Blood Eosinophilia as Predictor for Patient Outcomes in Chronic Obstructive Pulmonary Disease (COPD) Exacerbations

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Abstract

Introduction: The eosinophilic phenotype of chronic obstructive pulmonary disease (COPD) has been demonstrated to respond better to corticosteroids and associated with better outcomes. This review aims to clarify the correlation of blood eosinophilia and outcomes patients with COPD exacerbations.

Methods: This is a review of cohorts and case-control studies that looked into eosinophilia and outcomes in exacerbations using the meta-analysis of observational studies in epidemiology (MOOSE) guidelines. The primary study outcome was length of hospitalization; other outcomes include readmission and mortality rate within one year, in-patient mortality, and need for mechanical ventilation.

Results: Six studies were included in the review. Patients with blood eosinophilia had significantly shorter hospital stay compared to non-eosinophilic patients (mean difference 0.68 days (95% CI 1.09,0.27)). Eosinophilic patients had significantly less frequent readmissions (OR 0.69 (95% CI 0.55,0.87)) but there was no statistically significant difference in the one-year mortality rate (OR 0.88 (95% CI 0.73, .06)). Analysis showed a trend toward lower in-patient mortality among eosinophilic patients (OR 0.53 (95% CI 0.27,1.05)). Furthermore, COPD patients with eosinophilia had significantly less need for mechanical ventilation during an exacerbation (OR 0.56 (95% CI 0.35,0.89)).

Conclusion: COPD patients with blood eosinophilia had significantly shorter hospital stay, less frequent readmissions, and are less likely to require mechanical ventilation compared to the non-eosinophilic phenotype.

Keywords: COPD, eosinophilia, chronic obstructive pulmonary disease

Introduction

The natural course of chronic obstructive pulmonary disease (COPD) is characterized by a steady decline in lung function characterized by periods of exacerbations.[1,2] In the Philippines, COPD is the seventh cause of death over-all,[3] and fifth worldwide. Nonetheless, it is expected to steadily climb up in the succeeding years to become one of the top causes of mortality and morbidity.

Exacerbations of COPD pose a significant burden in health care cost and spending and is also associated with increased complications and mortality, particularly the hospitalized patients with moderate to severe exacerbations. Different treatment recommendations exist for the management of exacerbations, depending on the general level of severity and presence of comorbidities. Current Global Initiative for Obstructive Lung Disease (GOLD)[4] and National Institute for Health and Care Excellence (NICE)[5] guidelines reserve the use of corticosteroids in the management of COPD, particularly for those with severe COPD and frequent exacerbations (GOLD Class C and D), as these are also associated with significant adverse events.[6] COPD is both a complex and heterogenous disease, characterized by varying pathophysiologic mechanisms, different prognosis and response to treatment. This concept lead to research advances that characterize the phenotypes of COPD and the differences in response to various available therapy.[7] One commonly studied and described phenotype is the inflammatory phenotype characterized by sputum and/or blood eosinophilia. Sputum eosinophilia has been consistently shown in randomized controlled trials to benefit from corticosteroid therapy, compared to the non-eosinophilic counterpart.[8,9] Blood eosinophilia (defined as peripheral eosinophils >2% or >200 cells/μL) has also been shown to be a reliable surrogate marker for increased systemic inflammation and is currently the focus of a number of studies that look at the response of these patients to anti-inflammatory therapy and possibly better clinical outcomes versus the non-eosinophilic phenotype.[10]

It is therefore important to characterize this specific phenotype of COPD with regards to the factors that affect patient outcome and severity in exacerbations to guide decisions in therapy and prognosis.

This review aims to identify the correlation between blood eosinophilia and patient outcomes in hospitalized patients with COPD exacerbations and differences between

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eosinophilic and non-eosinophilic exacerbations. The primary outcome is the correlation between blood eosinophilia and length of hospital admission for an exacerbation. Other outcomes include readmission rate and mortality within one year, in-patient mortality during admission including mortality in the intensive care unit (ICU), and need for mechanical ventilation.

Methods

This review was performed in accordance with the meta-analysis of observational studies in epidemiology (MOOSE) guidelines[11] and was approved by a technical review board prior to commencement. An extensive literature search (current search as of June 25, 2016) in various databases including PubMed, MESH, EMBASE, Cochrane Database and GoogleScholar was conducted to search for studies that fulfil the inclusion criteria. Key terms for the search were "COPD", "chronic obstructive pulmonary disease", "eosinophilia", and "exacerbations". Unpublished studies were also extensively searched and individual authors were contacted for discrepancies and queries regarding their respective studies. Likewise, references of articles and their individual authors were also contacted via email for potential inclusion of their studies. No language nor time barriers were imposed during the search.

All studies including cohort (prospective or retrospective), case-control studies, and randomized controlled trials that looked into the association of blood eosinophilia and outcomes in hospitalized COPD exacerbations were included in the study. Studies were included for the review if they performed an analysis correlating eosinophilia with at least one of the study outcomes, and not necessarily of the primary outcome alone.

Analysis was performed using the most current version of Revman (5.3). Two study authors independently assessed all relevant studies for potential inclusion, and also assessed methodological quality of each of the studies. A dedicated data collection form for eligibility and a methodological assessment form - including risk of bias assessment that prescribes to the standards set by the Cochrane collaboration were used throughout the study. (Appendix A)

A standardized data extraction form for the measures of treatment effect was also used during the entire study and used the length of hospital stay, one-year readmission rate, one-year mortality, in-patient mortality and need for mechanical ventilation as the treatment effects.

Data were analyzed either as mean differences for continuous outcomes and odds ratio for dichotomous outcomes, all using 95% confidence interval for analysis. Random effects model was used throughout the analysis. Data are also presented visually as forest plots. Study outcomes were reported by different studies as different values (i.e. mean with standard deviation or median with interquartile range). For purposes of standardization and reporting of data, we used the equation published by Hozo et al.[12] to estimate the mean and standard deviation from the median and interquartile range. Heterogeneity was tested in all treatment effects via the I^2 and chi-squared statistic, with significant heterogeneity defined as I^2>50% or chi-square p<0.1.

Results

Eighteen studies met the inclusion criteria for the preliminary search. Twelve studies were excluded because either the studies did not meet the methodological criteria either analysed in relation to a treatment drug or were methodologically not fit for inclusion, or analyzed COPD patients with sputum rather than blood eosinophilia. (Appendix B)

A total of six studies[13,14,15,16,17,18] with a total population of 7,293 patients (1,562 in the eosinophilic group and 5,731 in the non-eosinophilic group) were included in this review (Appendix C). Four of the studies[14-17] were retrospective cohorts that compared outcomes between eosinophilic and non-eosinophilic COPD exacerbations, and included one or more of outcomes that are described in this review. One study[13] is a retrospective post-hoc analysis from a multi-centre randomized controlled trial that recruited patients admitted for a COPD exacerbation and involved a rehabilitation program; and one study[18] is a three-year prospective cohort that analysed differences in outcome among persistently eosinophilic versus non-eosinophilic patients. All studies analyzed the patients regardless of the treatment given during the exacerbation, particularly whether they were given corticosteroids or not. Furthermore, all studies admitted only patients with COPD exacerbations and excluded patients with other concomitant pulmonary diseases (e.g. pneumonia, lung cancer, or asthma). One study[16] included admissions of exacerbations in the intensive care unit, and analyzed general outcomes in the ICU.

Study outcomes

Length of hospital stay:

Four studies included the primary outcome in their analysis. Patients with blood eosinophilia had a significantly shorter hospital stay compared to the non-eosinophilic patients, mean difference 0.68 days less in the eosinophilic group versus the non-eosinophilic group (95% CI -1.09, -0.27days) (Figure 1). This treatment effect was significantly heterogenous (I^2=98%, chi-squared p<0.01) but sensitivity analysis nor subgroup analysis could not be performed due to homogeneity of the population and methodology.

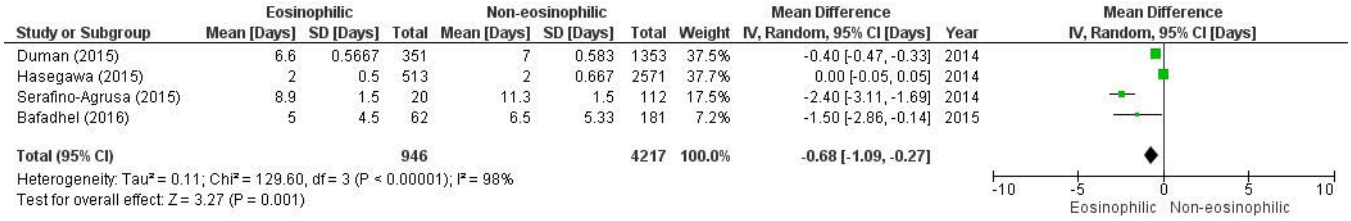

Figure 1. Hospital length of stay comparing eosinophilic and non-eosinophilic patients

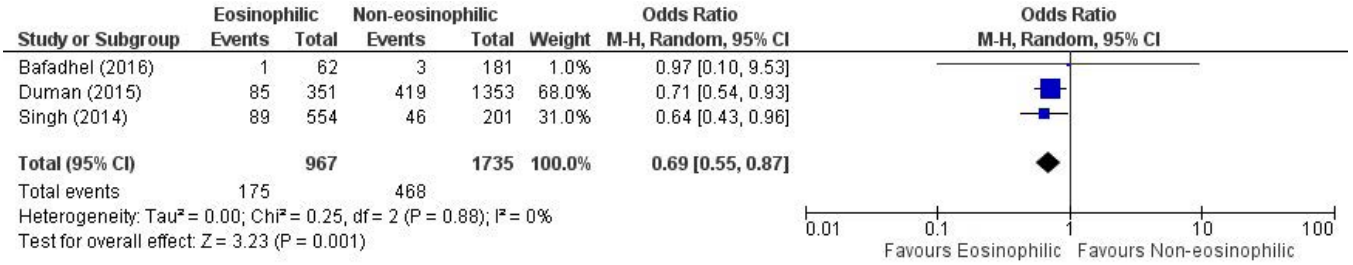

Figure 2. One-year readmission rate between eosinophilic and non-eosinophilic patients.

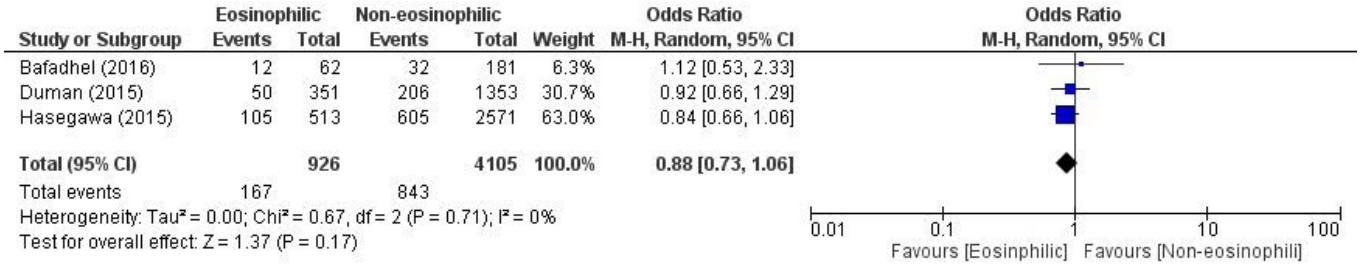

Figure 3. Difference in one-year mortality between the eosinophilic and non-eosinophilic group patients

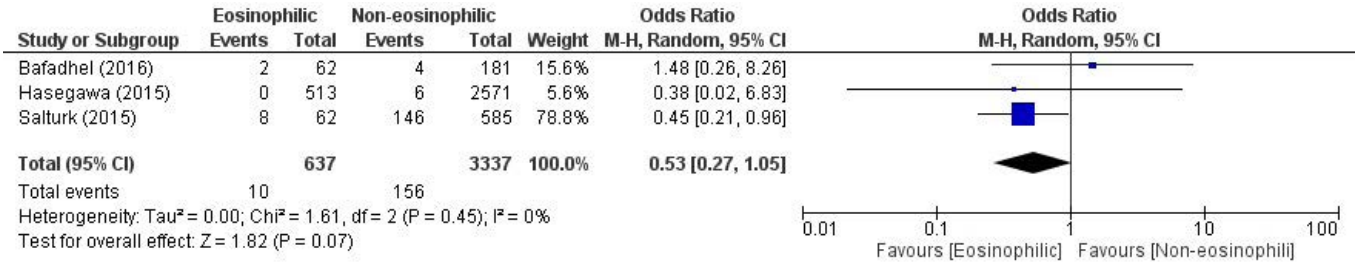

Figure 4. Comparison of In-patient mortality between eosinophilic and non-eosinophilic patients

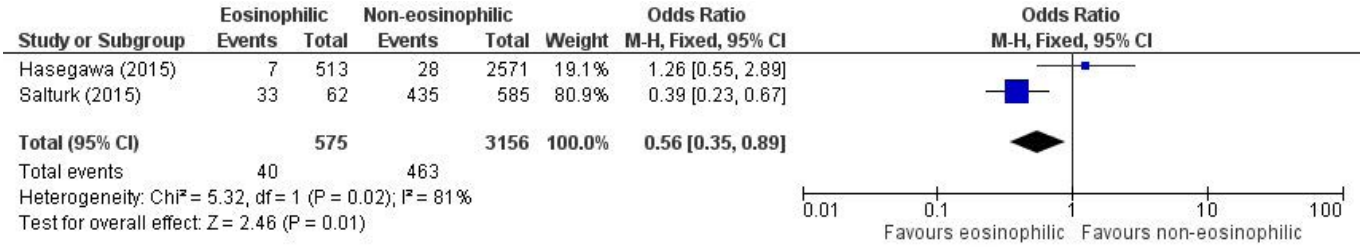

Figure 5. Need for mechanical ventilation between eosinophilic and non-eosinophilic patients

Re-admission in one year:

Three studies included readmission rate in their outcomes. Eosinophilic patients had 31% less frequent readmissions versus the non-eosinophilic patients, OR 0.69 (95% CI 0.55, 0.87), and this result is statistically significant (Figure 2). There is no significant heterogeneity across the studies (I^2=0%, chi-squared p=0.88).

One-year mortality:

Three studies reported one-year mortality in the study outcomes. There was no statistically significant differences in the one-year mortality rate among eosinophilic versus non-eosinophilic patients, OR 0.88 (95% CI 0.73, 1.06) (Figure 3). There was also no significant heterogeneity among the studies (I^2=0%, chi-squared p=0.71).

Mortality during admission:

Three studies had in-patient mortality included in their analysis of outcomes. Analysis showed a trend toward lower in-patient mortality among patients with eosinophilia versus no eosinophilia, although this difference is not statistically significant, OR 0.53 (95% CI 0.27, 1.05) (Figure 4).

Need for mechanical ventilation:

Only two studies involved mechanical ventilation as end-point. COPD patients with eosinophilia had significantly less need for mechanical ventilation during admission for an exacerbation compared with patients with no eosinophilia, OR 0.56 (95% CI 0.35, 0.89). However, this has a significantly heterogenous result (Figure 5).

Discussion

This review summarized the current available evidence on the correlation of blood eosinophilia and patient outcomes in COPD exacerbations. Significant improvements were observed in the length of hospital stay, one-year readmission rate and use of mechanical ventilation favouring eosinophilic over the non-eosinophilic patients. Although there were no statistically significant differences in more important outcomes, i.e. mortality both in-patient and one year mortality, the data show trends toward benefit, again, favouring the eosinophilic phenotype. These findings could be partially explained by the fact that most moderate/severe COPD patients and patients in exacerbation tend to be given corticosteroid therapy as part of the treatment regimen.

The findings of this review generally follow the current concept that eosinophilia is indeed a predictor for better patient outcomes in COPD because of response to available anti-inflammatory therapy.

The studies reviewed were good quality retrospective or prospective cohorts, which is apt for the specific outcomes. However, as blood eosinophilia is still continued to be explored as an established factor for patient outcomes in COPD, the studies showed a mix of results and outcomes were not consistently the same across studies.

Over-all, as the trend toward "personalized" COPD management is being explored, more and more studies are expected to be done, focusing on specific disease phenotypes and response to various therapies.

Conclusions

Patients with eosinophilic COPD exacerbations have better clinical outcomes in terms of length of hospitalization, readmission and need for mechanical ventilation compared to the non-eosinophilic patients. There is also a trend toward lower short- and long-term mortality among these eosinophilic patients.

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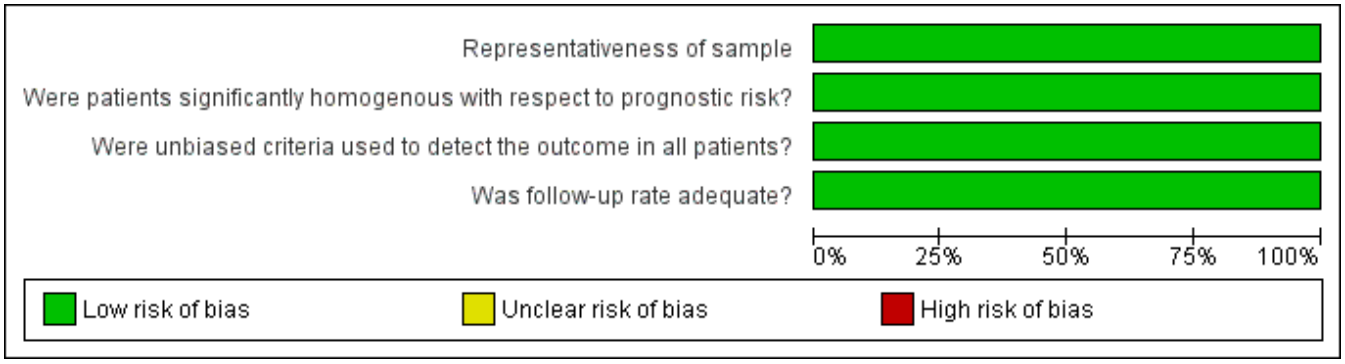
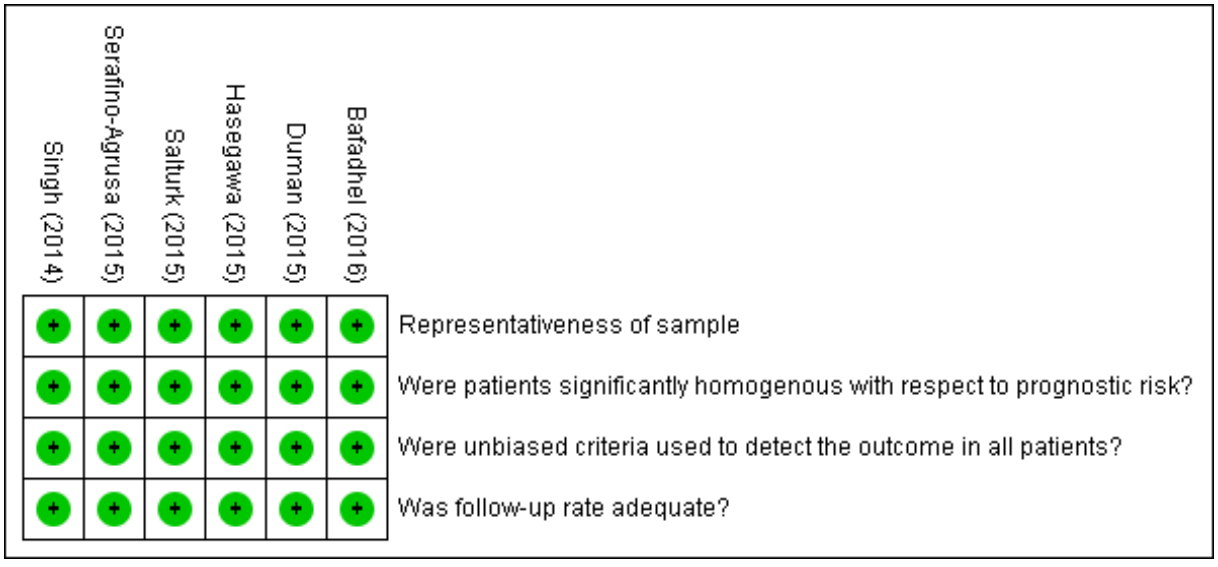
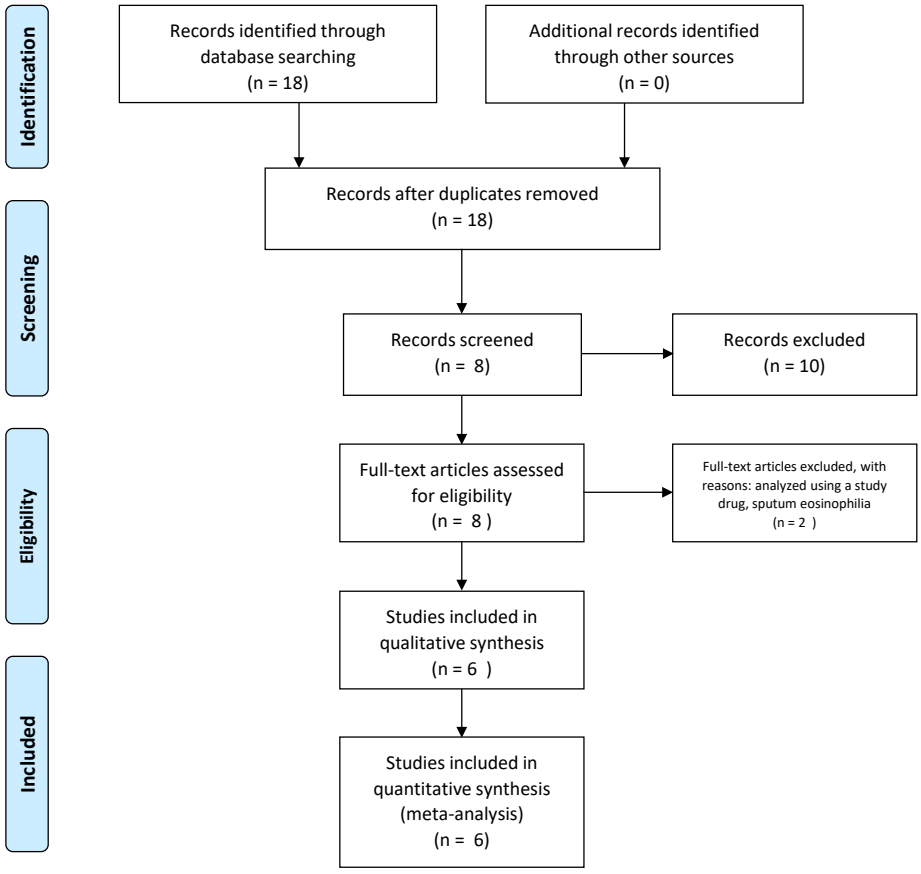
APPENDICES



Appendix A1. Risk of bias summary for the studies



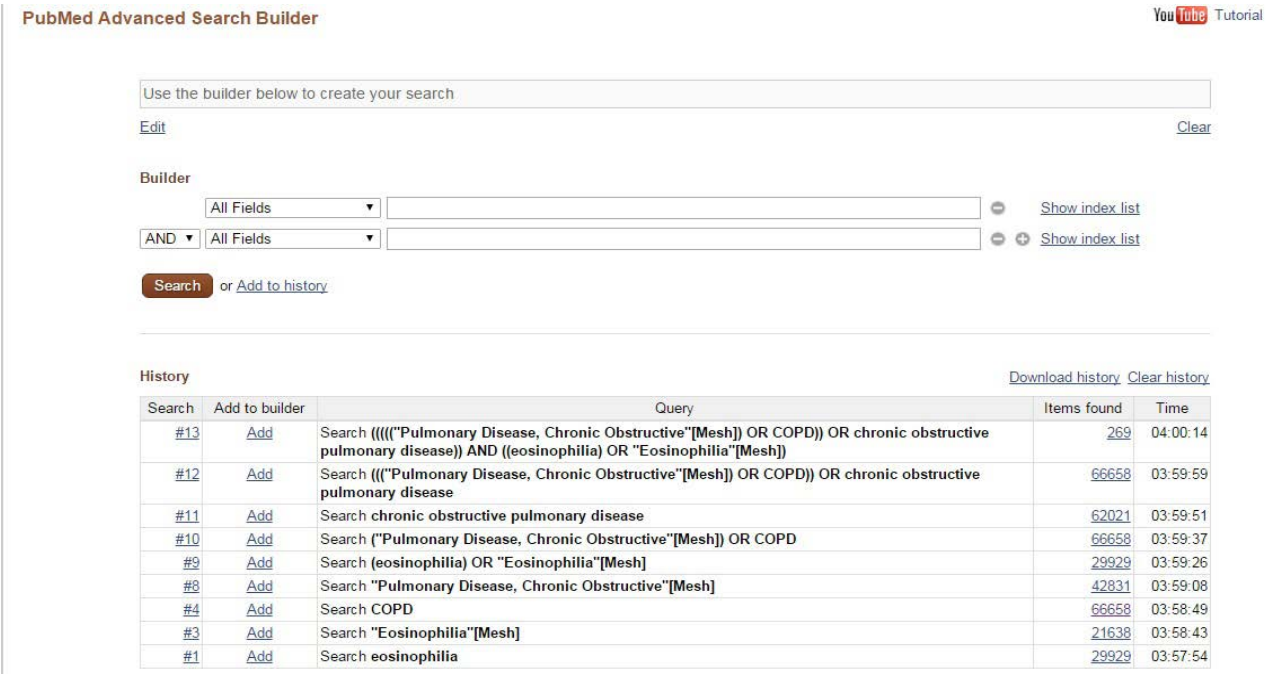
Appendix A2. Individual risk of bias summary



Appendix B. Flowchart of study selection process

Author (Year)	Title	Design	Duration	Outcomes	Comparison
Singh (2014)	Eosinophilic inflammation in COPD: prevalence and clinical characteristics.	Prospective Cohort	three-year follow-up period	Hospitalization, rate of exacerbation, admissions in one year, pulmonary function	Persistently no eosinophilia
Serafino-Argrusa (2015)	Blood eosinophils and treatment response in hospitalized exacerbations of chronic obstructive pulmonary disease: A case control study	Case-control study	Retrospective analysis of a two-year period	Primary outcome: length of hospitalization Other outcomes: comorbidities, steroid dose, duration of IV steroid treatment	Non-eosinophilic patient
Hasegawa (2015)	Prevalence of blood eosinophilia in hospitalized patients with acute exacerbation of COPD	Retrospective cohort	Retrospective cohort and analysis over a ten-year period	Hospital length of stay, intubation and mechanical ventilation rates, mortality	Non-eosinophilic patients
Salturk (2015)	Does Eosinophilic COPD exacerbation have a better patient outcome than non-eosinophilic in the intensive care unit?	Retrospective Cohort	Retrospective cohort over two years, analysing severe exacerbations admitted in the ICU	Intubation and NIV rates, ICU mortality	Non-eosinophilic patients
Duman (2015)	The utility of inflammatory markers to predict readmissions and mortality in COPD cases with or without eosinophilia.	Retrospective Cohort	Retrospective cohort	Hospital length of stay, one-year mortality, one year readmission rate	Non-eosinophilic patients
Bafadhel (2016)	Blood eosinophils and outcomes in severe hospitalised exacerbations of COPD	Retrospective post-hoc analysis of a randomized controlled trial involving pulmonary rehabilitation in COPD exacerbation patients	12 month follow-up period	Hospital length of stay, mortality during admission and within one year, readmission rate within one year	Non-eosinophilic patients

Appendix C. Characteristics of included studies



Appendix D. Search strategy used for Pubmed