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Relationship between blood eosinophils, clinical characteristics, and mortality in patients with COPD

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Abstract: In patients with COPD, there is controversy regarding the association of blood eosinophil (Eos) levels with 1) exacerbation frequency and 2) the effect of inhaled corticosteroids for prevention of exacerbations. To determine whether Eos define subgroups of patients exhibiting attributes of COPD clinical phenotypes, we compared clinical features and mortality rates in COPD patients from the Initiatives BPCO French cohort categorized using different thresholds of blood Eos levels. The following data were collected at inclusion: medical and smoking history, occupational exposures, dyspnea, cough and sputum production, exacerbations in the previous year, history of allergy and asthma, nasal symptoms, body mass index, St George Respiratory Questionnaire (SGRQ) total score, post-bronchodilator spirometry, comorbidities, and medications. Three-year survival between groups was compared using Kaplan–Meier analysis. Three sets of analyses were performed to compare patients with ≥2% versus <2%, ≥3% versus <3%, and ≥4% versus <4% Eos. Eos was available in 458 patients (mean age: 62 years, 72% male, mean forced expiratory volume in 1 second: 51% pred), including 235 patients with Eos ≥2% (49%), 149 with Eos ≥3% (33%), and 90 with Eos ≥4% (20%). For all cutoffs, there was no difference between Eos+ and Eos− groups in univariate analyses except for diabetes and SGRQ score (more frequent and more impaired, respectively, in lower Eos categories). In particular, there was no difference in exacerbation rate, history of asthma, or three-year survival. In conclusion, regardless of the cutoff, Eos+ COPD patients exhibited no specific characteristic in terms of symptoms, lung function, exacerbation rate, and prognosis. These findings suggest that the association of higher Eos with exacerbations reported in previous studies could be population specific, which does not support generalizing the use of Eos as a biomarker for COPD phenotyping.

Keywords: COPD, eosinophils, survival, exacerbations, quality of life

Introduction

Several studies have been conducted to better understand the heterogeneity of patients with COPD and to identify different phenotypes and endotypes. More specifically, identifying clinically relevant phenotypes with specific responses to treatments is an important goal for current and future research, in order to allow proper treatment personalization based on the predicted benefit/risk ratio of each available drug class in each individual patient.1 Biomarkers represent an important avenue of research in this area. Several studies suggest that, in patients with COPD, high sputum and blood eosinophil (Eos) counts are associated with specific clinical phenotypes defined by 1) more frequent exacerbations and 2) better response to inhaled corticosteroids (ICS) for exacerbation prevention.2,4 Additionally, ICS therapy has been suggested to reduce
the rate of decline in forced expiratory volume in 1 second (FEV₁) in patients with high blood Eos counts. However, in that study, higher Eos was associated with a decreased preventive effect of ICS on exacerbation risk. Contradictory data have also been found regarding the yield of Eos to predict outcomes and response to oral corticosteroids during acute exacerbations, a relation being shown in some, but not all, studies. Data on the relations between Eos count and long-term survival in COPD patients are scarce.

To determine whether Eos define subgroups of patients exhibiting attributes of COPD clinical phenotypes, possible associations between Eos and clinical characteristics and prognosis in COPD patients were further explored in a French cohort of subjects with spirometry-confirmed COPD.

Methods
Data from the Initiatives BPCO French cohort of smokers and ex-smokers (≥10 pack-years), aged >40 years with spirometry-confirmed COPD (n=1,128 when data were extracted), were analyzed. As previously described, patients from this cohort are recruited by respiratory physicians from tertiary care university hospital centers. A current main diagnosis of asthma is an exclusion criterion, but a past history of asthma represented 13% of the population but did not affect their clinical characteristics, lung function, comorbidities, and treatments. Eos+ patients were not more prone to exacerbations (median, 1 exacerbation/patient/year in both groups, P=0.247), which could not be explained by a more frequent use of ICS or history of asthma (14% vs 13.5% in Eos–, P=0.86) (Table 1). All analyses were repeated using thresholds of 3% and 4% to categorize patients, which provided comparable results (not shown). Even when the population was divided into four groups <2% (235 patients), ≥2%, <3% (74 patients), ≥3% and <4% (59 patients), and ≥4% (90 patients), the only significant differences regarded SGRQ total score and diabetes (Table 2). There was also no significant difference in terms of 3-year survival, among these four groups (Figure 2).

Discussion
The main finding from this real-life cohort study is the lack of noticeable difference in prognosis and in most clinical and lung function features between COPD patients with higher versus lower blood Eos levels, for all tested thresholds of Eos (2%, 3%, and 4%). In this population, half of the participants had Eos ≥2%, which is comparable to what was observed, for example, in the WISDOM study but less than in several other studies of patients with COPD identified from the general population or clinical trials. This finding underscores the heterogeneity of COPD patients recruited in different cohorts. Although patients with a current primary diagnosis of asthma were not recruited in the present cohort, patients with a past history of asthma represented 13% of the population but did not exhibit higher Eos levels (median: 1.9, IQR 0.9–3.4 in both patients with and without associated asthma). In addition, their clinical characteristics and outcomes were similar to
Table 1 Characteristics of 458 patients with COPD according to the 2% blood eosinophil cutoff

| Variables                                | Eos ≥2% (N=223) | Missing values | Eos <2% (N=235) | Missing values | P-values |
|------------------------------------------|-----------------|----------------|-----------------|----------------|----------|
| Sex, M/F                                 | 72.6% (162)/27.4% (61) | 0              | 71.5% (168)/28.5% (67) | 0              | 0.783    |
| Age, years                               | 62 (55–70)      | 0              | 62 (55–70)      | 0              | 0.715    |
| BMI (kg/m²)                              | 25.3 (21.9–29.4) | 0              | 24.2 (21.2–28.4) | 0              | 0.093    |
| Obesity (BMI >30 kg/m²)                  | 22.0% (49)      | 7              | 18.3% (43)      | 0              | 0.326    |
| Smoking habits                           |                 |                |                 |                |          |
| Former smoker                            | 67.6% (146)     |                | 62.6% (144)     |                |          |
| Current smoker                           | 29.6% (64)      |                | 34.3% (79)      |                |          |
| Never smoker                             | 2.8% (6)        |                | 3.0% (7)        |                |          |
| Cumulative smoking (pack-years)         | 36.0 (24.0–54.0) | 22             | 37.1 (22.5–52.5) | 25             | 0.704    |
| History of asthma                        | 13.5% (30)      | 15             | 14.0% (33)      | 13             | 0.855    |
| Hay fever                                | 9.9% (22)       | 0              | 12.3% (29)      | 0              | 0.400    |
| Eczema                                   | 7.6% (17)       | 0              | 8.1% (19)       | 0              | 0.854    |
| Rhinitis/sinusitis                       | 17.5% (39)      | 0              | 20.4% (48)      | 0              | 0.423    |
| Occupational exposures                   | 27.8% (62)      | 0              | 32.3% (76)      | 0              | 0.290    |
| Chronic cough and sputum production      | 65.9% (147)     | 14             | 71.9% (169)     | 0              | 0.166    |
| Exacerbation rate (per patient-year)     | 1.0 (0.0–2.0)   | 5              | 1.0 (0.0–3.0)   | 7              | 0.247    |
| Severe (hospitalized) exacerbation rate  | 0.0 (0.0–0.0)   | 5              | 0.0 (0.0–1.0)   | 7              | 0.174    |

Notes: Data are expressed as the median (quartile 1–quartile 3) or % (n). Data were assessed using chi-square tests or Fisher’s exact tests, as appropriate, for discrete variables, and Wilcoxon tests for quantitative variables.

Abbreviations: BMI, body mass index; Eos, eosinophils; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; mMRC, modified Medical Research Council; SGRQ, St George Respiratory Questionnaire.

that of other patients. This may relate to a tendency of investigators to refrain from including patients with higher Eos counts (Eos was <4% in >80% of the population) in COPD cohorts, even when this is not an exclusion criterion. A similar hypothesis may be proposed to explain why Eos (threshold: 2%) did not predict response to ICS in the Flame trial, where patients with blood Eos >600/mm³ could not be recruited, while higher Eos was significantly associated with response to ICS in several post hoc analyses from previous trials. Discrepancies between study results may also relate to differences in COPD severity: for instance, our population had less severe airflow obstruction than patients from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort (mean FEV₁: 51% pred vs 44% pred). Conversely, patients from the Copenhagen City Heart Study clinical COPD cohort (n=203) had similar FEV₁ levels compared to our population. In this later population, there was a higher rate of severe exacerbations in patients with an Eos level ≥2%, while this relation was surprisingly in the opposite direction for moderate exacerbations. In our population, neither moderate nor severe (ie, hospitalized) exacerbations were different between Eos+ and Eos− groups. Another point to consider when interpreting study results is that, in many cases, Eos count was measured.
### Table 2 Characteristics of 458 patients with COPD according to four different blood eosinophil cutoffs: <2%, ≥2% and <3%, ≥3% and <4%, and ≥4% and <4%

| Variables | <2% (N=235) | ≥2% and <3% (N=74) | ≥3% and <4% (N=59) | ≥4% (N=90) | Missing values | P-values |
|-----------|--------------|---------------------|--------------------|------------|----------------|----------|
| Sex, M/F  | 71.5% (168)  | 73.0% (54)          | 71.2% (42)         | 73.3% (66) | 0              | 0.983    |
| Age, years| 28.5% (67)   | 27.0% (20)          | 28.8% (17)         | 26.7% (24) | 0              |          |
| BMI (kg/m²)| 61 (25–70)  | 61 (55–69)          | 61 (54–69)         | 63 (56–72) | 0              | 0.712    |
| Obesity (BMI >30 kg/m²) | 18.3% (43) | 27.0% (20) | 22.0% (13) | 17.8% (16) | 0 | 0.372 |
| Smoking habits | 5 | 1 | 4 | 2 | 0.484 |
| Former smoker | 62.6% (144) | 72.6% (53) | 61.8% (34) | 67.0% (59) | 0 |
| Current smoker | 34.3% (79) | 27.4% (20) | 32.7% (18) | 29.5% (26) | 0 |
| Never smoker | 3.0% (7) | 0.0% (0) | 5.5% (3) | 3.4% (3) | 0 |
| Cumulative smoking (pack-years) | 37.1 (22.5–52.5) | 38.0 (24.0–50.0) | 39.0 (28.5–55.0) | 31.0 (20.0–55.5) | 11 | 0.379 |
| History of asthma | 14.0% (33) | 13.5% (10) | 11.9% (7) | 14.4% (13) | 0 | 0.972 |
| Hay fever | 12.3% (29) | 8.1% (6) | 5.1% (3) | 14.4% (13) | 0 | 0.240 |
| Eczema | 8.1% (19) | 4.1% (3) | 8.5% (5) | 10.0% (9) | 0 | 0.531 |
| Rhinitis/sinusitis | 20.4% (48) | 17.6% (13) | 18.6% (11) | 16.7% (15) | 0 | 0.866 |
| Occupational exposures | 32.3% (76) | 23.0% (17) | 22.0% (13) | 35.6% (32) | 0 | 0.142 |
| Chronic cough and sputum production | 71.9% (169) | 59.5% (44) | 62.7% (37) | 73.3% (66) | 0 | 0.113 |
| Exacerbation rate (per patient-year) | 5.7 | 7 | 1 | 2 | 0.581 |
| Severe (hospitalized) exacerbation | 0.5 | 7 | 0.3 | 1 | 0.4 | 0.195 |
| mMRC dyspnea grade | 2 | 21 | 7 | 2 | 5 | 6 | 0.665 |
| Ischemic heart disease | 11.5 (27) | 6.8% (5) | 13.6% (8) | 13.3% (12) | 0 | 0.533 |
| Chronic heart failure | 13.2% (31) | 12.2% (9) | 8.5% (5) | 12.2% (11) | 0 | 0.807 |
| Diabetes mellitus | 16.6% (39) | 12.2% (9) | 5.1% (3) | 6.7% (6) | 0 | 0.024 |
| SGRQ total score | 48 | 30 | 43 | 16 | 40 | 9 | 0.047 |
| FEV₁ predicted | 51 | 0 | 35 | 0 | 54 | 0 | 0.878 |
| ICS outside fixed-dose combinations | 23.0% (54) | 23.0% (17) | 15.3% (9) | 24.4% (22) | 0 | 0.570 |
| ICS + long-acting beta-agonist | 36.2% (85) | 43.2% (32) | 44.1% (26) | 38.9% (35) | 0 | 0.575 |
| Long-acting antimuscarinic agents | 34.0% (80) | 28.4% (21) | 35.6% (21) | 28.9% (26) | 0 | 0.655 |
| Oral steroids | 5.1% (12) | 2.7% (2) | 3.4% (2) | 1.1% (1) | 0 | 0.408 |
| Follow-up duration (months) | 51 | 0 | 46 | 0 | 53 | 0 | 0.885 |
| Death rate | 17.1% (40) | 17.6% (13) | 8.5% (5) | 12.4% (11) | 1 | 0.306 |

**Notes:** Data are expressed as the median (quartile 1–quartile 3) or % (n). Data were assessed using chi-square tests or Fisher’s exact tests, as appropriate, for discrete variables, and Wilcoxon tests for quantitative variables.

**Abbreviations:** BMI, body mass index; Eos, eosinophils; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; mMRC, modified Medical Research Council; SGRQ, St George Respiratory Questionnaire.

**Blood eosinophils 4 classes**

Figure 2 Kaplan–Meier analysis for comparison of survival between COPD patients with four different blood eosinophil cutoffs: <2%, ≥2% and <3%, ≥3% and <4%, and ≥4% and <4%. Only once, while it appears to vary above and below the 2% cutoff in up to half of the COPD subjects. Finally, it may be hypothesized that the Eos cutoff influences the results. However, the 2% threshold is the most extensively studied at present, and analyses with a 3% threshold (considering the Eos distribution in this cohort with a Q3 lower limit at 3.4%) did not change our conclusions. Even the analyses performed with a 4% threshold did not provide different results. In our COPD population as in the ECLIPSE cohort, COPD patients with higher Eos counts (≥2%) had significantly lower SGRQ scores, suggesting less impact of COPD despite similar lung function abnormalities. The reason for this is not fully understood. The higher prevalence of diabetes in patients with lower Eos counts is also difficult to explain.
One limitation of the study is that blood Eos were available in only slightly less than half of the population included at the time of data extraction. However, patients with and without available blood Eos levels did not differ in terms of clinical and lung function characteristics or outcomes (not shown), suggesting that Eos measurement was missing at random. Another limitation is the unavailability of absolute Eos counts, which were not recorded in this cohort. However, it is unlikely that they would have provided different results given the tight concordance between analyses performed with the 2%, 3%, and 4% cutoffs.

Given the contradictory data from our study and others regarding the association between Eos and exacerbation risk, exploring the potential predictive value of other biomarkers appears necessary. However, results of a combined analysis of the SPIROMICS and COPD gene studies have been disappointing and lead the authors to conclude that, although some blood biomarkers were significantly associated with the occurrence of exacerbations, none was robust between cohorts; in addition, biomarkers added little altogether to the predictive value of clinical features for exacerbations.17

Conclusion
In this COPD cohort, Eos+ patients (regardless the cutoff chosen) exhibited no specific clinical characteristic, especially regarding symptoms, lung function, exacerbations, and, most importantly, prognosis. Health-related quality of life was better only in Eos+ patients. These findings differ from that of several other studies, which may relate to differences in patients’ populations and underlines that Eos count may not be a generalizable biomarker to define clinical COPD phenotypes.

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Disclosure
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