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Blood Eosinophil Count During Severe Bronchiectasis Exacerbation and Risk of Hospital Readmission

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To the Director,

Bronchiectasis (BE) is the third most common chronic inflammatory airway disease, following asthma and chronic obstructive pulmonary disease (COPD). It is a heterogeneous and complex condition, and recent efforts have focused on identifying phenotypes, endotypes, and treatable traits that may guide precision and personalized treatments[1]. However, our current understanding of these aspects in BE is considerably less extensive than in asthma or COPD, leading to many uncertainties regarding the most effective therapeutic regimens[2-3]. Blood eosinophil count (BEC) is a biomarker of T2-high inflammation that has been widely accepted as a treatable trait, useful for guiding treatments such as inhaled corticosteroids or biologic therapies in asthma and COPD[4]. Recent research suggests that BEC in a stable state is associated with clinical outcomes in BE[5] and may predict responses to inhaled corticosteroids[6-7]. However, there is considerably less knowledge regarding the significance of BEC during exacerbations of BE. The objective of the present study was to investigate whether BEC during severe BE exacerbations requiring hospitalization is related to significant clinical outcomes, independent of BEC during stable phases.

This study involved a retrospective analysis of data from consecutive patients included in a registry of all individuals seen at the BE clinic of the Pulmonology Service of a second-level university hospital. Due to the retrospective design, all patients seen at the BE clinic and included in the registry were eligible for inclusion. Approval was obtained from the hospital and the ethical committee (CEIC Galicia, registry: 2015/63). Patients who were admitted to the hospital after their first visit (index date) to the BE clinic were included in the study. The primary outcome variable was hospital readmission following this initial admission. The following variables were recorded for all patients on the index date: age, sex, FEV_1%, FEV1/FVC%, oxygen saturation (SpO_2), eFACED (exacerbations, FEV_1, age, bronchial infection by *Pseudomonas aeruginosa* [PA], radiological

extension, dyspnea) score; isolation of PA during the previous year; isolation of any potential pathogenic microorganism (PPM) during the previous year; chronic bronchial infection at the index date; non-age-adjusted Charlson comorbidity index; BEC; polymorphonuclear leukocyte (PM) count; platelet count; C-reactive protein (CRP); and treatment at the index date (bronchodilators, inhaled corticosteroids, inhaled antibiotics, azithromycin). Variables obtained during the first hospital admission after the index date included: BEC, PM and platelet count as measured in the emergency room before treatment initiation; CRP; presence of purulent sputum; chest X-ray findings of pulmonary infiltrates; respiratory failure; hemoptysis; fever; isolation of any PPM during admission; isolation of PA during admission; and treatment with systemic steroids or antibiotics during admission. Differences between study groups were assessed using Student's t-test or the chi-square test, as appropriate. A univariable logistic regression analysis was performed with hospital readmission after the first hospital admission as the dependent variable. All variables with a p-value of less than or around 0.1 (i.e., < 0.2) were included in a multivariable Cox proportional hazards analysis, with readmission as the dependent variable. The correlation between BEC at the index date and during admission was evaluated using the Pearson correlation coefficient. Receiver-operating characteristic (ROC) analysis was conducted to identify the BEC cut-off value that best correlated with readmission risk, and Kaplan-Meier curves were generated using this value. Significance was defined as a p-value of < 0.05. Additional details on the statistical analysis are provided in the supplemental file.

A total of 180 patients were included in the registry. Of these, 89 (49%) experienced at least one severe exacerbation after the index date. The most common etiologies of BE were idiopathic, COPD, and post-infectious. The etiologies are detailed in the supplemental file (Table S1). Differences between patients who experienced an exacerbation after the index date and those who did not are presented in the supplemental file (Table S2). One patient died during admission and was excluded; the remaining 88 patients were included in the analysis. Among these, 62 (70.4%) were readmitted due to exacerbation, with a median of 350 days between admissions (interquartile range: 130 – 665). Table S3 in the supplemental file presents the results of the univariable logistic regression analysis, with hospital readmission as the dependent variable. In this analysis, BEC on admission (but not at the index date), the Charlson index, eFACED score, and respiratory failure during admission significantly correlated with the risk of readmission. Table 1 shows the results of the multivariable Cox proportional hazards analysis, using variables selected from the univariable analysis as independent variables and readmission as the dependent variable. The eFACED score and BEC on admission were both associated with an increased risk of readmission, with the hazard ratio of 1.003 per unit increase in BEC (cells/mm^3). ROC analysis (see supplemental file) identified a cut-off value of ≥ 150 eosinophils/m m^3 as providing the best combination of sensitivity and specificity for predicting readmission risk. Figure 1 illustrates the Kaplan-Meier curves for the risk of readmission based on this cut-off value. There was no significant correlation between BEC at the index date and during admission (R=0.07, p=0.49).

Several studies have analyzed the inflammatory profile of BE during stable states, frequently using BEC as a surrogate for airway inflammation. As seen in other chronic respiratory diseases, this biomarker has been associated with clinical outcomes. Specifically, both eosinopenia and eosinophilia have been linked to a higher risk of exacerbations[6]. It remains unclear whether the inflammatory profile during BE exacerbations correlates with that observed during stable phases of the disease or whether BEC during exacerbations has independent clinical significance. To our knowledge, only one study has assessed the clinical significance of BEC during BE exacerbations, finding that patients with higher BEC experienced longer hospital stays and incurred higher hospitalization costs[8]. In other inflammatory airway diseases, such as COPD, BEC in stable states

correlates to some extent with BEC during exacerbations, although the correlation is not perfect and does not allow precise predictions of the inflammatory profile of future exacerbations[9-10]. Indeed, the inflammatory profile of COPD exacerbations is heterogeneous[11], and BEC during these episodes has both prognostic[12] and therapeutic implications, potentially guiding the treatment of the exacerbation itself[13-14]. Hypothetically, the inflammatory profile during COPD exacerbations could also inform maintenance therapy, although this has not been fully demonstrated[15]. Therefore, it is of interest to study the potential significance of BEC during BE exacerbations. The results of the present study suggest that BEC during a severe BE exacerbation is correlated, independently of the BEC during stable phases and other clinical and analytical variables, with a significant clinical outcome: the risk of future readmission. This finding underscores the need for further research to explore whether the exacerbation phenotype of BE, specifically BEC during exacerbations, may constitute a distinct, independent treatable trait. Hypothetically, eosinophilia during BE exacerbations could guide decisions on whether to treat the exacerbation with systemic steroids or whether to add inhaled steroids as maintenance therapy to prevent future eosinophilic exacerbations. However, this remains entirely speculative at present.

Several limitations of the study must be acknowledged. We opted to use readmission risk as the primary outcome rather than more robust outcomes like mortality due to the small sample size, which resulted in few mortality events and limited the power of the analysis. Additionally, being a single-center, retrospective study, the results should be considered preliminary and require validation through further prospective, multicenter studies. The low sample size may have limited the detection of some associations due to a potential type II error. Moreover, steady-state BEC was measured only once, and it is known that this biomarker can vary significantly over time[16]. Consequently, the relationship between steady-state and exacerbation BEC may not be entirely reliable.

In conclusion, higher BEC during hospitalization for a BE exacerbation is associated with an increased risk of readmission. Further studies are needed to clarify other possible prognostic and therapeutic implications of this biomarker during BE exacerbations.

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Legend to Figure 1: Kaplan-Meier free-of-readmission survival curves for patients with Blood eosinophil count (BEC) on admission ≥ 150/mm3 versus < 150/mm3. Comparison of curves (log-rank test): $p < 0.0001$

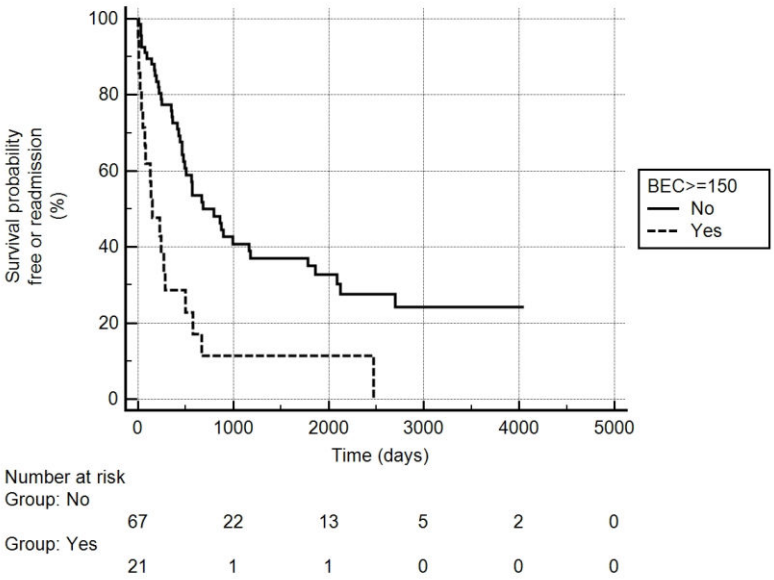

Table 1. Results of the multivariable Cox proportional hazards analysis using readmission as the dependent variable.

Variable	P	HR	95% CI of HR
age	0.67	0.991	0.950 – 1.033
BEC, admission	< 0.001	1.003	1.001 – 1.005
PM, index date	0.58	1.000	0.999 – 1.000
Pulmonary infiltrates	0.57	0.805	0.378 – 1.713
Charlson	0.55	1.093	0.812 – 1.469
eFACED	0.03	1.266	1.0215 – 1.570
Respiratory failure during admission	0.78	0.879	0.344 – 2.247
Male sex	0.20	1.623	0.772 – 3.410
Isolation of PPM during the admission	0.06	0.475	0.214 – 1.053
Isolation of PA during the admission	0.41	1.462	0.587 – 3.641
SpO_2 % index date	0.15	1.054	0.980 – 1.135
FEV_1%	0.81	1.002	0.980 – 1.025

BEC: blood eosinophil count; PM: polymorphonuclear leukocyte count; eFACED: exacerbations, FEV_1, age, colonization by Pseudomonas aeruginosa, radiological extension, dyspnea score; SpO_2: oxygen pulse saturation. FEV_1: forced expiratory value in the first second.

Supplemental file.

Manuscript title: Blood eosinophil count during severe bronchiectasis exacerbation and risk of hospital readmission.

Table S1. Etiologies of the bronchiectasis for the patients included in the study.

Etiology	N (%)
Idiopathic	46 (25.6%)
COPD	39 (21.7%)
Postinfectious	28 (15.6%)
Rheumatoid arthritis	11 (6.1%)
Asthma	8 (4.4%)
Gastroesophageal reflux	8 (4.4%)
Alpha-1-antitrypsin deficiency	6 (3.3%)
Kartagener syndrome	4 (2.2%)
Collagen vascular disease (other than rheumatoid arthritis)	4 (2.2%)
Hypogammaglobulinemia secondary to lymphoma	3 (1.7%)
Immunodeficiency secondary to mycophenolate mofetil treatment	3 (1.7%)
IgG subclasses deficiency	3 (1.7%)
Common variable immunodeficiency	2 (1.1%)
Allergic bronchopulmonary aspergillosis	2 (1.1%)
Antibody production deficiency	2 (1.1%)
Cilliary dyskinesia	2 (1.1%)
Radiotherapy	1 (0.6%)
Ulcerative colitis	1 (0.6%)
Benign bronchial stenosis	1 (0.6%)
HIV infection	1 (0.6%)
Immunodeficiency secondary to chronic lymphatic leukemia	1 (0.6%)
Immunodeficiency secondary to malnutrition (nervous anorexy)	1 (0.6%)
Sjögren syndrome	1 (0.6%)
Swyer-James-McLeod syndrome	1 (0.6%)
Tracheobronchopathia osteochondroplastica	1 (0.6%)

COPD: chronic obstructive pulmonary disease, HIV: human immunodeficiency virus.

Table S2: differences between patients who suffered or not a severe exacerbation requiring hospital admission, after the index date.

Variable	Exacerbators (n=89)	Non exacerbators (n = 91)	p
Age, years	69.3 ± 11.3	59.8 ± 15.2	< 0.001
Sex, male, n, %	51 (57.3%)	34 (37.4%)	0.011
FEV_1%	55.3 ± 23.0	84.1 ± 23.8	< 0.0001
FVC%	70.5 ± 18.3	88.2 ± 17.5	< 0.0001
FEV_1/FVC%	56.6 ± 15.9	70.5 ± 12.9	< 0.0001
SpO_2	92.0 ± 4.8	96.0 ± 2.8	< 0.0001
eFACED	4.2 ± 2.2	1.5 ± 1.7	< 0.0001
Previous isolation of any PPM, n, %	51 (57.3%)	35 (38.5%)	0.017
Previous isolation of PA, n, %	29 (32.6%)	15 (16.5%)	0.019
Chronic bronchial infection, n, %	28 (31.5%)	14 (15.4%)	0.017
Charlson index	1.9 ± 1.7	0.7 ± 1.3	< 0.0001

BEC (cells/mm^3), ID	200 (100 – 300)	200 (100 – 300)	0.96
PM (cells/mm^3), ID	4950 (3500 – 6300)	3600 (2800 – 4600)	0.0001
Platelets x 10^3/mm^3, ID	245 (193 – 290)	230 (196 – 265)	0.27
CRP, ID, mg/L	4.95 (2.17 – 13.85)	2.70 (0.68 – 7.72)	0.003
Bronchodilators, ID, n, %	79 (88.8%)	44 (48.4%)	< 0.0001
IC, ID, n, %	51 (57.3%)	37 (40.7%)	0.03
Azithromycin, ID, n, %	13 (14.6%)	9 (9.9%)	0.46
Inhaled antibiotics, ID, n, %	34 (38.2%)	17 (18.7%)	0.006
BMI Kg/m^2	27.9 (26.0 – 29.2)	26.3 (25.3 – 27.6)	0.14
Never smoker, n, %	44 (49.4%)	59 (64.8%)	0.11
Former smoker, n, %	36 (40.4%)	25 (27.5%)	
Current smoker, n, %	9 (10.1%)	7 (7.7%)	

SpO_2: oxygen pulse saturation; eFACED: exacerbations, FEV_1, age, colonization by *Pseudomonas aeruginosa*, radiological extension, dyspnea score; BEC: blood eosinophil count; PPM: potential pathogenic microorganism; PA: *Pseudomonas aeruginosa*; Eos: eosinophils; ID: index date; PM: polymorphonuclear leukocyte; CRP: c-reactive protein, IC: inhaled corticosteroids; BMI: body mass index.

Table S3: univariable logistic regression analysis using hospital readmission as the dependent variable.

Variable	P	OR	95% CI
Age	0.07	1.03	0.99 – 1.07
Male sex	0.14	1.97	0.78 – 5.00
BEC, ID	0.39	0.99	0.99 – 1.00
BEC admission	< 0.01	1.00	1.00 – 1.01
PM, ID	0.06	1.00	1.00 – 1.00
PM, admission	0.61	1.00	1.00 – 1.00
Platelets, ID	0.36	1.00	1.00 – 1.00
Platelets, admission	0.45	1.00	1.00 – 1.00
CRP admission	0.85	0.99	0.99 – 1.00
CRP, ID	0.29	1.02	0.97 – 1.07
Purulent sputum	0.26	0.58	0.23 – 1.49
Pulmonary infiltrates	0.06	0.39	0.14 – 1.05
Fever	0.21	0.53	0.20 – 1.42
Isolation of PPM during the admission	0.15	0.51	0.20 – 1.31
Isolation of PA during the admission	0.19	0.52	0.20 – 1.37
Chronic bronquial infection index date	0.38	0.65	0.25 – 1.71
Isolation of PA previous to index date	0.47	0.70	0.27 – 1.84
Treatment with steroids during admission	0.56	1.39	0.45 – 4.26
Treatment with antibiotics during admission	0.88	1.20	0.10 – 13.84
SpO_2 % index date	0.15	0.92	0.82 – 1.03
Charlson index	0.01	1.64	1.10 – 2.44
eFACED	0.04	1.24	1.00 – 1.54
Respiratory failure during admission	0.01	3.40	1.23 – 9.38
Hemoptysis during admission	0.76	1.28	0.24 – 6.83
FEV_1%	0.11	0.98	0.96 – 1.00
FEV_1/FVC%	0.52	0.99	0.96 – 1.02
Treatment with inhaled antibiotics on the index date	0.34	0.64	0.25 – 1.62

Treatment with azithromycin on the index date	0.58	1.47	0.37 – 5.86
Treatment with bronchodilators on the index date	0.97	1.02	0.24 – 4.31
Treatment with inhaled corticosteroids on the index date	0.56	0.75	0.29 – 1.93

BEC: blood eosinophil count; PM: polymorphonuclear leukocyte; CRP: c-reactive protein; PPM: potential pathogenic microorganism; PA: Pseudomonas aeruginosa; SpO_2: oxygen pulse saturation; eFACED: exacerbations, FEV_1, age, colonization by Pseudomonas aeruginosa, radiological extension, dyspnea score.

Statistical Analysis: Additional Considerations

For the univariable and multivariable analyses, variables were coded as follows: age was coded in 1-year increments; BEC, PM, platelet count, CRP, SpO2, Charlson index, eFACED, FEV1%, and FEV1/FVC% were coded in 1-unit increments; the remaining variables were coded dichotomously (yes/no).

Receiver Operating Characteristic (ROC) analysis was conducted to evaluate the predictive value of BEC upon admission for the risk of readmission. The area under the ROC curve was 0.69 (95% CI: 0.58 – 0.79). A cut-off value of ≥ 150 eosinophils/mm³ was determined from the complete ROC analysis as the optimal balance between high specificity and sufficient sensitivity. This cut-off value was used to classify patients into two groups for performing a Kaplan-Meier analysis to assess the risk of readmission (see the main body of the manuscript).