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Blood Eosinophils and Clinical Outcome of Acute Exacerbations of Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis

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Keywords
Acute exacerbation · Chronic obstructive pulmonary disease · Eosinophil · Corticosteroid

Abstract

Background: Numerous studies have shown the association between eosinophilia and clinical outcomes of patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). But the evidences are lack of consensus. ***Objective:*** The aim of this meta-analysis was to conduct a pooled analysis of outcome comparing eosinophilic (EOS) AECOPD and non-EOS AECOPD patients. ***Methods:*** We included PubMed, EMBASE, Web of Science, and Cochrane databases up to 2020 to retrieve articles. Randomized controlled trials and quasi-experimental studies about patients with and without EOS AECOPD in terms of in-hospital mortality, length of hospital stay, comorbidities, forced expiratory volume in 1 s (FEV1), gender, and BMI were included preclinical studies, review articles, editorials, commentaries, conference abstracts, and book chapters were excluded. The methodologic assessment of studies was performed with the Newcastle-Ottawa Scale and Cochran scale. Comprehensive Rev Man 5 was used for the statistical analysis. ***Results:*** Twenty-one studies with 18,041 patients fulfilled the inclusion criteria and were used in this meta-analysis. Comparing to the non-EOS group, those with EOS AECOPD patients had a lower risk for in-hospital mortality (odds ratio (OR) = 0.59, 95% confidence interval [CI] 0.36–0.95, $p = 0.03$), shorter length of hospital stay (OR = −0.72, 95% CI −1.44 to −0.00, $p = 0.05$), better FEV1 (mean difference = 0.14, 95% CI 0.08–0.20, $p < 0.00001$), and a lower risk of arrhythmias (OR = 1.50, 95% CI 1.01–2.21, $p = 0.04$). In addition, the non-EOS group had a higher percentage of male (OR = 1.34, 95% CI 1.15–1.56, $p = 0.0002$) than EOS group. The rate of steroid use (OR = 0.82, 95% CI 0.47–1.42, $p = 0.48$) and BMI (mean difference = 0.43, 95% CI −0.18 to 1.05, $p = 0.17$] had no difference between 2 groups. ***Conclusion:*** The results of our meta-analysis suggest that EOS AECOPD patients have a better clinical outcome than non-EOS AECOPD patients in terms of length of hospital stay, in-hospital mortality, FEV1, and risk of arrhythmias. In addition, the non-EOS AECOPD patients have higher percentage of male than EOS AECOPD patients.

Introduction

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) substantially contribute to high morbidity, mortality, and poor quality of life worldwide [1]. They are heterogeneous with respect to inflammation

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and etiology [2]. Increased eosinophil has been reported in exacerbation phase of patients with COPD, implying its potential role in AECOPD [3].

As we all known airway eosinophilia is a hallmark inflammatory response for asthma pathogenesis and is now known to be involved in the airway inflammatory process in COPD [4]. A diagnostic tool for the measurement and detection of airway eosinophilia is induced sputum assessment [5]. Sputum induction is thought to be a direct and reliable method for evaluating airway inflammation [6]. Previous studies [6, 7] have shown that a sputum eosinophilia is associated with a positive response to corticosteroid treatment in stable COPD, and the sputum eosinophil count can be used to titrate corticosteroid therapy to reduce exacerbations of COPD. However, it has several limitations: For example, it is unsuitable for point-of-care testing, requires experience, and has a failure rate of up to 30%. Due to these limitations, the search for minimally invasive and easily available methods that can evaluate eosinophil inflammation in asthma and COPD has been intensified [8, 9]. Blood eosinophil count is a simple and attractive tool in clinical practice and correlates with induced sputum eosinophil counts. Both measures have been used as biomarkers of eosinophil airway inflammation [10, 11]. There are studies [12] have been confirmed that eosinophils will increase in some patients with AECOPD. Thus, blood eosinophil could be a promising biomarker for therapy during COPD exacerbations.

Eosinophilia is generally defined as greater or equal to 2% eosinophils in either blood. Alternatively, an absolute blood eosinophil count of 0.34×10^9 cells per liter can be used as a threshold for risk stratification [13, 14]. Given this context, we considered that patients with AECOPD who had equal or >2% or 0.34×10^9 cells per liter of eosinophils, in the blood, as eosinophilic (EOS) AECOPD, <2% or 0.34×10^9 cells per liter of eosinophils, as non-EOS AECOPD. Numerous studies evaluated eosinophilia in relation to length of hospital stay, in-hospital mortality, forced expiratory volume in 1 s (FEV1), and relevant comorbidities about AECOPD. But the evidences are lack of consensus. So, we conducted a meta-analysis of clinical outcome comparing patients with AECOPD who had eosinophilia and those without eosinophilia.

Materials and Methods

Search Strategy

We searched (((Corticosteroid)) OR (Systemic Corticosteroid)) OR (steroid) AND (((AE COPD)) OR (AECOPD)) OR (acute exacerbation, chronic obstructive pulmonary disease) AND (((Eosinophil)) OR (Eosinophils)) OR (Eosinophilia)) OR (Eosinopenia) in PubMed (MEDLINE), Web of Science, Cochrane, and EMBASE databases up to 2020. The literature search was performed by 2 authors (Y.Y. and G.S.).

Inclusion and Exclusion Criteria

Randomized controlled trials and quasi-experimental studies were included, and included studies should meet the following criteria: (1) all patients in study were diagnosis of AECOPD according to Global Initiative for Chronic Obstructive Lung Disease criteria. (2) The exposure was blood EOS and non-EOS AECOPD patients. (3) In-hospital mortality, length of hospital stay, comorbidities, FEV1, and BMI should be included in the study outcomes. Preclinical studies, review articles, editorials, commentaries, conference abstracts, and book chapters were excluded.

Data Extraction

All articles identified in the initial database search were screened based on title, abstract, and full text to confirm eligibility and avoid overlapping data. Titles and abstracts were screened by 2 authors (Y.Y. and G.S.), and studies that were not pertinent to the topic were discarded. Relevant data were extracted from the eligible publications: the name of the first author, the year of publication, and the number of patients analyzed, baseline characteristics, length of hospital stay, in-hospital mortality, and FEV1. When there are disagreements on study judgments, they will be discussed by 2 authors (Y.Y. and G.S.).

Statistical Analysis

Meta-analysis compared patients with EOS and non-EOS AECOPD in terms of length of hospital stay, in-hospital mortality, and change of FEV1, the percentage of gender, BMI, and comorbidities. Continuous variables were presented as standardized mean differences with 95% confidence intervals (CIs). Pooled standardized mean difference with 95% CI was calculated, and $p < 0.05$ was accepted with statistical significance. Heterogeneity across studies was determined by the I^2 statistic using Cochrane Review Manager 5.3. An I^2 values ≥25, 50, and 75% were considered as mild, moderate, and high degree of heterogeneity, respectively. For pooled outcome measures with $I^2 > 50\%$, a random-effect model was used to evaluate the overall effect of a given comparison. Studies were weighted by inverse of variance. Categorical data were presented as odds ratio (OR) in 95% CI. Meta-analysis was done with the random-effects model.

Quality Assessment and Risk of Bias Assessment

To assess the quality and risk of bias assessment of the included studies, 2 reviewers independently rated the studies according to the Newcastle-Ottawa Scale (NOS) for cohort studies and Cochrane Scale for randomized controlled studies. The 9-point NOS contains 3 items: selection (0–4), comparability (0–2), and exposure (0–3). Studies scored over 7 points on the NOS were deemed to be of high quality. The Cochrane Collaboration risk of bias assessment tool was used to evaluate the risk of bias. The following 7 items were evaluated: random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias); and other bias. For each randomized controlled trial, each item was considered as low risk, high risk, or unclear risk. When disagreement existed between the 2 reviewers, a discussion would be carried out.

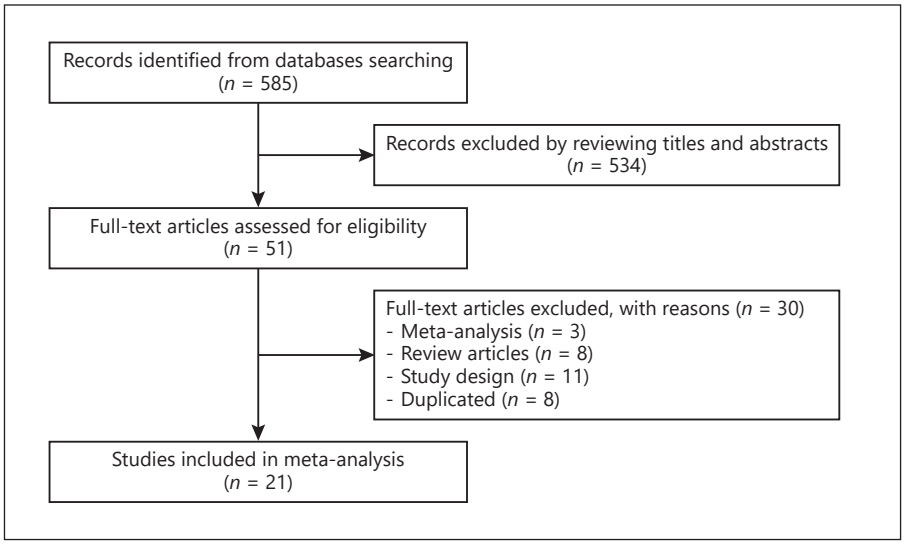

Fig. 1. Flow diagram of literature search and selection of studies.

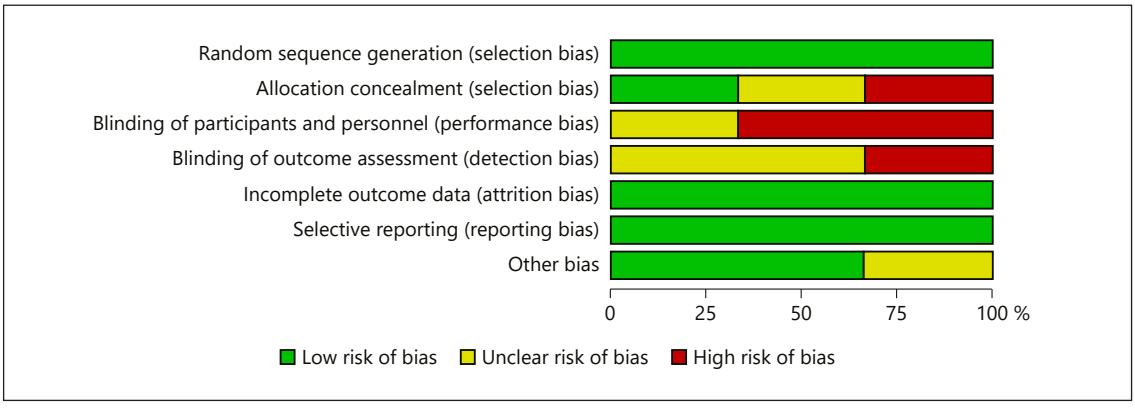

Fig. 2. Risk of bias graph.

Results

A total of 585 primary articles that were potentially relevant were obtained to determine further eligibility. Of these, 564 articles did not fulfill our inclusion criteria and were excluded. Twenty-one remaining publications published from 2001 to 2020 were included in this meta-analysis, a summary of the literature search following PRISMA statement is presented in Figure 1. The mean age of the subjects was 70.4 years with the proportion of male subjects ranging from 47 to 96.2%. Studies were carried out in Turkey, the Netherlands, Italy, UK, USA, Korea, Canada, Denmark, Australia, Republic of Korea, Iran, and China, respectively. The main features of the studies included in this meta-analysis were presented in Table 1.

In this meta-analysis, of 17 nonrandomize observational studies evaluated by NOS, the mean score was average 7 out of 9. The overall risk of bias was considered low as assessed by the Cochrane risk of bias tool (Higgins & Green, 2011) (Fig. 2). Other results showed that comparing to the non-EOS group, those with EOS AECOPD patients had a lower risk for in-hospital mortality (OR = 0.59, 95% CI 0.36–0.95, $p = 0.03$) (Fig. 3). Shorter length of hospital stay (OR = −0.72, 95% CI −1.44 to −0.00, $p = 0.05$) (Fig. 4). Better FEV1 (mean difference = 0.14, 95% CI 0.08–0.20, $p < 0.00001$) (Fig. 5). A lower risk of arrhythmias (OR = 1.50, 95% CI 1.01–2.21, $p = 0.04$) (Fig. 6). In addition, the non-EOS group had a higher percentage of male (OR = 1.34 95% CI 1.15–1.56, $p = 0.0002$) than EOS group (Fig. 7). The rate of steroid use (OR = 0.82, 95% CI 0.47–1.42, $p = 0.48$)

Table 1. Description of the included studies [12, 15–33]

First author	Year	Country	Single/ multicenter	Subjects, *n*	Study design	Mean age, years	Male, %	Baseline of FEV1	Smoking (pack-years)	Eosinophil measurement
Bafadhel et al. [12]	2012	UK	Single	164	RCT	69	65.2	1.19 L	54.5	Absolute and differential count
Russell et al. [16]	2019	UK	Single	423	Retrospective cohort	71	52	NR	NR	Absolute and differential count
Hasegawa [23]	2015	USA	Single	3,084	Retrospective cohort	70.5	52.5	NR	NR	Absolute and differential count
Aksoy et al. [20]	2018	Turkey	Single	2,727	Retrospective cohort	69.5	68.6	NR	NR	Absolute and differential count
Saltürk et al. [18]	2015	Turkey	Single	647	Retrospective cohort	68	81.5	NR	41.5	Absolute and differential count
Prins et al. [17]	2017	The Netherlands	Single	207	RCT	70.5	52.7	1.23 L	40	Absolute and differential count
Serafino-Agrusa et al. [22]	2016	Italy	Single	132	Case-control	73.1	77.5	45.5% Pred	65.15	Absolute and differential count
Bélanger [33]	2018	Canada	Single	479	Retrospective cohort	68.9±9.4	52	51.2±16.8% Pred	NR	Absolute and differential count
Choi [27]	2019	Republic of Korea	Single	736	Retrospective cohort	72.05±9.7	71.4	1.25±0.5 L	44.1±25	Absolute and differential count
Sivapalan et al. [21]	2019	Denmark	Multicenter	318	RCT	75	71.5	0.7 L	46.5	Absolute and differential count
MacDonald [31]	2019	Australia	Single	341	Retrospective cohort	72.65	56.1	1.14 L	NR	Absolute and differential count
Kang [22]	2016	Republic of Korea	Multicenter	605	Retrospective cohort	71.475±10.295	74.1	1.13±0.47 L	38.82±27.675	Absolute and differential count
Dahlén [25]	2001	Sweden	Single	43	Retrospective cohort	64	47	49±24% predicted	20	Absolute and differential count
Ko [24]	2019	China	Single	346	Prospective observational study	74.9±7.8	96.2	43.4±16.3% predicted	NR	Absolute and differential count
Rahimi-Rad [26]	2015	Iran	Single	100	Prospective study	70.5	69	NR	NR	Differential count
Çoban [32]	2017	Turkey	Single	1,490	Observational cohort study	67.5	65	NR	NR	Absolute and differential count
Wu [29]	2019	China	Multicenter	493	Prospective, observational cohort study	76	69.8	NR	NR	Absolute and differential count

Table 2 (continued)

First author	Year	Country	Single/ multicenter	Subjects, *n*	Study design	Mean age, years	Male, %	Baseline of FEV1	Smoking (pack-years)	Eosinophil measurement
Zhang [30]	2020	China	Single	829	Prospective observational study	≥60	71	NR	41.26±31.4	Absolute and differential count
Gonzalez-Barcala et al. [14]	2019	Spain	Single	1,626	Retrospective study	74.34	77.1	18.5% predicted	NR	Absolute and differential count
Pascoe [15]	2015	UK	Single	3,177	RCT	63.5	54.25	1.27 L	NR	Absolute and differential count
Holland [28]	2010	UK	Single	65	Retrospective study	76	NR	NR	NR	Absolute and differential count

NR, not report; RCT, randomized controlled trial; FEV1, forced expiratory volume in 1.

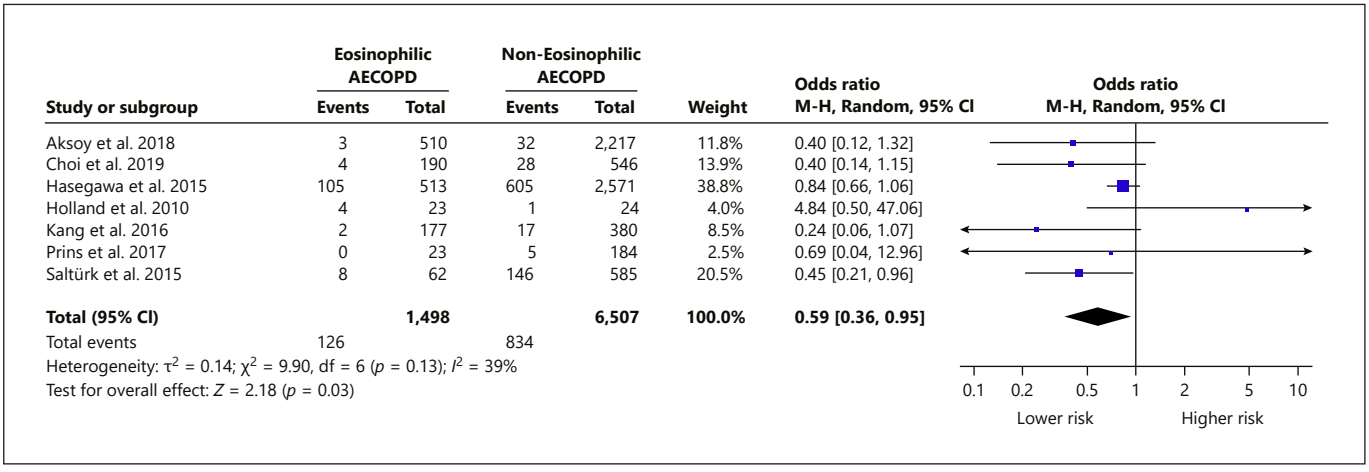

Fig. 3. Forest plots of studies comparing the risk for in-hospital mortality. EOS, eosinophilic; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval.

(Fig. 8) and BMI (mean difference = 0.43, 95% CI −0.18 to 1.05, $p = 0.17$) (Fig. 9) have no difference between 2 groups.

Discussion

The main results of our meta-analysis demonstrated that EOS AECOPD patients have a better outcome in length of hospital stay, in-hospital mortality, FEV1, and risk of arrhythmias compared with non-EOS AECOPD patients. In addition, we found non-EOS AECOPD patients are higher male gender than EOS AECOPD patients.

Bafadhel et al. [12] and Pascoe et al. [15] showed that the peripheral blood eosinophil count is a valid biomarker of COPD exacerbation; the 2% threshold value is a sensitive marker for the presence of an EOS attack that can be responsive to corticosteroids. Another study, Russell et al. [16] find that in exacerbations of COPD, a higher

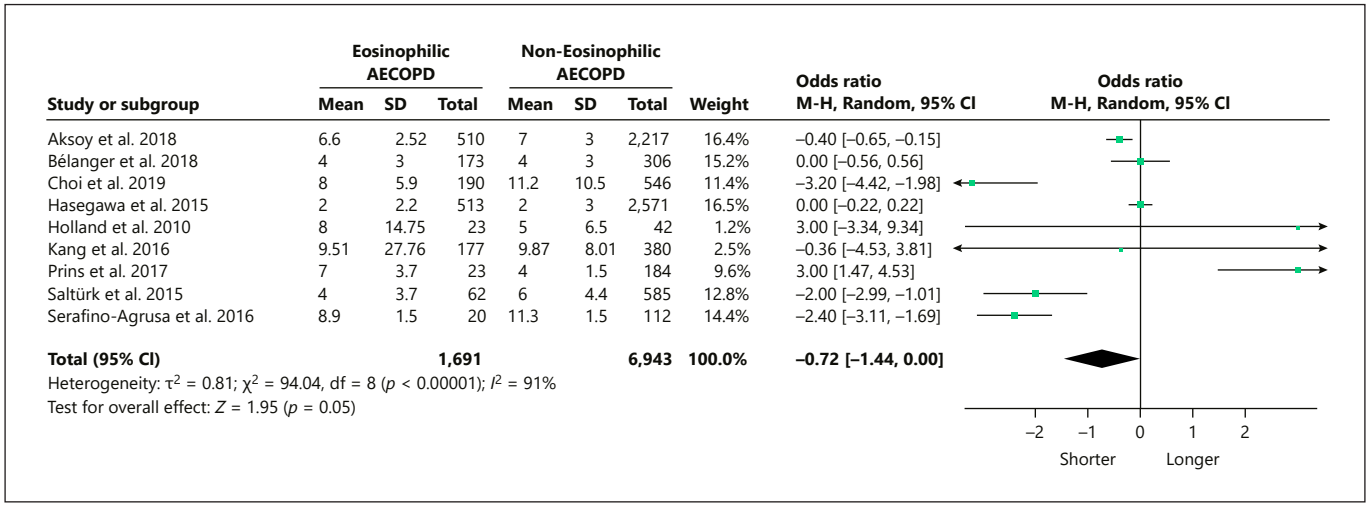

Fig. 4. Forest plots of studies comparing the length of hospital stay. EOS, eosinophilic; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval.

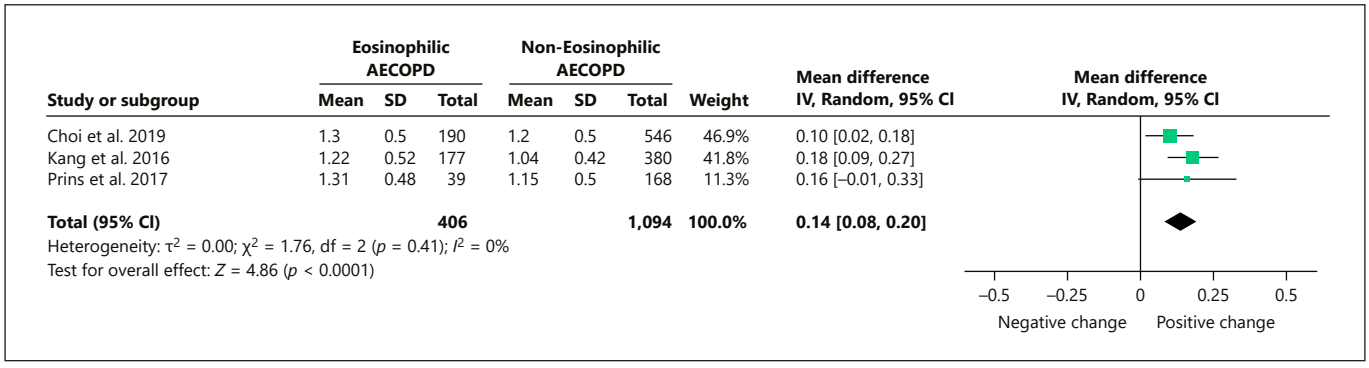

Fig. 5. Forest plots of studies comparing the mean difference of the change of FEV1. EOS, eosinophilic; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval; FEV1, forced expiratory volume in 1.

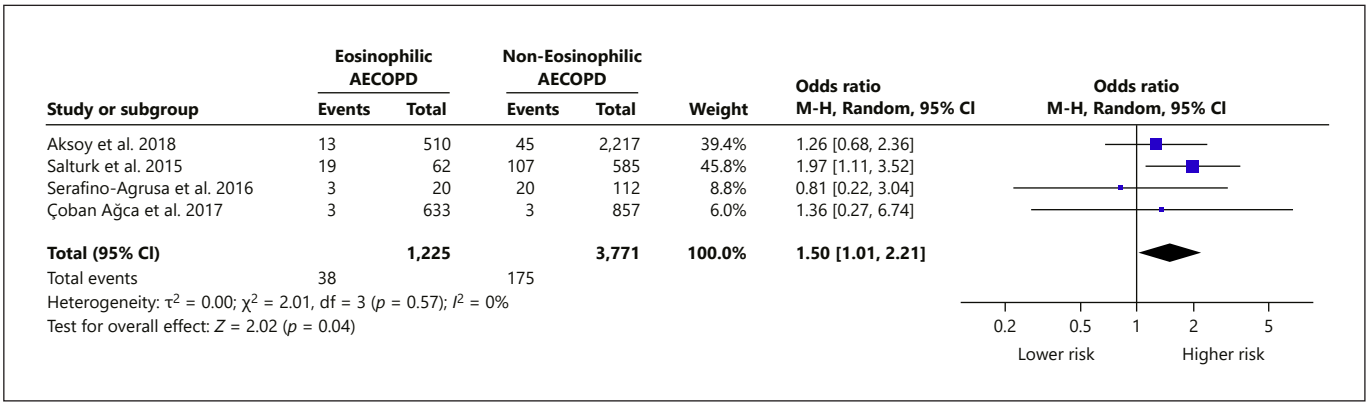

Fig. 6. Forest plots of studies comparing the risk of arrhythmias. EOS, eosinophilic; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval.

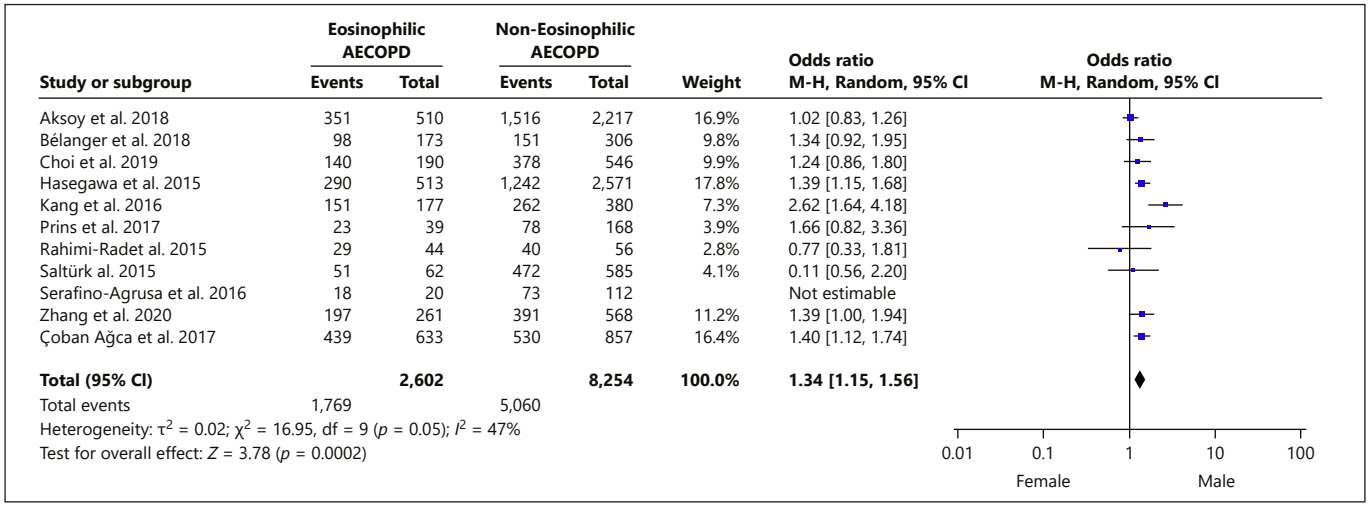

Fig. 7. Forest plots of studies comparing the percentage of male. EOS, eosinophilic; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval.

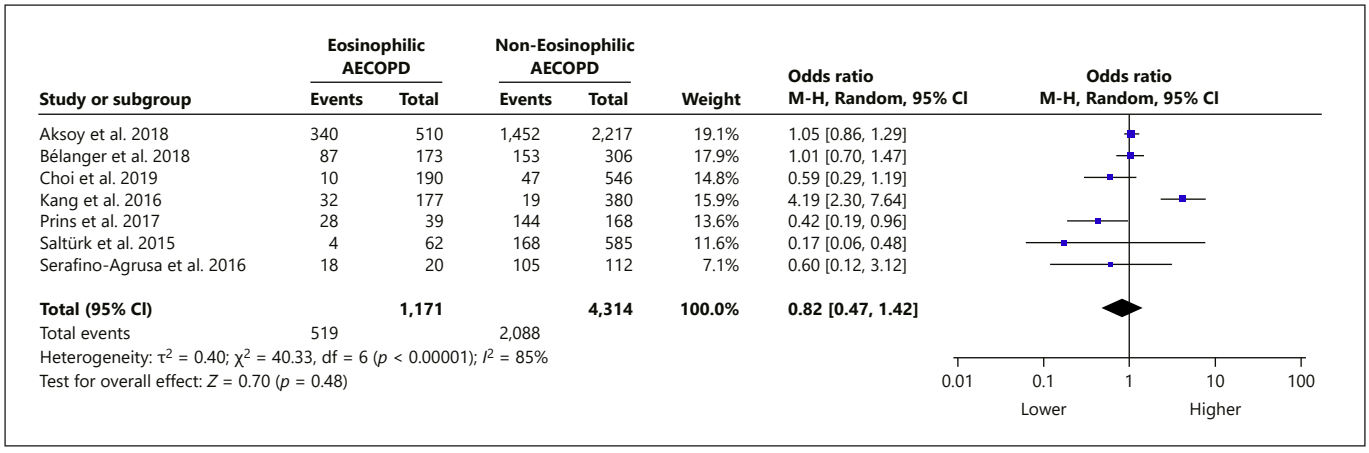

Fig. 8. Forest plots of studies comparing the percentage of Corticosteroid use. EOS, eosinophilic; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval.

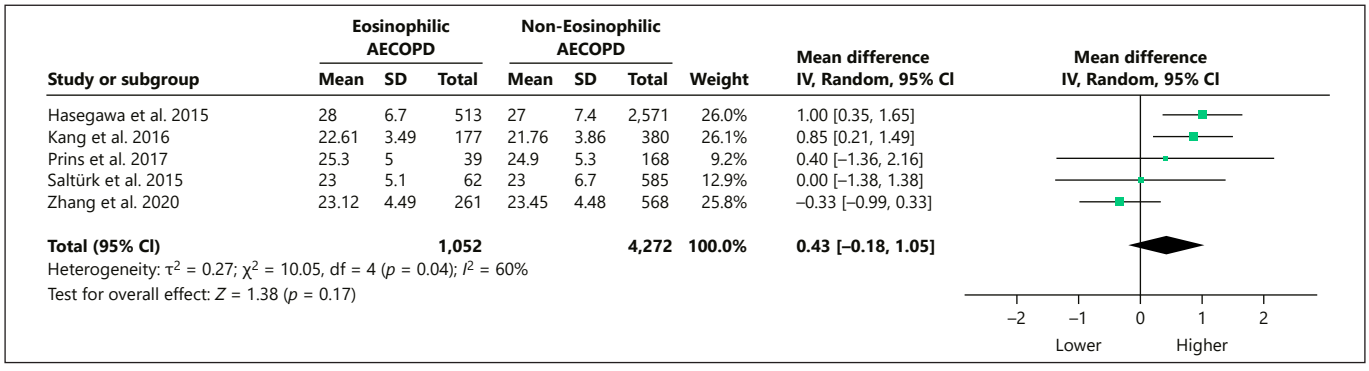

Fig. 9. Forest plots of studies comparing the BMI. EOS, eosinophilic; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval.

blood eosinophil count is associated with a shorter length of stay and reduced mortality. These are consistent with our study, EOS AECOPD patients have shorter length of hospital stay and a lower in-hospital mortality than non-EOS AECOPD patients, and this is also consistent with Prins et al. [17] studies showed that the median length of stay was 5 (IQR 4–6) days in the EOS group as compared to 7(IQR 5–10) days ($p = 0.001$) in the non-EOS group.

Saltürk et al. [18] study showed that comorbidities were similar in group 1 (EOS >2%) and group 2 (non-EOS ≤2%); except arrhythmia, the non-EOS AECOPD patients were significantly more severe than EOS AECOPD patients. Our results also showed that non-EOS AECOPD patients have a higher risk of arrhythmias (OR = 1.51, 95% CI 1.01–2.26, $p = 0.05$). In addition, Brightling et al. [34] published a randomized placebo-controlled phase IIa study, and their subgroup analysis did show that patients with baseline blood eosinophil concentrations of 200 cells per μL had a greater improvement of acute exacerbation of COPD and FEV1. This is consistent with our study show that EOS AECOPD patients are better than non-EOS AECOPD patients in change of FEV1 (mean difference = 0.14, 95% CI 0.08–0.20, $p < 0.00001$).

In Aksoy et al. [19] study, they showed that the rate of steroid use is similar between the 2 groups, and the EOS group had a significantly shorter LOS in hospital ($p < 0.001$). Bafadhe et al. [12] study indicates that patients with higher peripheral blood eosinophil counts are more likely to benefit from treatment with inhaled corticosteroids and systemic corticosteroids. Another study [20] which published in Lancet showed that the length of treatment with systemic corticosteroids and the mean cumulative systemic corticosteroid dose on day 5 were lower in the eosinophil-guided group than in the control group ($p < 0.0001$). Our study was consistent with them, the rate of steroid use had no difference between 2 groups (OR = 0.82, 95% CI 0.47–1.42, $p = 0.48$), but we could see that the EOS group has a better treatment response than non-EOS AECOPD patients. This means EOS AECOPD patients are more sensitive to steroid. Serafino-Agrusa L et al. [21]study showed that the BMI and prevalence of female gender were lower in patients with blood eosinophil-positive SAECOPD. Our study had the same result that the non-EOS group had a higher percentage of male (OR = 1.34, 95% CI 1.15–1.56, $p = 0.0002$), but our result showed no difference between 2 groups in BMI (mean difference = 0.43, 95% CI −0.18 to 1.05, $p = 0.17$).

It is well known that AECOPD may be triggered by infection with bacteria or viruses or by noninfectious environmental (e.g., temperature, pollution, allergens, and diet) or internal (immune dysregulation) factors. The cause of approximately one-third of exacerbations cannot be identified [35–37]. Traditionally, COPD exacerbation has been associated with neutrophilic airway inflammation. However, one study found that EOS airway inflammation accounted for a considerable proportion (nearly 30%) of COPD exacerbations [10]. Bafadhel with his colleagues [12] through cluster analysis using the highest loading biomarker from each factor (TNFRII, CXCL11, and CCL17) revealed 4 exacerbation types: bacterial predominant, viral predominant, eosinophil predominant, and pauciinflammatory. Each of these 4 types seemed to be associated with a distinct inflammatory profile during clinical stability. Similar results were later reported by Gao [38].

The cytokine(s) driving the increase of eosinophils in bronchial tissue during AECOPD has been reported. Saetta et al. [39] found no differences in the amount of IL-5 expressed in bronchial biopsies between patients with AECOPD and patients without an ongoing AECOPD at time of evaluation. One of the growth factors probably involved in eosinophil recruitment into the airways during AECOPD may be GM-CSF, as this mediator was found in increased amounts in BAL fluid and in serum of patients during AECOPD [40]. In addition, the number of cells staining positive for RANTES, a chemokine involved in eosinophil chemotaxis, was increased in AECOPD patients compared with stable COPD patients [41]. More studies have shown a more favorable treatment response to systemic corticosteroids in patients with higher blood eosinophil counts [21,42,43]. In daily clinical practice, the administration of systemic corticosteroids seems to lead to a decrease in blood eosinophils, and the clinical improvement, thereafter, indicates that systemic corticosteroids might be able to reduce EOS inflammation. However, the mechanism for corticosteroids effect in AECOPD patients with higher blood eosinophil counts remains unclear.

All in all, these findings may suggest that in routine clinical assessment, therapeutic strategies according to the level of this biomarker are important. In our study, we show that with no difference in steroid use rate, the EOS AECOPD patients have better outcome than non-EOS AECOPD patients. This means blood eosinophils could be the marker to direct corticosteroid treatment of AECOPD. So far, our current study is the first meta-analysis to investigate the outcomes between eosinophil and non-EOS AECOPD patients. There are some limitations in this systematic review according to a predefined data abstraction form. Minor alterations were made to facilitate data pooling. There were missing data on some of the

outcome measures of our interest, reducing the number of eligible studies. Despite these limitations, all of the studies included consisting of 18,041 patients were assessed as moderate to high quality. And most of the studies were in cohort design. These strengths granted us some confidence to speculate a difference between eosinophil and non-EOS AECOPD. However, our results should be interpreted with caution and need further researches in the light of several limitations.

Conclusions

EOS AECOPD patients are associated with a shorter length of hospital stay, lower risk in-hospital mortality, better FEV1, and a lower risk of arrhythmia than non-EOS AECOPD patients. In addition, the non-EOS AECOPD patients have higher percentage of male than EOS AECOPD patients. Given its association with eosinophil level in the airway, blood eosinophil count can be a predictive biomarker in patients with AECOPD.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Conflict of Interest Statement

The author reports no conflicts of interest in this work.

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Author Contributions

Guo Chao Shi: manuscript conception, data extraction, data analysis, risk of bias assessment, manuscript redaction, and final approval. Guarantor for the entire manuscript. Yajie You: literature search, study inclusion, data extraction, data analysis, risk of bias assessment, manuscript redaction, and final approval.

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