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Elevated blood eosinophils in acute COPD exacerbations: better short- and long-term prognosis

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ABSTRACT
Background: Elevated eosinophils in COPD is recognized as a potential risk factor for exacerbations, but the prognostic role of elevated eosinophils during exacerbations of COPD is unclear. We investigated short-term and long-term outcomes in patients with exacerbations of eosinophilic phenotype, compared with patients with low blood eosinophils.
Methods: A single-centre retrospective study of all patients admitted for a COPD exacerbation to Bispebjerg University Hospital in 2010–2011 was established by linking inpatient data with national patient and prescription registries, with a three-year follow-up period. Elevated eosinophils were defined as a blood eosinophil level at admission of $\geq 0.30 \times 10^9$ cells/L.
Results: A total of 811 patients were included; 13.2% had an eosinophilic exacerbation. The eosinophilic group had less need for non-invasive ventilation, shorter inpatient stay, and lower in-hospital mortality, compared to the non-eosinophilic group. However, the eosinophilic and non-eosinophilic groups showed similar risks of readmission (incidence rate ratio[95], 0.99 [0.73–1.36]). Three-year mortality was high in both groups, although lower in the eosinophilic group (40% vs. 54%, p = 0.006).
Conclusions: COPD exacerbations in patients with high blood eosinophil have a better short-term prognosis without higher risk of subsequent exacerbation. Eosinophilic exacerbations have also a lower three-year mortality.

Introduction

The role of eosinophilic inflammation in chronic obstructive lung disease (COPD) exacerbations is not as clear as in asthma but it has recently attracted extensive attention. Many studies have linked high blood eosinophils and COPD exacerbations with subsequent events. The results of these studies are somewhat ambiguous, as some investigators have linked it to a higher rate of exacerbations [1–4], others with less frequent exacerbations [5–7] and some have reported no relationship [8–10]. Blood eosinophils have also been associated with longer hospital stay [11,12] and higher risk of mortality [13–15], however, some have shown no difference in the mortality [6,16,17]. More recently, there has also been an increasing interest in investigating the association between blood eosinophils and response to systemic steroids during an acute exacerbation of COPD [18–20], and studies have used blood eosinophils count to guide steroid treatment [12,19,20].

The association between eosinophilic exacerbations and the long-term risk of readmissions and mortality

in COPD patients has been scarcely described. Previous studies attempted to address this question, but most of them have used blood eosinophils during stable state [21,22], or have followed patients for only a short period of time [2,21,23,24]. Hence, there is need for more evidence on long-term outcomes of elevated blood eosinophils at the time of an exacerbation, in clinically representative patient populations.

We designed a study to examine if COPD patients with high blood eosinophils at the time of admission: 1) are more severely ill at the time of admission, 2) are at higher risk of subsequent readmission, and 3) have a higher mortality compared with the non-eosinophilic phenotypes.

Methods

Study design

We conducted a retrospective study of all COPD patients admitted for an acute exacerbation between

1 January 2010 and 31 December 2011 to Bispebjerg Hospital, which is a public university hospital covering 455.000 residents in Copenhagen, Denmark. We followed patients for 3 years from discharge, or until they emigrated or died – whichever came first. No informed consent was required due to the design of the study. Approval for using data from patient record forms was obtained from the Danish Patient Safety Authority (reference number: 3-3013-1905/1/).

Participants

Subjects were identified in the hospital discharge database using ICD-10 codes for COPD (J41-J44). All patients had a diagnosis of COPD, were >40 years and had a clinical presentation of acute exacerbation of COPD (AECOPD). Thus, no spirometry criteria were used for re-confirming the COPD diagnosis. Acute exacerbation was defined as a flare-up of COPD symptoms, such as dyspnea, sputum production, volume and colour change, which is more than the daily variations. An exacerbation that required administration of systemic steroids and/or antibiotics without need for hospitalization was defined as *moderate exacerbation*, where an exacerbation leading to hospital admission was defined as *severe exacerbation*. *Figure 1* illustrates the flowchart of the cohort selection. *Short-term outcome* was defined as clinical severity, length of stay and in-hospital mortality. *Long-term outcome* was defined as subsequent readmission and 3-year mortality in the follow-up period.

We excluded patients: 1) with known COPD but not admitted with an exacerbation, 2) who were transferred from other departments or hospitals, i.e. not initially admitted for an acute exacerbation of COPD, 3) with no blood eosinophil count at admission, 4) who were discharged against medical advice, and 5) patients without national identification number or CPR-number.

We defined a cut-off value of peripheral blood eosinophils above or below 0.30×10^9 cells/L, which is previously [25] shown to be predictive of sputum eosinophilia (sensitivity = 60%, specificity = 76%). Patients with blood eosinophils $\geq 0.30 \times 10^9$ cells/L were defined as having an eosinophilic exacerbation, and patients with blood eosinophils $< 0.30 \times 10^9$ cells/L as a non-eosinophilic exacerbation.

Data sources

Data variables on each patient were captured at baseline and follow-up from the following sources, using the CPR-number, which is unique for all Danish residents, for linkage [26].
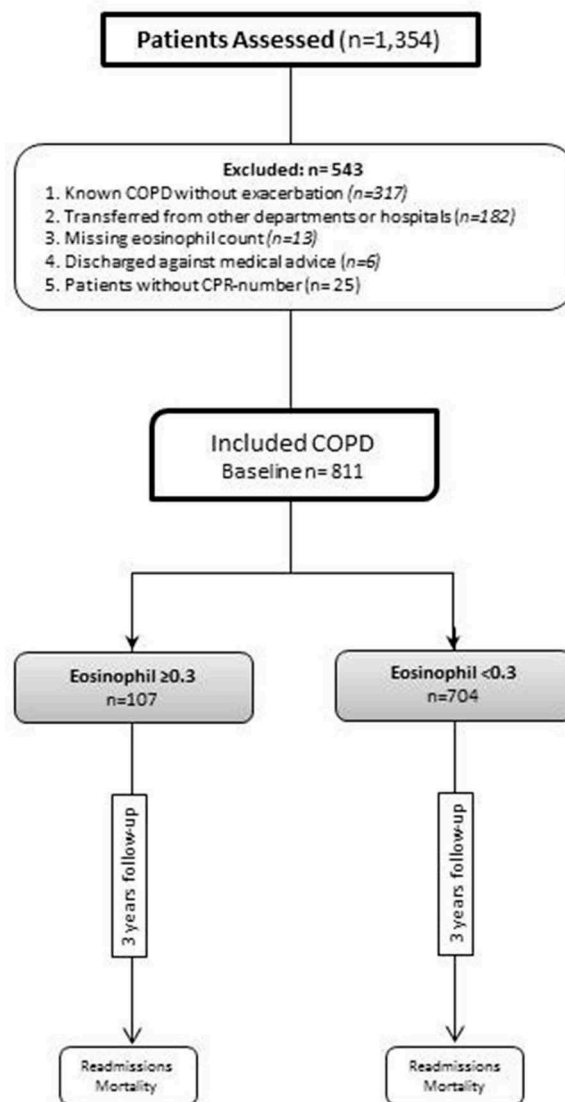
Figure 1. Flowchart of the cohort selection.

Patient record form (PRF)

The PRF is an electronic database, which contains notes on all admissions to any hospital in the capital region of Denmark. We collected data on smoking status, total pack years of smoking, spirometry results and long-term oxygen therapy (LTOT) depending on availability. Only the first value of vital signs, differential blood counts, arterial blood gases, c-reactive protein (CRP), results of sputum culture and chest x-ray during admission was recorded. Data on treatment during admission, such as supplementary oxygen therapy, medications administered (systemic steroids and/or antibiotics), need for non-invasive ventilation (NIV) or stay at intensive care unit, length of hospital stay, need for LTOT at discharge and in-hospital mortality was also collected from PRF.

National patient registries

Data on pre-admission medication and need for systemic steroids and/or antibiotics for the purpose of treating COPD exacerbation in the follow-up period, was obtained from the Danish National Prescription Register (DNPR) [27]. Pre-admission medication was defined as redemption of two or more prescriptions in the past 12 months, and pre-admission comorbidities were also defined based on information from DNPR, a list of ATC-codes used is shown in online supplementary.

Data on emergency room visits due to COPD without requiring hospitalization, visits to outpatient clinics, as well as deaths and cause of death were obtained from the Danish National Patient Register [28].

Statistical methods

Patient characteristics were described as median (25th–75th interquartile range; IQR) since continuous variables were generally not normally distributed. Comparisons between eosinophilic and non-eosinophilic groups were based on *chi-squared- tests* for categorical variables, and *Wilcoxon rank sum tests* for continuous variables. Count data was modelled using negative binomial regression, since the model assumptions for the nested Poisson regression were violated, and was adjusted for follow-up time. Binary data was modelled using logistic regression. Mortality was analysed using logistic regression, as the proportional hazards assumption necessary for Cox regression was violated. Baseline age, sex, smoking, in-home care and LTOT were included as additional covariates (potential confounders) in the regression models. Statistical analyses were performed using Stata 14 (StataCorp LP, College Station; www.stata.com; 2015).

In addition to adjusting for potential confounders, sensitivity analyses were conducted by excluding: 1) patients who received a course of steroid up to 4 weeks prior to baseline admission, 2) patients who had pneumonia or a probable pneumonia on chest x-ray, 3) patients who had asthma COPD overlap (ACO), defined as patients changing discharge diagnosis code from asthma to COPD or the other way around during two hospitalizations in the follow-up period, and 4) patients with bacterial exacerbations. Sensitivity analysis results are provided in the online supplementary.

Results

Baseline characteristics

A total of 811 patients were included in the study; 13.2% (n = 107) had an eosinophilic exacerbation of COPD, defined as blood eosinophils $\geq 0.30 \times 10^9$ cells/L at the time of admission.

Demographic and baseline characteristics of the patients are presented in Table 1. The cohort consisted of 41% men with a median age of 72 years (IQR: 62–81). There were no significant differences in age, sex distribution, forced expiratory volume in 1 s (FEV_1), LTOT or comorbidities of COPD patients with high blood eosinophils compared with those of low eosinophils.

There was an equal proportion of smokers in both groups; however, the non-eosinophilic group had slightly higher pack years (mean 45 vs. 40, *p = 0.04*). The proportion of patients who were seen regularly for their COPD in an outpatient respiratory clinic or by a private pulmonologist was significantly higher in the eosinophilic group (42% vs 31%, p = 0.04), whereas more patients received in-home care in the non-eosinophilic group (49% vs 31%, p < 0.001). CVD and depression were the most common comorbidities in both groups, while the proportional differences between the groups still being statistically not significant (as for all listed comorbidities).

Clinical severity and outcomes of baseline exacerbation

There were no marked differences with regard to vital signs and ABG parameters at baseline between the two groups (Table 2). A radiologic diagnosis of pneumonia, defined as new consolidation on chest x-ray, was less commonly observed in the eosinophilic group compared to the non-eosinophilic group (12% vs 24%, p = 0.003). In the non-eosinophilic group the median CRP (mg/L) was significantly higher (32 [IQR:12–84] vs. 12 [IQR:9–23]), more patients had a positive sputum culture for bacterial agents (22% vs 9%, p = 0.01), and as shown in Table 3 more patients were treated with antibiotics (81% vs 65%, p < 0.001).

Table 3 furthermore shows that the proportion of patients within the two groups that received systemic corticosteroids (95% of the eosinophilic and 91% of the non-eosinophilic group was not significantly different). Patients in the non-eosinophilic were discharged with long-term oxygen (LTOT) about six times more often than the eosinophilic group (6% vs. 1%, p = 0.002). Mean length of stay in patients with elevated eosinophils was significantly shorter [2 days, IQR: 1–5, *p = 0.001*] compared with non-eosinophilic group [3 days, IQR: 1–7, *p = 0.001*]. No significant differences were observed in the treatment at intensive care unit between the groups. Overall, 41 patients died during baseline admission and mortality was significantly higher in the non-eosinophilic group than eosinophilic group (6% vs 1%, p = 0.04) even though in the non-eosinophilic group more patients were

Table 1. Baseline characteristics of COPD patients at the time of admission.

		COPD (n = 811)		
		Eosinophils ≥300	Eosinophils <300	P-value
Number of patients		107 (13)	704 (87)	
Age		72 (62–81)	73 (65–81)	0.3
Sex (M)		49 (46)	286 (40.6)	0.3
Smoking status	Smoker or previous smoker	93 (87)	604 (85)	0.8
	Smoker	*56 (52)*	*348 (49)*	
	Previous smoker	*37 (35)*	*256 (36)*	
	Not smoker	6 (6)	31 (4)	
	Unspecified	8 (7)	69 (10)	
Pack years *(median(IQR))*		40 (25–50)	45 (30–60)	0.04
FEV$_1$ (% of predicted)*		42 (31–52)	40 (30–52)	0.5
COPD managed by	General practitioner	1 (1)	39 (6)	0.04
	Outpatient respiratory clinics (private or hospital)	45 (42)	221 (31)	
	No control	17 (16)	92 (13)	
	Unspecified**	44 (41)	352 (50)	
Comorbidities	Gastro oesophageal reflux	35 (33)	197 (28)	0.3
	Depression	52 (49)	348 (50)	0.9
	Cardio vascular diseases (CVD)	80 (75)	489 (70)	0.3
	Diabetes mellitus	12 (11)	80 (11)	1.0
	Osteoporosis	9 (8)	104 (15)	0.08
	Cancer	1 (1)	9 (1)	0.8
Long term oxygen therapy	Yes	10 (9)	69 (10)	0.8
In-home care	Yes	31%	49%	<0.001
Pre-admission medicine:				
SABA	Yes	56%	44%	0.005
LABA	Yes	6%	6%	0.86
LAMA	Yes	37%	40%	0.82
ICS	Yes	10%	13%	0.51
SABA/SAMA	Yes	22%	17%	0.15

Data presented as number (%) or median (25th-75th interquartile range), unless otherwise stated.

FEV1: Forced expiratory volume in n the first second

SABA: Short acting beta-2 agonist.

LABA: Long acting beta-2 agonist.

SAMA: Short acting muscarine antagonist.

LAMA: Long acting muscarine antagonist.

ICS: Inhalation Corticosteroids

*Last measured FEV1

**Unspecified = not mentioned in the patient record forms

treated with non-invasive ventilation (20% vs 8%, p = 0.002).

Long-term risk of exacerbations

Figure 2 illustrates that the risk of exacerbation during the three-year follow up was similar in the two groups. Negative binominal regression analysis, adjusted for age, sex, smoking, in-home care and LTOT, showed that the eosinophilic group, had a similar risk of readmission with an acute exacerbation, compared to the non-eosinophilic group (IR [95] 0.99 [0.73–1.36]). There was no statistically significant difference in the risk of moderate exacerbations (i.e. exacerbations treated with steroids and/ or antibiotics) between the eosinophilic and non-eosinophilic group (steroids: IR [95] 1.25 [0.92–-1.68]), (antibiotics: IR [95] 1.18 [0.97–1.44]). The eosinophilic group had, however, a lower risk of emergency room visits than those in the non-eosinophilic group (IR [95] 0.59 [0.37–0.85]).

To investigate whether pneumonia diagnosed at the baseline admission had an effect on the prognosis of the eosinophilic and non-eosinophilic AECOPD, we conducted a sensitivity analysis excluding patients with radiologically verified pneumonia or probable pneumonia, but it essentially did not alter the results – table provided in online supplement.

We did attempt to adjust for severity of COPD at baseline by including potential severity markers in a regression analysis (age, smoking history, need for home care and LTOT) in a regression analysis, but this did not substantially alter the results as reported in the online appendix.

Long-term mortality

The overall three-year mortality rate was generally high (53%), but lower in the eosinophilic group (40% vs. 54%, p = 0.006; Figure 3). Logistic regression analysis showed that an eosinophil count of 0.3×10^9 cells/L or more was associated with a lower risk of all-cause mortality (OR [95], 0.60 [0.38–0.96], p = 0.006) compared to an eosinophilic count less than 0.3×10^9 cells/L (Figure 2). This effect remained significant even after adjusting for age, sex, smoking, in-home care and LTOT.

Table 2. Clinical severity of COPD exacerbation at baseline admission.

Clinical outcomes		Total admissions at baseline (n = 811)		
		Eosinophils ≥300 (n = 107)	Eosinophils <300 (n = 704)	P-value
Vital signs	Pulse	92 (81–103)	98 (83–113)	0.01
	Respiration rate	24 (18–28)	24 (20–28)	0.5
	Saturation with oxygen	95 (92–97)	93 (90–96)	0.02
	Temperature, mean	36.4 (36–37)	36.8 (36–37)	<0.001
Chest x-ray	Pneumonia	13 (12)	160 (23)	0.003
	Probable pneumonia	13 (12)	154 (22)	
	Normal	65 (61)	295 (42)	
	Not available	6 (6)	22 (3)	
	Other findings	10 (9)	73 (10)	
Arterial blood gas	pH	7.4 (7.4–7.4)	7.4 (7.3–7.4)	1.0
	pCO2	6 (5.1–7.1)	6 (5.1–7.6)	0.6
	pO2	9.6 (8.4–11.1)	9.3 (8.1–10.9)	0.3
White blood cell counts	Total leukocytes	10 (8.2–12.5)	10.8 (8.3–14.3)	0.07
	Eosinophils	0.4 (0.4–0.6)	0 (0–0.1)	<0.01
	Neutrophils	6.9 (4.6–8.8)	8.5 (6.2–12.0)	<0.001
C-reactive protein mg/L		12 (9–23)	32 (12–84)	<0.001
C-reactive protein >10 mg/L	Yes	63 (59)	552 (78)	<0.001
	No	42 (39)	144 (21)	
	Unspecified	2 (2)	8 (1)	
Blood glucose *mmol/L*		6.5 (6–8)	7.3 (6–9)	<0.001
Growth of bacterial pathogens	Yes	10 (9)	151 (21)	0.01
	No	31 (29)	167 (24)	
	Unspecified	66 (62)	386 (55)	

Data presented as number (%) or median (25th-75th interquartile range), unless otherwise stated.

Discussion

Our results show that patients with AECOPD and elevated eosinophils have a better short-term prognosis than patients with low eosinophils; however, the risk of subsequent exacerbations was the same. Similarly, 3-years all-cause mortality was high in both groups, although lowest in the eosinophilic group. The clinical features and treatment outcome of eosinophilic and non-eosinophilic exacerbations at the baseline (Tables 2 and 3) were mostly similar to subsequent exacerbations at follow-up period – data provided as online supplementary.

Table 3. Clinical outcomes of COPD exacerbation at baseline admission.

Treatment during admission	Total admissions at baseline (n = 811)		
	Eosinophils ≥300	Eosinophils <300	P-value
Need for supplementary O$_2$	79 (74)	579 (82)	0.04
Nebuliser treatment (Ipratropium, Salbutamol)	102 (95)	647 (92)	0.2
Antibiotics (oral or iv)	69 (65)	567 (81)	<0.001
Corticosteroids (oral or iv)	102 (95)	639 (91)	0.1
Non-invasive ventilation	8 (8)	138 (20)	0.002
Treatment at intensive care unit	5 (5)	30 (4)	0.07
Discharged with long-term oxygen therapy*	1 (1)	44 (6)	0.02
Length of stay, *mean* in days	2 (1–5)	3 (1–7)	<0.001
In-hospital mortality	1 (1)	40 (6)	0.04

Data presented as number (%), median (25th-75th interquartile range), unless otherwise stated.
*Not applicable for patients who already had home oxygen or who died under index admission.

### Clinical severity and long-term prognosis

The short-term outcome of elevated eosinophils during an exacerbation was good in our study population, as shown previously [9,22,23,29], but we did not find elevated blood eosinophils to be a predictor of future exacerbations, as reported by others [2–4,30]. The lack of association between elevated eosinophils and risk of exacerbations in the present study could reflect the patient population studied: the majority of patients had low eosinophils (87%), which was associated with more severe exacerbations with a greater need for NIV, as well as higher in-hospital mortality. Additionally, acute exacerbations in patients with non-elevated eosinophils appeared to be commonly caused by pneumonia, as this group likewise had significantly higher CRP and higher positive sputum culture for bacterial agents. Hence, patients with acute exacerbation and low eosinophil count may represent a more severely ill group of COPD patients, compared to the eosinophilic group, with other competing causes for recurrent exacerbations and readmissions, namely a higher risk of infections.

Equally, the longer length of stay in COPD patients with low blood eosinophils in the present study is consistent with previous findings [5,11,12,31,32], and may reflect the poorer response to treatment with systemic steroids in this group.

The prevalence of elevated blood eosinophils in our study population was relatively low at 13.2%, compared to previous studies, which have reported a prevalence

Risk among eosinophilic compared to non-eosinophilic patients
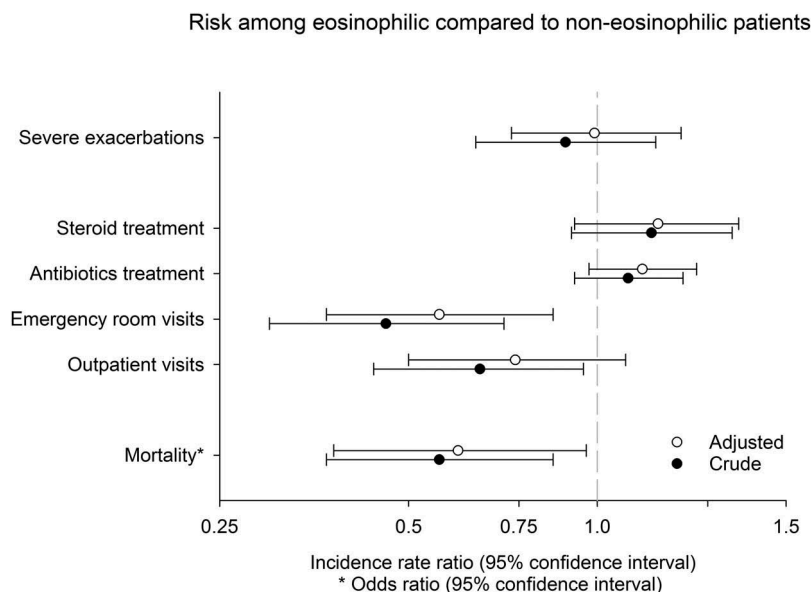
Figure 2. Risk of exacerbations and mortality in eosinophilic compared to non-eosinophilic COPD.
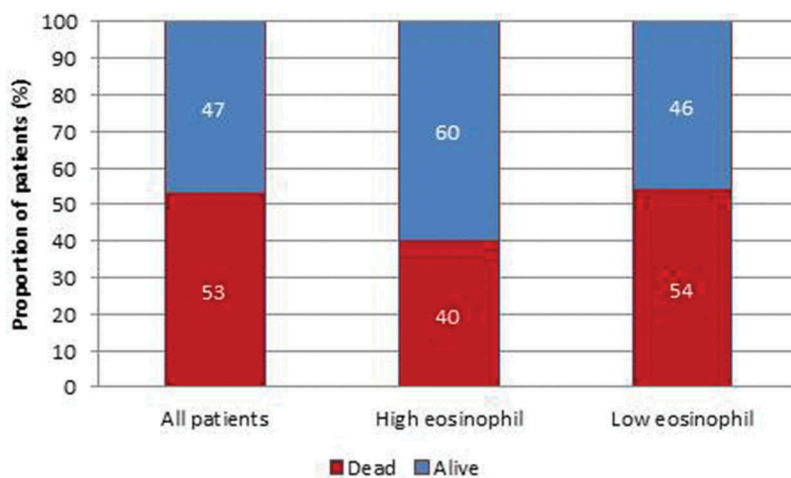
Figure 3. All-cause mortality in follow-up period.

ranging from 10% [14] to 37% [4]. The wide difference between these findings depend on many factors, such as stability of COPD, eosinophil measurement methods and different threshold values, among others. For instance, some studies have reported eosinophils as differential count by cells per μL [6,12,33], some by percentage [14,34,35] and others have used both [31,32,36]. The different measurements of eosinophils can, however, result in vastly different prevalence of high blood eosinophils in COPD patients. For instance, in the WISDOM trial [36] an eosinophils count of ≥300 cells per μL was found in 20% of COPD patients, but by choosing an eosinophil percentage of ≥3%, this number was 32%. The difference is even broader (64%) in studies at population level [3]. A possible explanation for the low level of

eosinophils in our study could be that a significant proportion of our patients (86.8%) had signs of bacterial infection, which is shown to significantly decrease blood eosinophils during an exacerbations [33]. Hence, patients with an otherwise eosinophilic phenotype of COPD might become non-eosinophilic during an exacerbation. Our sensitivity analyses did not indicate that either pre-admission course of systemic corticosteroids or administration of corticosteroids at ER before blood samples were taken altered our results – see online supplementary data.

All-cause mortality
In our study, the overall three-year mortality rate of patients after an AECOPD was very high (53%; Figure 3). Previous studies have reported a wide range of mortality

which depends on follow-up period, for example, 16% for 90-day mortality [37], 19-26% for 1-year mortality [32,38] to 64% for 5-year mortality [38]. Due to the retrospective nature of our study, we were not able to use any indices such as BODE (Body mass index, airway Obstruction, Dyspnea, and Exercise capacity) or CCI (Charlson Comorbidity Index) to predict the mortality in COPD patients, as did other [39]. Our pre-admission data (Table 1) shows that around 50% of the patients in both groups were still smokers. This is worrying, as the GOLD strategy document [40] recommends smoking cessation as first step in the treatment of COPD patients. Furthermore, more than 70% of patients in both groups had serious co-morbidities such as CVD and depression; 10% of the patients were already on LTOT before admission, and every third patient in the COPD group with elevated blood eosinophils and every second patient in the other group had such a low-performance status that they required in-home care.

Compatible with findings from previous studies, the eosinophilic group had significantly lower in-hospital and all-cause mortality compared to patients with non-elevated eosinophils [11,22,34,41,42]. Our results are, however, not in compliance with some authors that have reported no difference in the in-hospital mortality of eosinophilic and non-eosinophilic groups [5,6,32], these findings are, however, statistically not significant.

An explanation for the better clinical outcome for the eosinophilic AECOPD could be a combination of different factors. Singh et al. found that these patients had higher FEV_1, fewer symptoms with lower SGRQ and mMRC scores and less emphysema [43]; others showed that these patients have less frequent readmissions [5–7], fewer comorbidities [44], fewer pneumonias [35,45] and shorter length of stay [5,11,14,31,32], which combined would allow for a better overall long-term survival in COPD patients with elevated eosinophils.

We could not investigate the effect of steroids in our subgroups, as almost all our patients had received steroids. Treatment of AECOPD with systemic steroids in patients with low blood eosinophils can be problematic, as it has been associated with worse outcomes [19]. Furthermore, a recent post hoc meta-analysis has shown that these patients have a higher risk of developing pneumonia when treated with inhaled corticosteroids [45]. This could also explain the higher mortality in our COPD patients with low blood eosinophils, as we showed that these patients had twice as many pneumonias as patients with high blood eosinophils.

Strengths and limitations

Our study has several strengths. First, it represents a real-life study of a large COPD cohort of all patients admitted to hospital over a two-year period (n = 811). Second, the long follow-up period allows for gathering important data on different outcomes. A further unique feature is that it combines clinical and paraclinical data with high-quality data from the national registries, thus ensuring a complete follow-up of the whole study population for readmissions and mortality, which to our knowledge is quite novel. As all studies using register data, our study also has its clear limitations. We had missing data for some variables, for example, FEV_1 and smoking status, as the data were not collected prospectively. Likewise, it was not possible to spirometrically verify the diagnosis of COPD. The percentage of patients receiving pre-admission LABA or LAMA, defined as redemption of ≥2 prescriptions in the past year, was very low. A possible explanation could be that either our cohort did not have a good adherence to treatment, and/or that these patients were not on optimal treatment.

In conclusion, in this real-life retrospective cohort, we found that patients with eosinophilic COPD exacerbations are clinically less severe, have shorter length of stay and have a lower mortality (both in-hospital and 3-year) compared to patients with low blood eosinophils. The risk of subsequent exacerbations was similar in both groups. Despite better short-term prognosis, our findings describe a very high morbidity and mortality in this complete, real-life COPD population, and underline the importance of better management strategies for preventing COPD exacerbations and mortality.

Disclosure statement

No potential conflict of interest was reported by the authors.

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