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Blood eosinophil count-guided corticosteroid therapy and as a prognostic biomarker of exacerbations of chronic obstructive pulmonary disease: a systematic review and meta-analysis

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and dyspnea, as well as an increase in the number of leukocytes in the airways, lungs, and pulmonary vessels. A 'One size fits all' approach to COPD patients with different clinical features may be considered outdated. The following are the two major objectives of this meta-analysis: the first is to determine if blood eosinophil counts (BEC) can serve as a prognostic biomarker of COPD outcomes, and the second is to determine which level of BEC is effective for inhaled corticosteroid (ICS) treatment.

Methods: We searched articles published before 15 May 2021 in the following four electronic databases: Web of Science, Cochrane Library, EMBASE, and PubMed.

Results: A total of 42 studies, comprising a sampling of 188,710 subjects, were summarized and compared in this meta-analysis. The rate ratio (RR) of exacerbations of COPD (ECOPD) between ICS and non-ICS treatment was statistically significant for the COPD patients with a baseline BEC $\geqslant$ 2% or $\geqslant$ 200 cells/μl, RR = 0.82 (0.73, 0.93) or 0.79 (0.70, 0.89) respectively, while the RR of ECOPD between ICS and non-ICS treatment was statistically insignificant for the COPD patients with baseline BEC $<$ 2% or $<$200 cells/μl, RR = 0.97 (0.87, 1.08) or 0.97 (0.86, 1.08), suggested that ICS therapy was beneficial to the improvement of ECOPD in patients with a baseline BEC $\geqslant$ 2% or BEC $\geqslant$ 200 cells/μl.

Conclusion: Our research shows that a BEC $\geqslant$ 200 cells/μl or $\geqslant$2% is likely to become the cutoff value of ICS treatment for ECOPD. Moreover, we believe that the baseline BEC can be used as a biomarker for predicting ECOPD. The stability of BEC requires special attention.

Keywords: biomarker, chronic obstructive pulmonary disease, eosinophil, exacerbations of COPD, inhaled corticosteroid

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Introduction

Chronic obstructive pulmonary disease (COPD) is an inflammatory lung disease that affects 384 million people worldwide and causes 3.2 million deaths each year.[1] At present, the drug treatment for COPD is usually a combination of airway relaxants and inhaled anti-inflammatory drugs. The guidelines generally recommend a 'one size fits all' approach to COPD patients with different clinical features. However, despite the use of all the recommended therapies, some patients still have poor control of symptoms. In the era of personalized medical treatment, the simplicity of recommending only one treatment option in each situation of airway diseases may be considered outdated, and there is an urgent

need for more targeted treatment strategy for patients.

Eosinophils (EOSs) develop and circulate briefly in the bone marrow, redistribute to the organs, including the thymus and gastrointestinal tract, and spread to the lungs to a lesser extent.[2] Transcription factors and cytokines, such as interleukin-3, interleukin-5, and granulocyte macrophage colony-stimulating factor, are critical for the differentiation of EOSs, while interleukin-5 plays a key role in their maturation, recruitment, and activation at the inflammatory site. Currently, studies have shown that EOSs lead to airway inflammation and bronchial hyperresponsiveness and are important cells leading to asthma. However, the role of EOSs in COPD remains unclear. Some studies reported that the risk of exacerbations of COPD (ECOPD) increased with the change of blood EOS counts (BECs) in the general and clinical populations,[3–5] as well as in *post hoc* analysis of clinical trials;[6–9] while others reported that there was a lack of correlation between BEC and ECOPD.[10–14] Recently, a clinical trial revealed that mepolizumab, an anti–IL-5 monoclonal antibody (mAb), could reduce the moderate or severe exacerbation of COPD patients with high BEC,[15] indicating that BEC was a useful biomarker for the identification of eosinophilic inflammation that can be targeted for therapy. Whether BEC can be a biomarker to predict ECOPD patients and the exact BEC threshold before inhaled corticosteroids (ICSs) have an effect is debated.

The following are the two major objectives of this meta-analysis: the first is to determine if BEC can serve as a prognostic biomarker of COPD outcomes, and the second is to determine which level of BEC is effective for ICS treatment.

Methods

Protocol and guidance

The guidelines used in this review and meta-analysis are the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA).[16]

Eligibility criteria

In this study, randomized controlled trials (RCTs) and *post hoc* analyses of RCTs were included to evaluate whether BEC was a marker of the response of patients with COPD to ICS. The patients in the included studies were all patients with COPD divided into two groups according to the cutoff point of BEC, that is, above and below the cutoff point. Patients with asthma/allergy were excluded. The intervention measures in all studies were treatment with ICS, while the controls were not treated with ICS. The outcome of all studies was the change in forced expiratory volume in 1 s (FEV_1) from baseline, Saint George's Respiratory Questionnaire (SGRQ) total score change from baseline, or the rate ratio (RR) of ECOPD.

The observational cohort studies were included to evaluate whether the BEC is a prognostic biomarker in patients with COPD. The patients in the included studies were all patients with COPD divided into two groups according to the cutoff point of BEC, that is, above and below the cutoff point. The outcome of all studies was the RR of prognostic ECOPD or the all-cause mortality hazard ratio (HR).

Information sources and search strategy

We searched articles published before 15 May 2021 in the following four electronic databases: Web of Science, Cochrane Library, EMBASE, and PubMed. These articles were manually screened, regardless of the language or data, using the following search terms: ((biomarker [Title/Abstract]) OR (marker [Title/Abstract])) AND (eosinophil) AND ((COPD[Title/Abstract]) OR (chronic obstructive pulmonary disease [Title/Abstract]) OR chronic obstructive pulmonary disease [MeSH Terms]).

Study selection

The titles and abstracts of the studies were independently screened by two methodologically competent reviewers to determine whether the cited articles met the eligibility criteria. Only after they reached an agreement over differences through consensus discussion or arbitration by a third reviewer could they read the full text and extract relevant data. The reasons for inclusion or exclusion were documented in detail. Case reports, letters, and minutes of meetings were not included. The PRISMA flowchart was used to summarize the study selection processes.

Data extraction

Two investigators initially used a predefined data extraction sheet to independently perform data

extraction from each included study, such as sputum or BEC cut point, primary endpoint, counts and effect estimates, country, follow up years, title, conclusion, and other data, including study design, grouping and number of people in the group, sample size, authors, publication year, population, age, and male%. The third investigator independently verified the data to ensure accuracy. If no data were available in digital format, we estimated data from the graphs using the free software Plot Digitizer.

Definition of outcomes

Primary outcomes

1. The difference in the mean change in FEV_1 between ICS therapy and non-ICS therapy.
2. The difference in the mean change in SGRQ score between ICS therapy and non-ICS therapy.[17]
3. The RR of ECOPD between ICS therapy and non-ICS therapy.
   Remark: Each of the three outcomes above has the following two pooled effect values: one is for COPD patients whose BEC is above the cutoff point and the other is below the cutoff point.
   The above three outcomes were used to determine whether ICS is a useful treatment for patients with COPD and high BEC.
4. The RR of prognostic ECOPD between patients with baseline BEC above and below the cutoff point (cutoff point = 2%, 3%, 4%, 5%, 150, 200, 300, 400, and 500 cells/μl).
5. The HR of all-cause mortality between patients with a baseline BEC ⩾ cutoff point and a BEC < cutoff point.
   The above two outcomes were used to determine whether BEC can serve as a prognostic biomarker of COPD outcomes.

Secondary outcomes. The mean difference in baseline FEV_1/FVC and the odds ratio (OR) of the baseline GOLD III + IV between a BEC ⩾ 2% and a BEC < 2% among patients with COPD.

Statistical analysis

The random effects model and inverse variance method were used to summarize the effect size assuming heterogeneity always existed. We reported the pooled estimates as the weighted mean difference along with their respective 95% confidence interval (CI). Cross-study heterogeneity was assessed using the Cochran Q test, and a p-value < 0.10 was considered significant. We also calculated the I^2 statistic as a measure of cross-study inconsistency, and statistical heterogeneity was considered significant when the I^2 index > 50%. This meta-analysis was performed using RevMan v5.3 (Cochrane Collaboration, Copenhagen, Denmark). We originally intended to assess publication bias by using visual inspection of funnel plots and the Egger regression asymmetry test. We were unable to conduct a formal test because there were fewer than 10 studies available for comparisons.

Assessment of risk of bias in individual studies

The qualities of RCTs were assessed using the Cochrane Handbook for Systematic Reviews of Interventions. We assessed the risk of bias for the following domains: selection (random sequence generation, allocation concealment); performance (blinding of participants and personnel); detection (blinding of outcome); attrition (incomplete outcome data); reporting (selective reporting); and other unclear bias.[18] To assess the risk of bias of observational studies, we followed the Newcastle-Ottawa Quality Assessment Scale. The NOS statement was judged on three broad perspectives (selection, comparability, and outcome) consisting of eight items.[19]

Additional analysis

In addition to the cutoff point of BEC 2%, we planned to analyze multiple cutoff points of BEC (3%, 4%, and 5%, and 150, 200, 300, 400, and 500 cells/μl).

Results

Study selection

The initial search of four databases yielded 724 publications. After reading the title and abstract and excluding duplicate and irrelevant articles, we obtained 232 articles. After manually reading the full text, 157 articles were excluded, including review articles ($n = 59$), invalid grouping ($n = 43$), and no available data ($n = 88$). In the end, 42 articles were included in the meta-analysis (Figure 1).

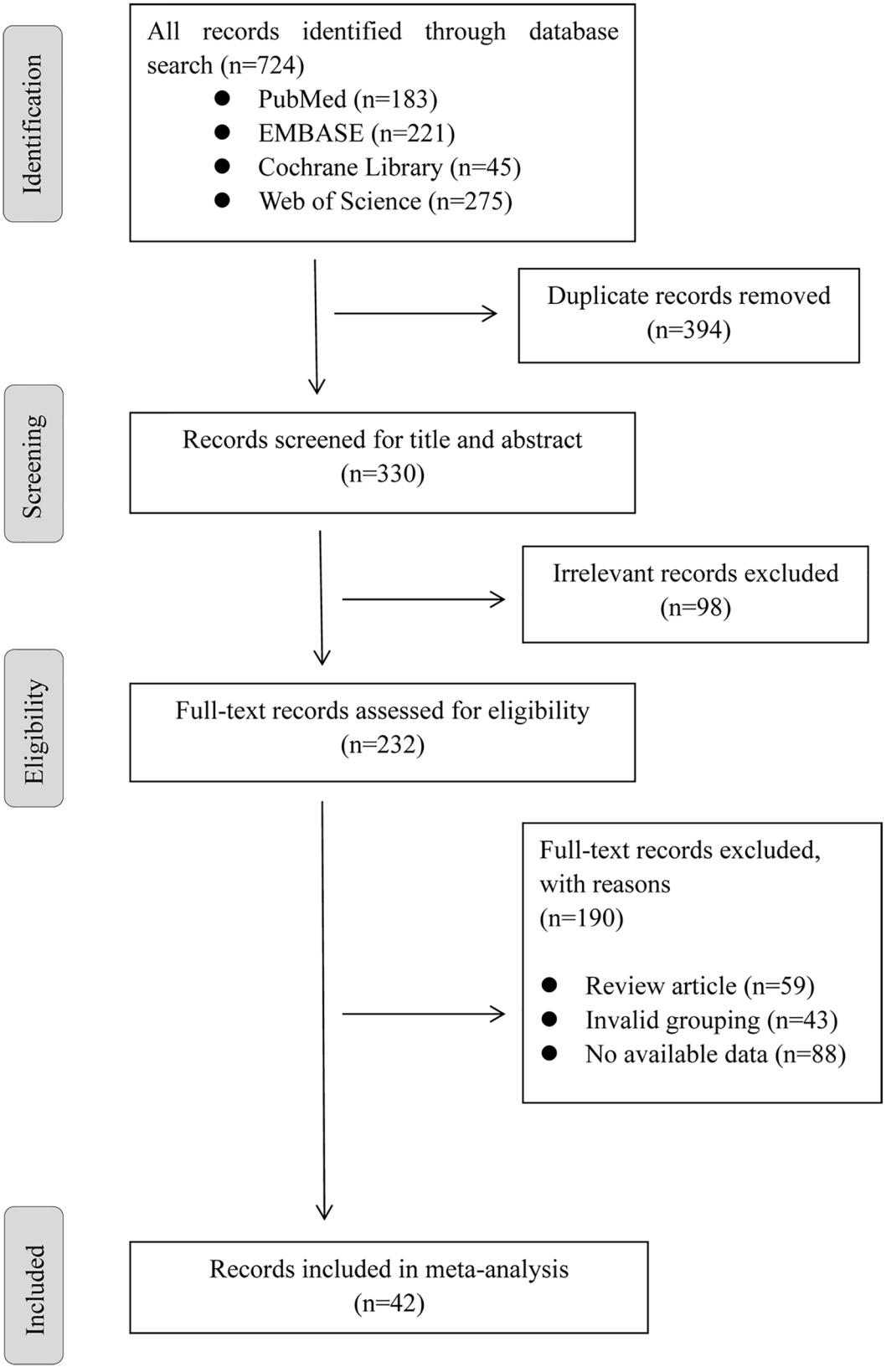

Figure 1. Flowchart of study selection.

Study characteristics and risk of bias within studies

A total of 42 studies, comprising a sampling of 188,710 subjects, were summarized and compared in this meta-analysis. Among them, 13 RCTs (three RCTs from the same study Pavord *et al.*[20]) were used to assess whether BEC was a marker of response to ICS in COPD patients. All 13 RCTs were double-blind, ten of which did not use placebo, and the randomization was described. Since Singh 2020 pooled data from 11 clinical trials, there may be a high risk of selection bias and reporting bias. We know that continued smoking is associated with an impaired response to ICS and thereby affects the attainment of important clinical outcomes in COPD patients; therefore, in all RCTs included in this study, smoking status was balanced between groups. We used 29 cohort studies to analyze the relationship between BEC and the clinical characteristics of patients with COPD and whether the level of BEC was a marker for the prognosis of COPD patients. Most of these cohort studies obtained records from electronic healthcare records, and there were no studies with low quality, as evaluated from patient selection, comparability, exposure assessment, or outcome assessment. The mean age of the population in all studies was greater than 60 years, of which 16 studies had a mean age greater than 70 years. The detailed information of each study is listed in Table 1. Risk-of-bias assessments of RCTs are reported in Supplemental Figures S1 and S2, and risk-of-bias assessments of observational studies are reported in Supplemental Table S1.

Synthesis of results

Primary outcomes

FEV_1: mean change from baseline; RCT, randomized control trial. Relative BEC: First, the mean difference in the change in FEV_1 was significant between ICS and placebo users or between ICS and non-ICS users in COPD patients with a baseline BEC $\geq$ 2% [mean difference (MD) = 38.76 (20.18, 57.34) and 32.03 (1.95, 62.11), respectively]. In contrast, a significant mean difference change in FEV_1 was not found in COPD patients with a baseline BEC $<$ 2%. The results showed that the effect of ICS on FEV_1 was significantly better than that of placebo or non-ICS in COPD patients with a baseline BEC $\geq$ 2%. Second, a mean difference change in FEV_1 was not found between ICS + long-acting b2-agonist (LABA)/long-acting muscarinic antagonist (LAMA) and LABA/LAMA users, regardless of whether the COPD patients had a baseline BEC $\geq$ 2% or $<$2% (Table 2).

Absolute BEC: We analyzed the thresholds of 150 and 300 cells/μl, and there was no difference in FEV1 mean changes between ICS and non-ICS therapy, whether in the group below the threshold or above the threshold (Table 2). The results suggested that dividing patients by a cutoff point of 150 or 300 cells/μl could not distinguish whether ICS was beneficial to the improvement of FEV_1 (Table 2).

SGRQ: mean change from baseline. A mean difference change in SGRQ was not found between ICS and placebo users, between ICS and non-ICS users, or between ICS+LABA/LAMA and LABA/LAMA users, regardless of whether the COPD patients had a baseline BEC $\geq$ 2% or $<$2% (Table 2).

The RR of ECOPD between ICS therapy and non-ICS therapy. Relative BEC: First, the RR of ECOPD between ICS and non-ICS treatment was statistically insignificant, regardless of whether the COPD patients had a baseline BEC $\geq$ 3% or $<$3% [RR = 0.83 (0.66, 1.04) and 0.98 (0.86, 1.12), respectively]. The results suggested that dividing patients by a cutoff point of 3% could not distinguish whether ICS was beneficial to the improvement of ECOPD. Second, the RR of ECOPD between ICS and non-ICS treatment was statistically significant for COPD patients with a baseline BEC $\geq$ 2% [RR = 0.82 (0.73, 0.93)], while the RR of ECOPD between ICS and non-ICS treatment was statistically insignificant for COPD patients with a baseline BEC $<$ 2% [RR = 0.97 (0.87, 1.08)]. The results suggested that ICS therapy was beneficial to the improvement of ECOPD in patients with a baseline BEC $\geq$ 2%, but it showed no difference in COPD patients with a baseline BEC $<$ 2% (Table 3).

Absolute BEC: We analyzed the thresholds of 150, 200 and 300 cells/μl. Only the RR of ECOPD between ICS and non-ICS treatment was statistically significant for the COPD patients with a baseline BEC $\geq$ 200 cells/μl [RR = 0.79 (0.70, 0.89)], while for the thresholds of 150 and 300 cells/μl, the RR of ECOPD between ICS and non-ICS treatments was not statistically significant for COPD patients regardless of whether baseline BEC was greater than or less than the threshold. The results suggested that ICS therapy was beneficial to the

Table 1. Characteristics of included studies.

Study	Study design	Age	Male %	Sample size	Cut point	Country	Follow-up
Aksoy *et al.*[21]	Observational cohort	67 (59–75)	72.0	10,593	2%	Turkey	0
Bafadhel *et al.*[22]	Observational cohort	72 (48–89)	47.7	243	⩾200 cells/μl and/ or ⩾2%	UK	1 year
Bafadhel *et al.*[23]	RCT double-blind	70 (49–87)	55.0	109	2%	UK	6 weeks
Barnes *et al.*[9] ISOLDE [9]	RCT double-blind	63.5 ± 7.34	82.0	738	2%	UK	3 years
Bélanger *et al.*[24]	Observational cohort	68.7 ± 9.4	56.6	479	⩾200 cells/ml and ⩾2%	Canada	1 year
Chan *et al.*[25]	Observational cohort	74.2 ± 8.3	91.5	247	2%	Hong Kong	1 year
Chapman *et al.*[26]	RCT	65.3 ± 7.80	70.6	743	2% 150, 300 cells/μl	UK	26-weeks
Cheng and Lin[27]	Observational cohort	68.7 ± 19.2	81.2	248	3%	Taiwan	0
Couillard *et al.*[28]	Observational cohort	69.3 ± 11.0	50.9	167	2%	USA	1 year
Disantostefano *et al.*[29]	Observational study	–	59.7	4071	2%	USA	0
Duman *et al.*[30]	Observational cohort	70 (61–80)	66.9	1704	2%	Turkey	6 months
Ferguson *et al.*[31]	RCT	64.9 (7.8)	72.0	1902	150 cells/μl	USA	24 weeks
Gonzalez-Barcala *et al.*[32]	Observational cohort	74.34 (11.1)	77.1	358	200, 300, 400 cells/μl	Spain	30 days
Hasegawa and Camargo[33]	Observational cohort	71 (62–79)	57.0	3084	300 cells/μl	USA	1 year
Hastie *et al.*[14]	Prospective cohort (SPIROMICS)	65 (59–71)	59.0	2499	200/μl	USA	1 year
Hegewald *et al.*[34]	Observational cohort	68.4 ± 11.6	50.7	2445	70, 220, 300, 400, 500 cells/μl	USA	1 year

(Continued)

Table 1. (Continued)

Study	Study design	Age	Male %	Sample size	Cut point	Country	Follow-up
Kerkhof *et al.*[4]	Observational cohort	70 ± 10	56.0	8318		UK	>1 year
Landis *et al.*[35]	Observational cohort	71.1 (10.6)	51.5	55114		UK	1 year
Lv *et al.*[36]	Observational cohort	65.69 ± 9.96	55.7	174	2%, 4%	China	0
Mendy *et al.*[37]	Observational cohort	–	75.1	431	2%	USA	36 months
Nishimura *et al.*[38]	Observational cohort	74.9 ± 6.7	91.1	135	100, 300 cells/μl	Japan	0
Oh *et al.*[39]	Prospective cohort	66.9 ± 7.5	97.5	629	High (⩾5%), middle (2–5%), low (<2%).	South Korea	2.2 years ± 1.8
Oshagbemi *et al.*[40]	Observational cohort	64.8 (10.8)	55.5	32,693	2%, 4%, 6%, 340 cells/μl	Netherlands	3 years
Papi *et al.*[41]	RCT	63.8 (7.92)	75.5	1765	2%, 3%, 4%	Italy	52 weeks
Papi *et al.*[42]	RCT	64.4 (7.7)	72.0	1532	200 cells/μl, 2%	Italy	52 weeks
Pascoe *et al.*[6]	A secondary analysis of data from two double-blind RCTs	63.8 (9.2)	59.0	3177	2%	USA	1 year
Pavord *et al.*[20] (SCO30002)	RCT double-blind	64.4 (9.08)	87.0	373	2%	UK	1 year
Pavord *et al.*[20] (SCO40036)	RCT double-blind	64.3 (8.06)	82.0	1269	2%	UK	1 year
Pavord *et al.*[20] (SFCB3024)	RCT double-blind	63.1 (8.49)	77.0	1403	2%	UK	1 year
Peng *et al.*[43]	Observational cohort	71.1 ± 9.6	73.2	123	200, 300, 400 cells/μl	China	12-month
Poder *et al.*[44]	Observational cohort	68.9 ± 9.4	52.0	479	⩾200 cells/Ml and/or ⩾2%	Canada	1 year
Prins *et al.*[45]	Observational cohort	70.4 (8.7)	59.0	207	2%, 300 cells/μl	Netherlands	180 days

(Continued)

Table 1. (Continued)

Study	Study design	Age	Male %	Sample size	Cut point	Country	Follow-up
Roche *et al.*[46]	Observational cohort	64.8 (7.73)	77.8	3079	(2%, 3% and ⩾3%, 5%) 150, 300 cells/μl	France	1 year
Serafino-Agrusa *et al.*[47]	Case control	72.9 ± 8.6	90.0	132	2%	Italy	2 years
Siddiqui *et al.*[7]	A secondary analysis of data from double-blind RCT	63.6 (8.3)	73.6	1184	110.4, 181.6, 279.8	UK	48 weeks
Singh *et al.*[48]	RCT	65.1 (8.6)	74.1	22,125	150 300 cells/μl	UK	Minimum of 48 weeks
Song *et al.*[49]	Prospective cohort	69.5 ± 7.4	95.9	467	200, 300, 400, 500, 600 cells/μl	Republic of Korea	1 year
Vedel-Krogh *et al.*[50]	Prospective study	71 (66–78)	75.0	7180	⩾340 cells/μl	Denmark	3.7 years
Vestbo *et al.*[51]	RCT	63.4 (8.7)	77.0	2691	200 cells/μl, 2%	Italy	52 weeks
Watz *et al.*[8]	A secondary analysis of data from double-blind, parallel-group RCT	64.1 (8.6)	82.0	2420	2%, 4%	Germany	1 year
Yun *et al.*[52] (COPDGene)	Observational cohort	68.27 (8.29)	64.5	1553	300 cells/ml	USA	3 years
Yun *et al.*[52] (ECLIPSE)	Observational cohort	63.86 (6.8)	72.7	1895	300 cells/ml	USA	3 years
Zeiger *et al.*[5]	Observational cohort	71.5 (9.6)	57.1	7245	50 150 300 400 500	USA	1 year
Zhang *et al.*[53]	Observational cohort	90% > 60	70.9	829	150, 200, 300 cells/μl	China	46 months (33–54)
Zysman *et al.*[10]	Observational cohort	62 (55–70)	72.6	458	2% 3% 4%	France	48 months
Total studies	42			188,710			

Table 2. FEV_1 mean change and SGRQ score change from baseline.

Outcome	Comparisons	Effect size (BEC < 2%)	Effect size (BEC ⩾ 2%)	Studies included
MD of FEV_1 change	ICS *versus* non-ICS	2.36 (−26.23, 30.95)	30.71 (−0.11, 61.52)	9
	ICS *versus* placebo	23.56 (−24.64, 71.77)	38.76 (20.18, 57.34)	4
	ICS + LAMA/LABA *versus* LAMA/LABA	0.82 (−42.17, 43.82)	27.15 (−13.10, 67.39)	6
	ICS *versus* non-ICS	Effect size (BEC < 150 cells/μl)	Effect size (BEC ⩾150 cells/μl)	3
		−22.33 (−64.20, 19.54)	8.33 (−66.82, 83.49)	
		Effect size (BEC < 300 cells/μl)	Effect size (BEC ⩾ 300 cells/μl)	
		0.52 (−63.72, 64.77)	38.16 (−63.44, 139.77)	
MD of SGRQ score change	ICS *versus* non-ICS	−1.30 (−4.05, 1.45)	−1.12 (−2.60, 0.35)	6
	ICS *versus* placebo	−1.97 (−6.62, 2.68)	−2.85 (−7.95, 2.26)	2
	ICS + LAMA/LABA *versus* LAMA/LABA	−0.62 (−3.35, 2.11)	−0.32 (−1.29, 0.65)	5

BEC, blood eosinophil counts; FEV_1, forced expiratory volume in one second; ICS, inhaled corticosteroid; LABA, long-acting b2-agonist; LAMA, long-acting muscarinic antagonist; MD, mean difference; SGRQ: Saint George's Respiratory Questionnaire.

Table 3. Rate ratio of the exacerbations of COPD between ICS therapy and non-ICS therapy in patients with baseline BEC ⩾ cutoff points and BEC < cutoff points.

Cutoff points	⩾Cutoff points	<Cutoff points
2%	0.82 (0.73, 0.93)	0.97 (0.87, 1.08)
3%	0.83 (0.66, 1.04)	0.98 (0.86, 1.12)
150 cells/μl	0.79 (0.62, 1.01)	0.93 (0.77, 1.11)
200 cells/μl	0.79 (0.70, 0.89)	0.97 (0.86, 1.08)
300 cells/μl	0.76 (0.48, 1.21)	1.06 (0.92, 1.23)

BEC, blood eosinophil counts; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid.

improvement of ECOPD in patients with a baseline BEC ⩾ 200 cells/μl (Table 3).

RR of ECOPD between patients with baseline BEC higher than thresholds versus *baseline BEC lower than thresholds.* Relative BEC: The pooled RRs of ECOPD between patients with a baseline BEC above 2%, 3%, 4%, and 5% and below 2%, 3%, 4%, and 5% suggested that patients with a baseline BEC above the cutoff points always had a significantly (except 2% which was no difference) higher exacerbation rate of COPD during 6 months to 3-years follow-up than their counterparts with a baseline BEC below the cutoff points, and the higher the cutoff point, the bigger the RR (Table 4).

Absolute BEC: The pooled RRs of ECOPD between patients with a baseline BEC above 150, 200, 300, 400, and 500 cells/μl and below 150, 200, 300, 400, and 500 cells/μl suggested that patients with baseline BECs above the thresholds always had a significantly higher exacerbation rate of COPD during the 6-month to 3-year follow-up than their counterparts with baseline BECs below the thresholds, and the risk of ECOPD showed an upward trend with the increase of the thresholds (Table 4).

HR of all-cause mortality in patients with baseline BEC ⩾ thresholds versus *BEC < thresholds.* Relative BEC: The HR of all-cause mortality between patients with a baseline BEC ⩾ 2%

Table 4. Rate ratio of ECOPD in patients with baseline BEC higher than cutoff point *versus* BEC lower than cutoff point.

Item	Cutoff points	Effect size	Studies included
ECOPD	BEC ⩾ 2%	1.19 (0.82, 1.72)	11
	BEC ⩾ 3%	1.38 (1.15, 1.66)	9
	BEC ⩾ 4%	1.52 (1.30, 1.77)	4
	BEC ⩾ 5%	1.75 (1.47, 2.09)	3
	BEC ⩾ 150 cells/μl	1.06 (1.00, 1.12)	3
	BEC ⩾ 200 cells/μl	1.42 (1.10, 1.85)	6
	BEC ⩾ 300 cells/μl	1.24 (1.14, 1.35)	12
	BEC ⩾ 400 cells/μl	1.51 (1.31, 1.75)	7
	BEC ⩾ 500 cells/μl	1.77 (1.46, 2.14)	2
Survival	BEC ⩾ 2%	0.85 (0.57, 1.24)	4
	BEC ⩾ 200 cells/μl	0.80 (0.62, 1.02)	3
	BEC ⩾ 300 cells/μl	0.81 (0.71, 0.93)	5

BEC, blood eosinophil count; COPD, chronic obstructive pulmonary disease; ECOPD, exacerbations of COPD.

Table 5. Secondary outcomes.

Outcome	Effect size	Studies included
OR of GOLD III+IV in patients with baseline high BEC *versus* low BEC	0.98 (0.89, 1.08)	9
MD of baseline FEV_1/FVC in patients with baseline BEC ⩾ 2% *versus* BEC < 2%	0.85 (−0.26, 1.96)	7

BEC, blood eosinophil counts; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; MD, mean difference; OR, odds ratio.

and < 2% was 0.85 (0.57, 1.24), indicating that a difference was not found between patients with a baseline BEC ⩾ 2% and <2% in the prognosis of all-cause mortality during the 6-month to 3-year follow-up (Table 4).

Absolute BEC: The HR of all-cause mortality between patients with a baseline BEC ⩾ 200 and <200 cells/μl was 0.80 (0.62, 1.02), and the HR of all-cause mortality was 0.81 (0.71, 0.93) for the 300 cells/μl threshold, suggesting that the difference was significant between patients with a baseline BEC ⩾ 300 cells/μl and <300 cells/μl in the prognosis of all-cause mortality during the 6-month to 3-year follow-up (Table 4).

Secondary outcomes. The mean difference in the pooled baseline FEV/FVC was statistically insignificant between COPD patients with a baseline BEC ⩾ 2% and <2% [MD = 0.85 (−0.26, 1.96)], while the OR of the pooled GOLD⩾III was statistically insignificant between the COPD patients with a higher baseline BEC and those with a lower baseline BEC [OR = 0.98 (0.89, 1.08)], suggesting that the BEC level cannot distinguish the severity of the disease (Table 5).

Each effect size in Table 2–5 corresponds to a Forest plot. Please refer to the Supplemental Figures S3–S42.

Discussion

A total of 42 studies involving 188,710 patients were included in this study. We discussed the possibility of using BEC as a biomarker for COPD in the following two ways: the first was to assess whether BEC could serve as a prognostic biomarker of COPD outcomes and the second was to assess whether inhaled corticosteroid (ICSs) are a useful treatment for patients with COPD and a high BEC.

BEC threshold to guide ICS treatment

The main goal of COPD patient management is to prevent disease exacerbation. The general treatment for ECOPD is the use of bronchodilators, and the effect of ICS is uncertain. However, the main treatment for asthma is inhaled corticosteroids. Almost all asthma patients can benefit from ICS.[54] If RCTs do not exclude asthma patients, the response to ICS will be overestimated. Therefore, all RCTs included in this study excluded patients with asthma. In patients with COPD, the individual patient response is uncertain, and there is concern about the potential for serious side effects of ICS therapy, such as an increased risk of pneumonia.[55–58] Therefore, current COPD guidelines recommend that treatment should be based not only on the degree of pulmonary impairment but also on the presence of other risk factors.[59] BEC is an easily accessible and interpretable indicator that may be suitable for use as a biomarker to identify which patients are most likely to benefit from inhaled corticosteroids.[6] Many opinions currently hold that $\geqslant$2% is likely to be a relatively appropriate cutoff point for determining treatment efficacy with ICS.[6,20,60] Oshagemi *et al.*[61] found an overall reduction in the risk of moderate or severe exacerbations in patients with an absolute BEC ranging from $\geqslant$100 to $\geqslant$340 cells/μl. Harries *et al.*[62] found three blood eosinophil thresholds of 2%, 150 cells/μl and 300 cells/μl. Our meta-analysis explored more BEC thresholds (including relative BEC of 2% and 3% and an absolute BEC of 150, 200, and 300 cells/μl) to identify the exact phenotypes of COPD that benefit from ICS. We confirmed 2% and 200 cells/μl and rejected 150 and 300 cells/μl and 3%. We found that among COPD patients with a BEC $\geqslant$ 2%, patients treated with ICS had a 17% lower risk of ECOPD than patients not treated with ICS, while no difference was found in COPD patients with a BEC $<$ 2%. Regardless of having a BEC $\geqslant$ 3% or $<$3%, there was no difference in the risk of ECOPD in COPD patients with ICS compared with non-ICS treatment. In addition, we found that among COPD patients with a BEC $\geqslant$ 200 cells/μl, patients treated with ICS had a 21% lower risk of ECOPD than patients not treated with ICS, while no difference was found in COPD patients with a BEC $<$ 200 cells/μl. At BEC thresholds of 150 and 300 cells/μl, there was no difference in the risk of ECOPD in COPD patients with ICS compared with non-ICS treatment. We found that 2% and 200 cells/μl were expected to be the thresholds for guiding ICS.

It is worth noting that the association between EOS and ICS may be more complex than has been anticipated thus far. A study suggested that ICS may affect EOS levels, so the resting EOS threshold to guide ICS treatment of ECOPD may not be appropriate for every individual. The degree of change in EOS after ICS treatment might be a more accurate predictor of whether ICS benefits ECOPD.[63] More clinical trials may be needed to confirm this.

BEC is a potential biomarker of ECOPD

COPD patients are susceptible to periodic deterioration of their disease, which is mainly caused by bacterial and viral pathogens, known as ECOPD. Frequent ECOPD can accelerate lung function decline and has a significant impact on quality of life, morbidity and mortality.[64] Therefore, it is generally believed that a biomarker is needed to predict ECOPD. A recent study by Bafadhel *et al.*[65] showed that BEC predicted the risk of exacerbations. However, it remains controversial to choose a suitable cutoff point. Observational cohort studies were included in our study to evaluate which BEC threshold (150, 200, 300, 400, or 500 cells/μl, 2%, 3%, 4%, or 5%) was a prognostic survival and exacerbation biomarker. We found that in the real world, COPD patients with a baseline BEC above the threshold always have a significantly higher risk of ECOPD than patients with a baseline BEC below the threshold during a follow-up period of 6 months to 3 years,

and the risk ratio increased as the threshold increased. However, this trend did not apply to survival and seemed to be the opposite. Since there are few studies on the association of BEC and survival, this result needs to be interpreted with caution.

Limitations

First, a clear explanation of the mechanism by which BEC pathways regulate the response to ICS and their impact on the progression of the disease is currently lacking. Second, as a biomarker for predicting ECOPD, the stability of BEC is particularly important. Studies have shown that age and sex will affect BEC stability.[66,67] However, the articles included in this study were all based on the BEC at the baseline timepoint, without considering the stability of BEC over a considerable period of time.

Conclusions

In summary, our research shows that a BEC $\geqslant$ 200 cells/μl or $\geqslant$2% is likely to become the cutoff value of ICS treatment for ECOPD. Moreover, we believe that the baseline BEC can be used as a biomarker for predicting ECOPD. The stability of BEC requires special attention. COPD is a multiphenotypic disease with complex causes. We hope to make a contribution to the precise treatment of COPD through our research on the BEC threshold.

Abbreviations

BEC, Blood Eosinophil counts; CI, Confidence Interval; COPD, Chronic Obstructive Pulmonary Disease; ECOPD, Exacerbations of COPD; EOS, Eosinophil; FEV_1, Forced Expiratory Volume in One Second; FVC, Forced Vital Capacity; HR, Hazard Ratio; ICS, Inhaled Corticosteroid; LABA, Long-acting b2-agonist; LAMA, Long-acting Muscarinic Antagonist; MD, Mean Difference; OR, Odds Ratio; RCT, Randomized Controlled Trial; RR, Rate Ratio; SGRQ: Saint George's Respiratory Questionnaire.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

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