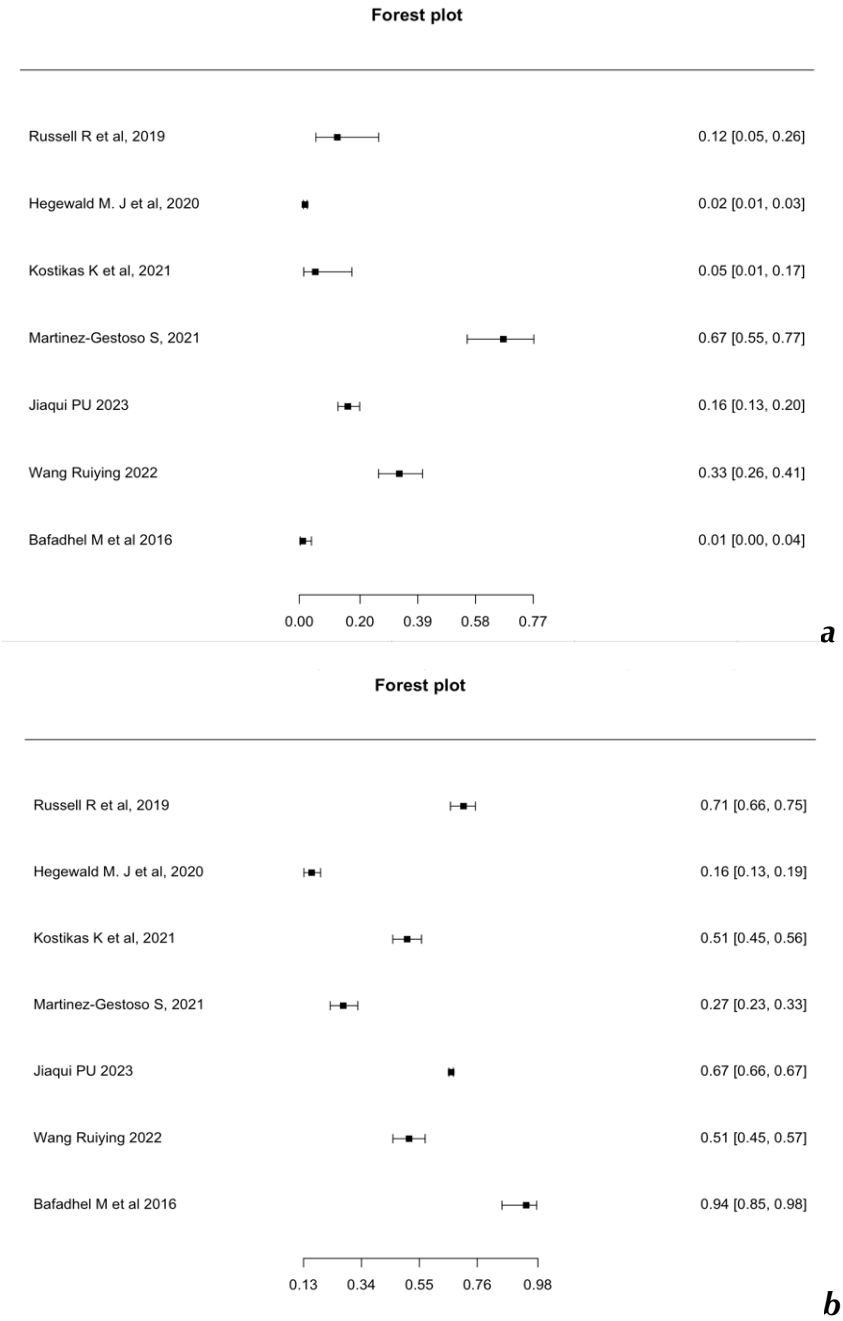


Figure 3. Forrest plot evaluating the pooled sensibility (a) and pooled specificity (b) of blood eosinophils in predicting secondary short-term outcome. CI, confidence interval.