ORIGINAL ARTICLE

Chronic obstructive pulmonary disease acute exacerbation: Prognostic value of eosinophilia in terms of recurrence

Exacerbations aigues de bronchopneumopathie chronique obstructive: Valeur pronostique de l'hyperéosinophilie en termes de recurrence

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Abstract

Introduction: Chronic obstructive pulmonary disease (COPD) acute exacerbation (AE) increases morbidity and has an impact on health status. Inflammation plays a key role in these events. Current evidence supports use of biomarkers to guide corticosteroid therapy, which is included in the treatments of COPD AE.
Aim: The aim of our study was to determine the prognostic value of hypereosinophilia (HEo +) in patients admitted to emergency department (ED) with COPD AE in terms of recurrence (Recurrence+).
Methods: A prospective and observational study was conducted over nine months including patients admitted to ED with COPD AE. Patient history, clinical, paraclinical and therapeutic data was collected. HEo+, was defined as blood eosinophil count (BEC)≥200 cells/mm3. One month follow-up was performed. We compared two groups: Recurrence+ vs Recurrence- patients and HEo+ vs HEo- patients. Both univariate and multivariate analysis were performed to identify factors associated with COPD AE recurrence at one month.
Results: We included 252 patients. Prevalence of HEo+ was 50%. Patients with HEo+ had less severe clinical signs on admission (p=0.03), less COPD AE recurrence (p <0.001) and required less hospitalization at one month (p=0.003). Mortality was higher in HEo- patients (p=0.05). Recurrence-patients had HEo+ more frequently (61% vs 19% ; p<0.001). In multivariate analysis, we identified two predictors of recurrence of COPD: COPD group D (adjusted OR 2,3; [95% IC 1,5-3,7]; p<0,001) and non-invasive ventilation on admission (adjusted OR 3,9; [95% IC 1,1-13]; p=0,03). HEo+ was a protective factor of COPD AE recurrence (adjusted OR 0,3; [95% CI] [0,17-0,4]; p<0,001).
Conclusion: Recurrence of COPD AE one month after ED visit was less frequent in patients with HEo+. BEC may predict systemic corticosteroid treatment failure or success. Identification of responders to corticotherapy can lead to less prescription of prednisone or equivalent and could be integrated into a therapeutic management algorithm.

Key words: chronic obstructive pulmonary disease , eosinophilia, exacerbation, prognosis

Résumé

Introduction: Les exacerbations aigues (EA) de bronchopneumopathie chronique obstructive (BPCO) aggravent l'évolution de la maladie et ont un impact sur l'état de santé du patient. L'inflammation joue un rôle clé lors de ces évènements, Les études actuelles encouragent l'utilisation des biomarqueurs afin de guider la prescription des corticoïdes, qui représentent l'un des volets thérapeutiques devant toute EA de BPCO.
Objectif: Déterminer la valeur pronostique d'une hyperéosinophilie (HEo+) chez les patients admis aux urgences pour une EA de BPCO en termes de récidive (récidive+).
Méthodes: Nous avons mené une étude prospective observationnelle sur neuf mois. Nous avons inclus les patients admis aux urgences pour une EA de BPCO. Nous avons recueilli les paramètres anamnestiques, cliniques, paracliniques et thérapeutiques. Une HEo était définie par un taux de polynucléaires éosinophiles supérieur à 200 éléments/mm3. Un suivi d'un mois a été réalisé. Nous avons comparé deux groupes : récidive+ versus récidive- puis HEo+ versus HEo-. Une analyse univariée puis multivariée a été réalisée afin d'identifier les facteurs prédictifs d'une récidive à un mois.
Résultats: Nous avons inclus 252 patients. Une HEo+ a été retrouvée chez 125 patients (50%). Les patients HEo+ avaient moins de signes de gravité à l'admission (p=0,03). Ils avaient présenté moins de récidive (p<0,001) et moins d'hospitalisation (p=0,003) à un mois. Le taux de mortalité était plus élevé (p=0,05) chez les patients HEo-. Les patients Récidive- avaient plus fréquemment une HEo+ (61% vs 19% ; p<0,001). En analyse multivariée, nous avons identifié deux facteurs prédictifs de récidive : groupe D BPCO (OR ajusté 2,3 ; [IC 95% 1,5-3,7] ; p<0,001) et la ventilation non invasive (OR ajusté 3,9 ; [IC 95% 1,1-13] ; p=0,03). PNE>200 éléments/mm³ est ressorti comme facteur protecteur d'une récidive à un mois (OR ajusté 0,3 ; [IC 95% 0,17-0,4] ; p<0,001).
Conclusion: Une récidive de l'EA. BPCO dans le mois suivant la consultation index était moins fréquente chez les patients présentant une HEo+. Intégrer le dosage des PNE dans un algorithme de prise en charge thérapeutique pour prédire l'échec ou le succès de la corticothérapie est une perspective à considérer.

Mot clés: bronchopneumopathie chronique obstructive, hyperéosinophilie, décompensation, pronostic

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What this article adds ?

What is already known on the study topic?

- Corticosteroids are a commonly used treatment option for COPD AE recommended by GOLD 2019
- Eosinophils are almost recognised as a characteristic feature of COPD

How is this study structured?

- This was a single-center, prospective cohort study that includes data from 252 patients.
- Half of patients had hypereosinophilia

What does this study tell us?

- Recurrence of COPD AE one month after an ED visit was less frequent in patients with eosinophilia

Introduction

Chronic obstructive pulmonary disease (COPD) represents a global health challenge. It is a major cause of morbidity and mortality around the world. Its prevalence varies depending on the country between 8 and 15% (1). It is an inflammatory disease characterized by a progressive and persistent airflow limitation (2).

COPD acute exacerbation (AE) results in worsening of symptoms (cough, dyspnea and expectoration) often requiring a visit to emergency department (ED). These acute episodes are responsible for an accelerated decline in respiratory function and deterioration of quality of life and they represent a burden on health care. Thus, reducing the number of exacerbations could potentially slow down the progression of COPD disease (3).

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) is interested in the management of COPD AE (4). The treatment is based on four components: bronchodilator treatment, ventilatory support, corticosteroid therapy and treatment of decompensation cause.

Corticosteroid therapy constitutes a major pillar in the treatment of these exacerbations. Current evidence supports use of biomarkers to guide corticosteroid therapy (4). The latest GOLD recommendations suggest the determination of blood eosinophil count (BEC) before initiating treatment and administration of corticosteroids only for patients with hypereosinophilia (HEo+) (5,6).

Furthermore, the latest studies based on the «Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points» (ECLIPSE) and «Subpopulations and Intermediate Outcome Measures in COPD Study» (SPIROMICS) highlight the search for eosinophilia in COPD AE patients (7).

Few studies have searched for the dosage of BEC during COPD AE. Most of the studies were carried out in the medical wards and intensive care units.

It is in this context that our study, which was carried out a general ED of a secondary level hospital, aimed to determine the prognostic value of HEo + in patients admitted to ED with COPD AE in terms of recurrence.

Methods

Study design

This is a prospective observational study conducted in the ED of a regional hospital of a developing country during a period of nine months (from May 2019 to January 2020).

Study population

We included patients aged over 18 years, who were admitted to ED for respiratory symptoms related to COPD AE. This diagnosis was set by emergency physicians and based on anamnestic criteria and clinical findings. All patients were followed in a pneumology department for a COPD. We did not include patients who were known allergic to corticosteroids, who were unable to take oral corticosteroids and patients on long-term systemic corticosteroid therapy. We excluded patients who did not adhere to the therapeutic protocol after discharge and patients whose follow-up was not possible.

Endpoints

The primary outcome was recurrence of COPD AE one month after the index visit.

The secondary outcomes were the length of stay in the ED, hospitalization at the index visit, death or hospitalization in the month and the progression of the modified Medical Research Council (mMRC) dyspnea scale after one month.

Study protocol

For each patient, we obtained written and free consent to participate. Anamnestic, clinical, paraclinical and therapeutic data were collected. Personal data have been protected. Blood count was collected for all patients. HEo+, was defined as BEC ≥200 cells/mm3. A one-month follow-up was performed by study investigators with a telephonic call.

We compared two groups: Recurrence+ vs Recurrence- patients and HEo+ vs HEo- patients. Univariate and multivariate analysis were performed to identify factors associated with COPD AE recurrence at one month.

Treatment of COPD AE was based on the recommendations of GOLD 2019 and was based on four components: bronchodilator treatment, ventilatory support, corticosteroid therapy and treatment of the cause of decompensation.

All patients received oral corticosteroids (Prednisone 40mg) for five days. We used oral corticosteroids for all patients to uniform treatment. All patients had a standardized bronchodilator treatment following GOLD recommendations.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences SPSS (version 20.0). Continuous normal variables were summarized as mean and

standard deviation (SD) and if not applicable they were reported with medians and IQRs. Categorical variables were summarized as absolute numbers and percentages. Comparison of categorical variables were performed by the chi-2 test if applicable and the Fisher test if not. For continuous variables, the student test or analysis of variance was done for data with normal distribution and the non-parametric test was done for data not showing normal distribution. A p-value <0.05 was considered statistically significant. To identify the risk factors directly linked to the recurrence of COPD AE, we conducted a multivariate analysis. Logistic regression was used to calculate each factor directly related to recurrence of COPD AE: an adjusted OR, its 95% confidence interval [95% CI] and the corresponding "p" value.

Ethical Approval

An ethical approval was obtained from the XXXX before starting the inclusion (approval number: 01/2019 ; approval date: 01/04/2019)

Results

During the study period, the total number of patients attending the ED was 62.288. COPD AE has been diagnosed in 1085 patients. Two-hundred and fifty-two patients (23%) fulfilled the inclusion criteria. The figure 1 illustrates the flow chart.

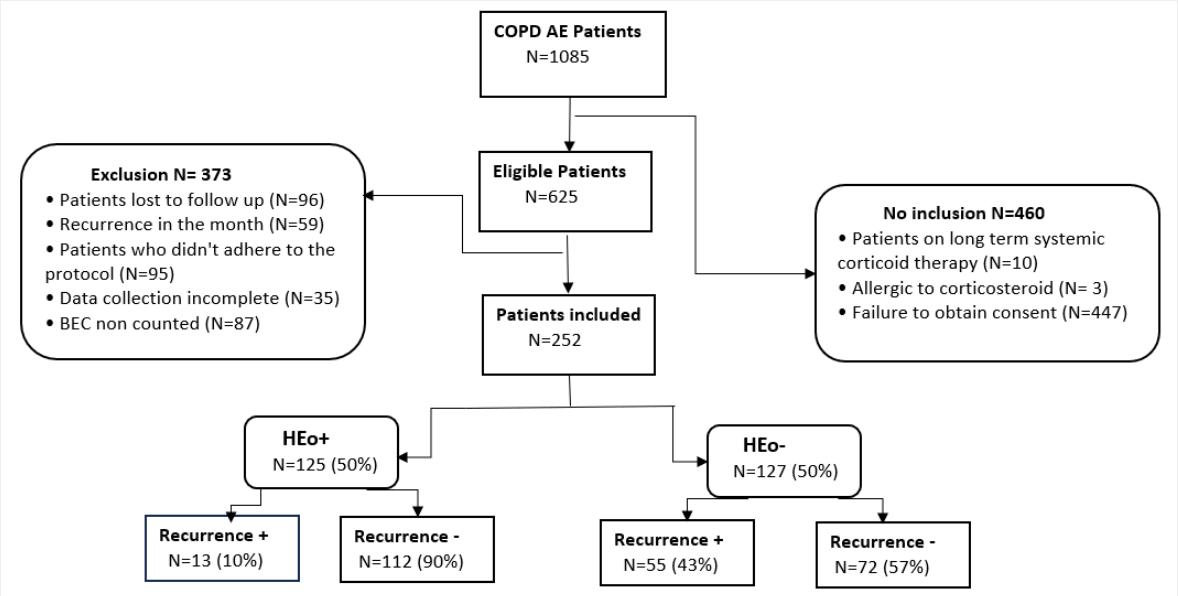

Figure 1. Selection of patients

COPD : chronic obstructive pulmonary disease, **BEC** : blood eosinophils count, **HEo+** : hypereosinophilia

Mean age was 66±11 years and male/female ratio was 3,13. Smoking was noted in 209 patients (83%). Comorbidities most associated with COPD were hypertension (25%) and diabetes (14%). Mean duration of COPD disease was 8 years. Previous COPD AE hospitalization was reported in 128 cases (51%). A history of non-invasive ventilation (NIV) during exacerbation was noted in 80 patients (32%) and history of invasive ventilation was found in two patients. More than half of patients (56%; n = 141) belonged to groups C and D of GOLD classification. Two hundred and sixteen patients (86%) were on long-term treatment for their COPD.

On admission, one hundred and fifty-eight patients (63%) had mild COPD AE, fifty-eight patients (23%) had moderate COPD AE and only 14% had severe COPD AE. HEo+ was noted in 125 patients (50%).

Comparison of two groups: Recurrence+ Versus Recurrence-

The comparison of two groups Recurrence + and Recurrence- did not find a significant difference in mean age, gender, exposure to smoking and comorbidities. On the other hand, COPD Group D patients were significantly more frequent in Recurrence + group (p<0.001). Patients with the history of previous hospitalization for COPD AE (p=0.03) and previous requirement for NIV (p=0.02) were significantly more frequent in the Recurrence + group. In addition, patients in Recurrence + group had significantly more signs of clinical severity (p=0.01) and more oxygen desaturation (p=0.001). Patients in Recurrence- group had significantly more mild exacerbation (p=0.02) and less severe exacerbation (p=0.001). Table 1 shows these differences between the two groups.

HEo was significantly more frequent in Recurrence – (61% vs 19% ; p<0.001). The comparison of therapeutic features showed that the need for NIV (p=0.01) and antibiotic therapy (p=0.02) was significantly more fréquent in Recurrence + group. There was no significant difference in the length of stay and the hospitalization unit. Table 2 summarizes these findings.

Table 1. Comparison of demographics and clinical data between Recurrence+ and Recurrence- groups

	Recurrence+ n=68	Recurrence- n=184	p
Demographic data			
Mean age ±SD (years)	68±10	64±12	NS
Age>65 years n(%)	42(62)	94(51)	NS
Male gender n(%)	56(82)	135(73)	NS
Comorbidities			
Diabetes n(%)	14(21)	22(11)	NS
Hypertension n(%)	19(28)	43(23)	NS
COPD characteristics			
COPD group D	49(72)	67(36)	0.001
History of COPD AE n(%)	44(65)	84(46)	0.03
History of NIV n(%)	29(43)	51(28)	0.02
Clinical characteristics			
Severe signs n(%)	31(46)	52(28)	0.01
Respiratory rate mean±SD (cpm)	26±5	26±11	NS
Oxygen Saturation mean± SD (%)	91±6	94±4	0.001
Exacerbation severity			
Mild n(%)	31(46)	127(69)	0.02
Moderate n(%)	22(32)	36(20)	0.01
Severe n(%)	15(22)	21(11)	0.001

***SD** : Standard Deviation; **NS**: Not Significant; **COPD**: Chronic Obstructive Pulmonary Disease; **AE**: Acute Exacerbation ; **NIV**: Non-iInvasive Ventilation; **GCS**: Glasgow Coma Scale

Table 2. Comparison of management data between Recurrence+ and Recurrence- groups

	Recurrence+ n=68	Recurrence- n=184	p
Biology			
BEC mean±SD (cells/mm³)	169±152	412±382	<0.001
HEo+ n(%)	13(19)	112(61)	<0.001
Treatment			
NIV n(%)	8(12)	9(5)	0.01
Antibiotic therapy n(%)	8(12)	10(5)	0.02
Length of stay in ED mean±DS (hours)	5±2	3±2	NS
Hospitalization unit			
ED n(%)	42(62)	97(53)	NS
Pneumology n(%)	4	17(9)	NS
Intensive care unit n(%)	0	0	-

***SD** : Standard Deviation; **NS**: Not Significant; **BEC**: Blood Eosinophil Count; **HEo**: Hypereosinophilia; **NIV**: Non-Invasive Ventilation; **ED**: Emergency Department

Comparaison of two groups : HEo+ Versus HEo-

There was no significant difference between the two groups regarding age, gender and, comorbidities. On the other hand, COPD group D patients were significantly more frequent in HEo- group (p=0.006). Patients with HEo+ had less severity clinical signs on admission (p=0.03) and less oxygen desaturation (p=0.006). HEo+ patients had significantly more mild COPD AE (p=0.001) and less severe COPD AE (p=0.001). The comparison of therapeutic features showed that there was significantly more use of antibiotic therapy (p=0.025) in the HEo- group. The length of stay was significantly longer in the group HEo- (p=0.02). Patients with HEo+ had significantly less COPD AE recurrence (p <0.001) and required less hospitalization at one month (p=0.003). Mortality was higher in HEo- patients (p=0.05). The comparison of all these characteristics is shown in table 3.

Table 3. Comparison between HEo+ and HEo- groups

	HEo+ n=125	HEo- n=127	*p*
Mean age ±DS (years)	65±11	68±11	0.06
Co-morbidities			
Group D of COPD n(%)	46(37)	69(54)	0.006
mMRC=3 n(%)	42(17)	62(25)	0.04
Clinical characteristics			
Clinical signs of severity n(%)	29(23)	54(42)	0.03
Oxygen Saturation mean±SD	93±5	91±7	0.006
Heart rate mean±DS	93±17	99±19	0.01
Type of exacerbation			
Mild n(%)	92(74)	66(52)	0.001
Moderate n(%)	22(18)	36(28)	0.001
Severe n(%)	11(9)	25(20)	0.001
Treatment			
Antibiotic therapy n(%)	4	14(11)	0.025
Length of stay in ED <6 hours n(%)	117(54)	98(46)	0.02
Follow-up			
Recurrence after one month n(%)	13(10)	55(43)	<0.001
Hospitalization after one month n(%)	2	14(11)	0.003
mMRC=4 after one month n(%)	8(6)	9(7)	0.003
Death n(%)	3	11(9)	0.05

***HEo** : Hypereosinophilia ; **SD** : Standard Deviation; **NS**: Not Significant; **COPD**: Chronic Obstructive Pulmonary Disease ; **NIV**: Non-Invasive Ventilation

Univariate and multivariate analysis

We have identified five predictors of recurrence of COPD AE one month after ED visit in the univariate analysis as shown in table 4.

Table 4. Univariate analysis

Variables	OR	[CI 95%]	p
BEC >200 cells/mm³	0.08	[0.04-0.2]	<0.001
Age>65 years	1.9	[1.1-3.8]	0.05
COPD Group D	7.6	[3.6-16]	<0.001
Clinical severity signs	2.5	[1.2-5]	0.01
NIV need	9.9	[1.2-81]	0.03

***OR** :Odds Ratio ; **CI** : Confidence Interval; **BEC**: Blood Eosinophil Count; **COPD**: Chronic Obstructive Pulmonary Disease, **NIV**: Non-Invasive Ventilation

BEC was a protective factor of recurrence of COPD AE one month after ED with an OR of 0.08 (CI 95% [0.04-0.2] ; p<0.001

In the multivariate analysis, we identified two predictors of recurrence of COPD AE at one month :

- COPD group D (aOR 2,3; [95% CI 1,5-3,7]; p<0,001)
- and non-invasive ventilation on admission (aOR 3,9; [95% CI 1,1-13]; p=0,03).

HEo+ was a protective factor of COPD AE recurrence (0,3; [0,17-0,4]; <0,001).

Discussion

Our study investigated the prognostic value of HEo+ in the management of patients admitted to ED for COPD AE in terms of recurrence at one month. We noted a better response in patients with HEo. The length of stay in ED

was significant higher in HEo- (p = 0.02). These results concur with the findings obtained by Bafadhel M et al (9,10) which showed for a total of 243 patients admitted for COPD AE in England, a shorter mean length of stay in HEo+ patients (BEC ≥2%) (5 days versus 6.5; p = 0.015). Similarly, in a prospective study conducted by Prins HJ et al (11), which took place at a Dutch pulmonology department during 2017, including 207 patients with COPD AE: the prevalence of HEo+ (BEC≥300 cells/mm³ and/or ≥2%) was 18.8%. The length of stay was shorter in HEo + group with p = 0.012.

In our study, the mortality rate was lower in HEo + group with p = 0.05.

Similar findings were reported in a retrospective study conducted by Viinanen A et al (12) which took place in a Finnish pneumology department including 9042 patients. These patients were grouped according to BEC≥ or <300 cells/mm³. HEo - patients had a higher mortality rate (p <0.001). Likewise, in the CHAIN study by Casanova C et al (13) containing 24 cohorts of COPD patients in Spain, the mortality rate was higher in HEo- group (15.8% versus 33.7%; p = 0.026). We also found in our study that patients with HEo+ developed less recurrence of COPD AE one month after the index consultation with p <0.001. Thus, BEC> 200 cells/mm³ was a protective factor against the risk of recurrence in both univariate and multivariate analysis.

Results of literature are controversial regarding the relationship between BEC and the recurrence of COPD AE. In a retrospective study conducted by Duman D et al (14) which took place from January 2014 to November 2014 in Turkey, 1704 patients hospitalized for COPD AE were included. Patients were grouped according to BEC> or ≤ 2%. Follow-up after six months of hospitalization concluded that HEo- patients had a higher risk of recurrence (p <0.01). However, in the meta-analysis of Ho et al (15), the comparison of the two groups HEo + and HEo- didn't show a significant difference concerning the risk of recurrence at one year (OR = 1.07; [95% CI] [0.86-1.32]; p = 0.55).

In the study by Siva et al (16) which took place from February 2003 to January 2004 in England, HEo + patients had more recurrence of COPD AE. Likewise, a reduction in the rate of BEC in sputum was correlated with a decrease in recurrence (p = 0.037). In addition, the study of Vedel-Krogh et al (17) showed by exploring the registry of patients admitted for COPD AE in Copenhagen, that HEo + patients (BEC ≥340 cells/mm³) had a greater risk of developing moderate and severe COPD AE (p<0.001).

In SPIROMICS cohort (18), 1091 patients with a history of COPD were stratified according to the number of BEC (<1%, 1 –3%, and> 3%). Patients with BEC ≥3% were older (63 ± 9, 64 ± 9 and 65 ± 8 years; p = 0.017) and were more frequently men (47%, 49% and 59%; p = 0.0036). HEo+ patients had a lower exacerbation frequency compared with patients with lower eosinophil counts (0.28 (BEC ≥3%) versus 0.36 (BEC 1 –3%,) versus 0.57 (BEC<1%) ; p=0.009). Another study conducted in Copenhagen, analyzing 7225 patients admitted for COPD AE, showed that more men and fewer smokers had BEC≥2% with no significant difference between the two groups in mMRC score and forced expiratory volume in one second (FEV1) (17).

However, in our study we noted the absence of significant difference between the two groups concerning age (p=0.06), gender (p = 0.3) and exposure to tobacco (p = 0.06). In the comparative study conducted by Zhang et al (8), the results were similar to our study regarding demographic characteristics. Patients were grouped according to BEC lower or higher than 150 cells/ mm³. This study concluded that there was no significant difference in age, gender and exposure to tobacco (p = 0.051, p = 0.73 and p = 0.58 respectively). In contrast, HEo+ patients tended to have a lower Charlson Comorbidity Index score (p <0.001), a lower polynuclear neutrophils rate (p <0.001), a lower use of antibiotics (p = 0.027) and a shorter length of stay (p = 0.002).

Recent studies highlighted the interest of measuring BEC in blood and/or sputum to predict the efficacy of corticosteroids in patients with COPD AE (19). The study of Bafadhel et al (20) showed, after analyzing a total of 243 patients randomized into two groups: 95 patients who didn't receive prednisone versus 148 patients who received prednisone, that patients with BEC>2% had a reduced treatment failure rate compared to placebo group (20% vs 45%; p <0.001). Another study reinforcing these results (21), reported that patients with BEC> 2% who received oral corticosteroids had a significantly shorter length of hospital stay.

We noted some strengths in our study. First, the number of patients included was greater than the number of those included in several international studies. Second, it is a prospective study, so missing data were negligible. Third, our study was carried out in the ED, which reduced selections found in studies conducted in pulmonology or intensive care units.

Limitations

Despite numerous strengths, there were some limitations. There was a lack of functional respiratory exploration for the diagnosis of COPD disease severity. Second, the group was heterogeneous and we included patients with the three level of severity. Patients who were intubated on admission had received intravenous corticosteroid therapy. Third, it was a monocentric study. Thus, we did not record the time of the last exacerbation before the index consultation. Another limitation that may interfere with the results, was the proportion of patients who did'nt consent to participate to the study (41%).

Conclusion

Our findings consolidate that BEC could be a biomarker to guide the risk of recurrence of COPD AE and mortality at one month. It would therefore be interesting to measure BEC in all patients with COPD AE. This test is easy, inexpensive, and easily accepted by patients.

We can recommend the adoption of this biomarker in the management of COPD AE in the ED by offering practical protocols adapted to local specificities and to reduce harmful effects of corticosteroids therapy. A prospective

multicenter study based on a common predefined protocol would be a perspective to be considered. These data suggested that patients with increased BEC had a lower risk of recurrence one month after ED visit. BEC can be used as a biomarker in the management of COPD AE. It may predict systemic corticosteroid treatment failure or success. Identification of responders to corticotherapy can lead to less prescription of prednisone or equivalent and could be integrated into a therapeutic management algorithm.

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