Supplementary information

Blood eosinophils on hospital admission for COPD exacerbation do not predict the recurrence of moderate and severe relapses

Balázs Csoma[1], András Bikov[1, 2], Ferenc Tóth[3], György Losonczy[1], Veronika Müller[1], Zsófia Lázár[1]

[1]Department of Pulmonology, Semmelweis University, 25-29 Tömő Str, 1083 – Budapest, Hungary

[2]Manchester University NHS Foundation Trust, Wythenshawe Hospital, Southmoor Road, Manchester, M23 9LT, UK.

[3]Multitárs Ltd., 46/b Bercsényi Str, 1188 – Budapest, Hungary

Corresponding author:

Dr. Zsófia Lázár, MD, PhD

25-29 Tömő Str.

1083 – Budapest, Hungary

Phone: +36 1 355 9733

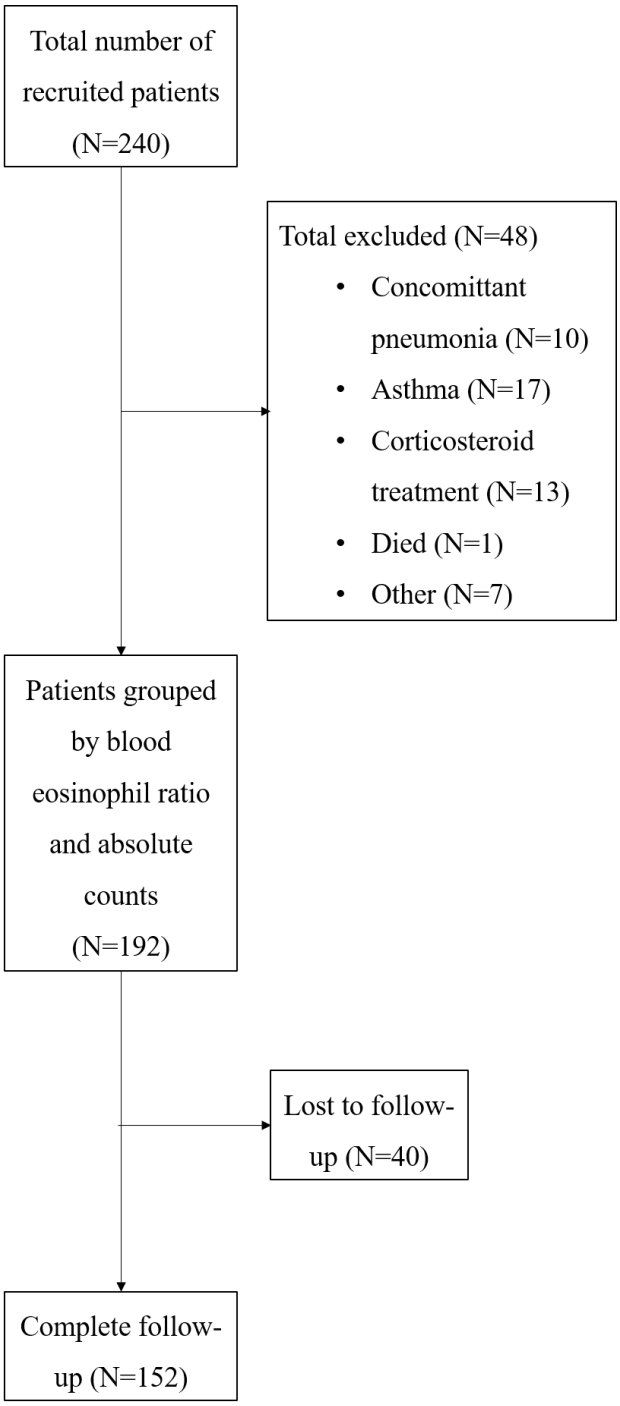
Email: lazar.zsofia@med.semmelweis-univ.hu

Methods

Subjects

All patients admitted with the primary diagnosis of COPD exacerbation (acute worsening of respiratory symptoms in the last 72 hours including increased dyspnoea, chest tightness, sputum production, sputum purulence) to the Department of Pulmonology, Semmelweis University, Budapest, Hungary between 15 February 2017 and 15 August 2018 were screened (Supplementary Figure S1). COPD had been previously diagnosed by a respiratory specialist according to the GOLD recommendations.[1] Exclusion criteria included a history of asthma or a previous positive reversibility testing (>200 ml or 12% increase in post-bronchodilator FEV_1), concurrent chronic pulmonary disease other than COPD, history of pulmonary malignancy in the last 3 years, concomitant pneumonia during the current hospitalization, need for invasive ventilatory support and systemic corticosteroid or antibiotic treatment for any reason 4 weeks prior to admission. Admission corticosteroid use was only allowed when a single dose of methylprednisolone was administered by the ambulance or at the emergency care department (<4 hours before blood sample taking).

Figure S1. Flow chart of patient enrolment



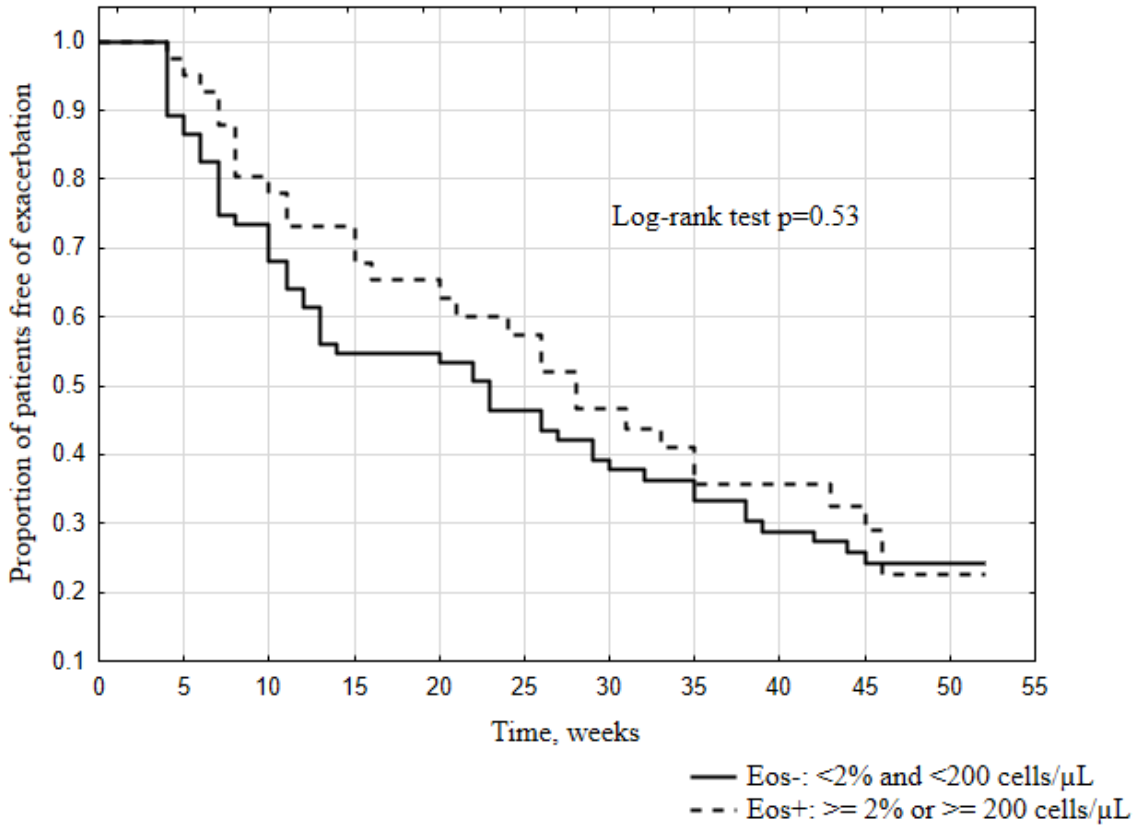
Results

Re-exacerbations in the eosinophilic and non-eosinophilic groups without the patients who received systemic corticosteroid prior to the blood test

One hundred and sixteen patients did not receive systemic corticosteroid before the analysis of full blood count, and 41 patients had an eosinophilic exacerbation (≥ 2% of leukocytes and/or ≥ 200 eosinophils/μl). The proportion of patients with no relapse or with a moderate to severe re-exacerbations did not differ between the groups (Fisher exact test p=0.83).

The time to the first relapse was similar between the groups (Eos+: 26 /11-43/ weeks vs. Eos-: 22 /7-42/ weeks, Mann-Whitney U-test: p=0.38, log-rank test: p=0.53; Supplementary Figure S2), and there was no difference in the Cox proportional hazard ratio, either (HR of the eosinophil group:1.15, 95% confidence interval (CI)=0.73-1.80, p=0.55)

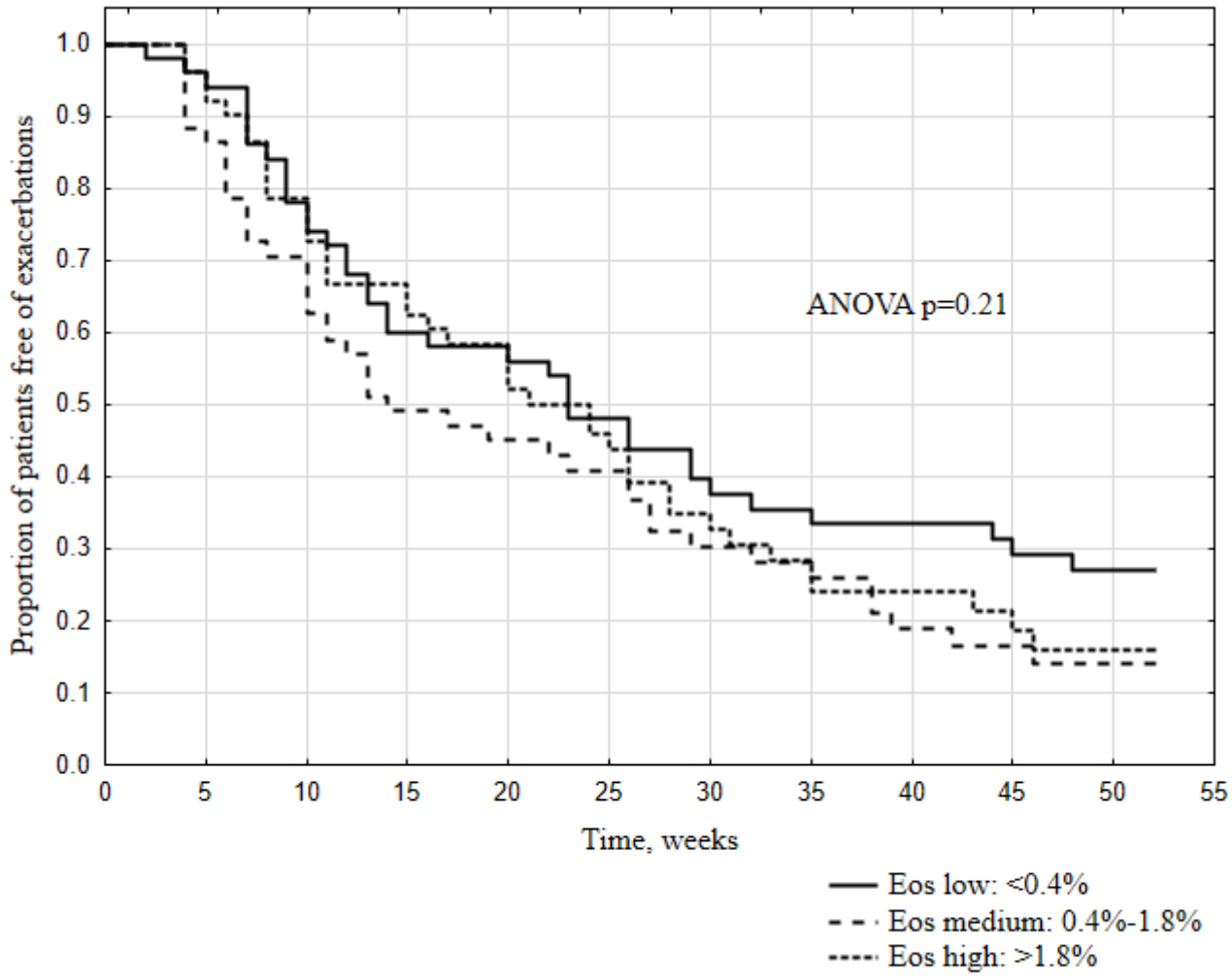
Figure S2. Time to re-exacerbation based on blood eosinophil ratio without the patients who received systemic corticosteroid prior to the analysis of full blood count



Comparing tertiles

We also divided the patients into 3 groups using the tertiles of the eosinophil ratios (<0.4% N=50, 0.4-1.8% N=51, >1.8% N=51). No differences could be detected among the groups in the occurrence of the next exacerbations (no relapse/moderate exacerbation/severe exacerbation Eos low: N=14/11/25, Eos medium: N=9/16/26, Eos high: N=11/12/28, Chi-square p=0.67) or in median exacerbation-free periods (Eos low: 23 /10-52/ weeks, Eos medium: 14 /7-35/ weeks, Eos high: 20 /10-35/ weeks, analysis of variance (ANOVA) p=0.21) as also shown by the Kaplan-Meier curves in Supplementary Figure S3.

Figure S3. Time to re-exacerbation in tertiles of patients based on blood eosinophil ratio



Stability of the types of exacerbations

We determined the type of the exacerbations on recurrence during hospitalization in 73 patients using the same cut-off values as in the original manuscript (eosinophilic: ≥2% of total leukocytes and/or ≥200 eosinophils/µl, non-eosinophilic: <2% of total leukocytes and <200 eosinophils/µl). 75.3% of these exacerbations were of similar type that of the index event. However, 48.1% (13 out of 27) of patients with an index eosinophilic exacerbation had a non-eosinophilic relapse as the next episode, and 10.9% (5 out of 46) of patients with an index non-eosinophilic relapse suffered a subsequent eosinophil exacerbation. The rate of eosinophilic exacerbations was lower on re-admission than during the first relapse ($p<0.001$, Fisher's exact test, Supplementary Table S1).

Table S1. Variability of the rate of eosinophilic (Eos+) and non-eosinophilic (Eos-) exacerbations between the index hospitalization and re-admission by the next relapse

	Re-admission Eos+	Re-admission Eos-	Total
Index exac Eos+	14	13	27
Index exac. Eos-	5	41	46
Total	19	54	73

Adjustment of inhaled drug therapy during hospitalization

Inhaled drug therapy was recorded during hospital admission and discharge and shown in the Eos+ and Eos- groups separately (Supplementary Table S2 and Supplementary Table S3).

Twenty-five patients had not been using inhaled therapy regularly before enrolment to the study (Eos+ N=10 /19.6%/ vs. Eos-: N=15 /14.6%/, p=0.49). In both groups, LABA+LAMA or triple therapy was initiated in most cases (Eos+: 6/10, Eos-: 11/15). During hospital stay, 5 patients in the Eos+ group and 17 patients in the Eos- group had a change in inhaled regimen (p=0.33). In the Eos+ group ICS was retrieved from 2 patients and added to 1 patient, while 4 patients received a second bronchodilator. Among Eos- patients, 7 received add-on ICS and it was withdrawn from 6 patients, and 6 patients were prescribed a second bronchodilator. In addition, during hospital treatment the inhaled drug was switched within class in some patients (Eos+ N=4, Eos- N=4). Importantly, there was no difference in the inhaled drug combinations at discharge between Eos+ and Eos- subgroups (p=0.90).

We also compared the number of inhalers and inhaler types (dry powder inhaler, metered dose inhaler) between patient groups. On admission to hospital, there was no difference neither in the inhaler types (p=0.54), nor in the number of inhalers between patients with Eos+ and Eos- exacerbations (p=0.25).

At discharge from hospital, there was no difference between the study groups in the inhaler types (p=0.44) or in the number of inhalers (p=0.29), either. The inhaler type was changed in 3 patients with Eos+ exacerbations and in 14 patients with Eos- exacerbations during hospitalization (p=0.26).

Table S2. Inhaled drug therapy on hospital admission and at discharge in the eosinophilic (Eos+) group.

	Patients with Eos+ exacerbations	Discharge					
		LAMA	LABA	LAMA+LABA	LABA+ICS	LAMA+LABA+ICS	Total
Admission	no therapy	**2**	0	**3**	**2**	**3**	10
	LAMA	1	0	**1**	0	**1**	3
	LABA	0	0	0	0	0	0
	LAMA+LABA	0	0	9	0	0	9
	LABA+ICS	0	0	**1**	1	**1**	3
	LAMA+LABA+ICS	0	0	**1**	0	25	26
	Total	3	0	15	3	30	51

Table S3. Inhaled drug therapy on hospital admission and at discharge in the non-eosinophilic (Eos-) group.

	Patients with Eos- exacerbations	Discharge					
		LAMA	LABA	LAMA+LABA	LABA+ICS	LAMA+LABA+ICS	Total
Admission	no therapy	**3**	0	**5**	**1**	**6**	15
	LAMA	4	0	**2**	0	0	6
	LABA	0	0	0	0	**1**	1
	LAMA+LABA	0	0	9	0	**6**	15
	LABA+ICS	0	0	**1**	2	**2**	5
	LAMA+LABA+ICS	**2**	0	**3**	0	54	59
	Total	9	0	20	3	69	101

References

1. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report: GOLD Executive Summary. Eur Respir J. 2017;49(3).