Factors predictius, pronòstics i resposta inflamatòria del fracàs de tractament a les Aguditzacions de la Malaltia Pulmonar Obstructiva Crònica (AMPOC) i del reingrés als 30 dies de l'alta hospitalària

Mónica Guerrero Pérez

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ORIGINAL RESEARCH

C-Reactive Protein at Discharge, Diabetes Mellitus and ≥1 Hospitalization During Previous Year Predict Early Readmission in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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Abstract

Recurrent hospitalizations in acute exacerbation of chronic obstructive pulmonary disease (AECOPD) patients have clinical and economic consequences; particularly those readmitted soon after discharge. The aim of our observational study was to determine predictors of early readmission to hospital (30 days from discharge).

Prospective data on 125 hospitalized AECOPD patients were collected over a 30-month period at two Spanish university hospitals. Based on readmission after discharge, patients were divided into non-readmitted (n = 96) and readmitted (n = 29). Measures of serum inflammatory biomarkers were recorded on admission to hospital, at day 3 and at discharge; data on clinical, laboratory, microbiological and severity features were also recorded.

In a multivariate model, C-reactive protein (CRP) at discharge ≥7.6 mg/L, presence of diabetes and ≥1 hospitalization for AECOPD during previous year were significant risk factors for predicting readmission. Presence of all 3 risk factors perfectly identified the readmitted patients (positive and negative predictive values of 1.000; 95% CI, 1.00–1.00).

A combination of 3 readily available clinical and biochemical parameters is accurate in identifying hospitalized AECOPD patients at risk for early readmission.

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease with considerable worldwide prevalence (1), and it is estimated that COPD will be the fourth leading cause of global mortality by 2030 (2). In the clinical course of COPD, acute exacerbations (AECOPD) appear to accelerate the progressive decline of lung function (3), reduction of physical activity (4), deterioration of quality of life (5) and risk of death (6).

Exacerbation frequency is not evenly distributed among patients with COPD, with some COPD patients experiencing frequent episodes and increased susceptibility to exacerbations, a phenotype now defined as "frequent exacerbators" (7). Furthermore, exacerbations tend to cluster together over time, with increased chances of recurrence or relapse following the initial episode (8). As a consequence, after an index hospitalization for AECOPD, readmission to hospital in differing lengths of time from discharge is common and a readmission rate about 20% within a period

Keywords: acute exacerbation, chronic obstructive pulmonary disease, inflammatory response, predictors, readmission

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of 30 days has been reported (9, 10). Moreover, while hospitalization represents more than 70% of all COPD-related health care costs (11, 12), the costs for AECOPD patients readmitted in a period of 30 days were, on average, 18% higher than for patients without reported readmission (13).

Several prospective (14–22) and retrospective (23–26) studies have described risk factors for hospital readmission after AECOPD, including demographic and patient-related functional variables (14–20, 23–26), socioeconomic status, health-related quality of life, depressive symptoms and use of psychotropic drugs (15, 19, 21, 24, 25), and cured meat consumption (22). Few studies, however, have evaluated risk factors specifically predicting the 30-day readmission rate (16, 17) and none of these studies involve serial assessment of systemic inflammatory response at admission and at discharge. The primary aim of our observational study was, therefore, to determine clinical and inflammatory risk factors for readmission to hospital in a period of 30 days from discharge and to integrate these factors in a prediction model.

Methods

Study cohort and ethical aspects

Prospective data on hospitalized adult AECOPD patients at two tertiary university hospitals in Spain (Hospital La Fe, Valencia and Hospital Clinic, Barcelona) was collected over a period of 30 months (between January 2004 and June 2006). The study was approved by the Ethics Committee of both hospitals (project numbers CEIC 2003/0048 and CEIC 2004/1855 for Hospital La Fe and Hospital Clinic, respectively) and conducted in accordance with good clinical practice and the declaration of Helsinki. Written informed consent was obtained from enrolled patients.

Definitions of COPD, AECOPD and readmission in a period of 30 days

In accordance with the GOLD (global initiative for chronic obstructive lung disease) guidelines (27) and based on spirometry performed at least 6 months prior to hospital admission, a respiratory medicine specialist defined the diagnosis and severity of COPD. A threshold of 10 pack-years was considered as a positive smoking habit.

Anthonisen's criteria, based on an acute increase in dyspnea, sputum volume and sputum purulence, was used to define AECOPD (28); patients were then classified as type I if they presented all three symptoms, type II with any two of the three symptoms and type III if any one of these symptoms was present (29).

Early readmission to hospital is defined as a second hospitalization within 30 days of discharge from the index hospitalization with a new occurrence of symptoms and signs of exacerbation, defined with the same criteria. Patients readmitted for reasons other than an exacerbation of COPD were not considered for this study.

Exclusion criteria

At index hospitalization and at readmission to hospital were excluded from the study: a) patients with a documented history of concomitant chronic respiratory conditions (asthma and bronchiectasis) and b) patients in whom suspected community-acquired pneumonia (CAP) and acute heart failure were identified clinically and by means of chest x-ray.

Microbiological sample collection

Sputum from patients was obtained from spontaneous cough on the first day of admission to hospital; if it was an adequate sample, containing more than 25 leukocytes and less than 10 epithelial cells per low power field, was processed using Gram stain and sputum culture.

Inhalation of a 5% hypertonic saline solution for 5 to 10 minutes, delivered via a nebulizer device (Ultraneb 2000; DeVilbiss Healthcare Inc., Somerset, PS, USA) , was used to obtain induced sputum production when spontaneous sputum samples were not obtainable.

Clinical and inflammatory measurements

Data on demographic variables, smoking habit, presence of co-morbidities (chronic heart and renal failure, neurologic and non-cirrhotic liver disease, diabetes and non-active cancer), baseline dyspnea grade as per medical research council (MRC) scale, use of long-term oxygen therapy (LTOT) and domiciliary inhaled bronchodilators (short-acting β_2 agonist (SABA); long-acting β_2 agonist (LABA); anticholinergics), inhaled corticosteroids and theophylline were recorded on admission to hospital. Characteristics of exacerbations occurring in the preceding year (prevalence of patients with ≥2 and ≥4 events, rate of exacerbation requiring an antibiotic treatment or hospitalization) were also recorded.

Symptoms and signs of exacerbation (fever, chills, cough, sputum characteristics), gas analysis variables (pH, partial arterial carbon dioxide pressure ($PaCO_2$), the ratio of partial arterial oxygen pressure to the fraction of inspired oxygen (PaO_2/FiO_2), serum bicarbonate (HCO_3^-) and base excess (BE)) were assessed at admission.

Variables related to the index hospitalization that were assessed included length of stay in hospital (LOS), intensive care unit (ICU) admission, use of noninvasive mechanical ventilation (NIMV), prevalence of abnormal mental status, treatment with systemic corticosteroids and antibiotics. Serum laboratory data (total leukocyte counts, hematocrit, glucose, creatinine, sodium, potassium, aspartate transaminase-AST, alanine transaminase-ALT, total bilirubin, creatine phosphokinase-CPK and lactate dehydrogenase-LDH) were recorded at admission.

Measurements of C-reactive protein (CRP), procalcitonin (PCT), tumour necrosis factor-alpha (TNF-α)

and cytokines (interleukin (IL) -1, IL-6, IL-8 and IL-10) were performed on admission to hospital, after 3 days and at discharge. A commercial immunoturbidimetric method (Bayer Diagnostics, Leverkusen, Germany) was used to measure CRP, while an immunoluminometric technique using a LUMItest assay (BRAHMS Diagnostica GmbH) was used to determine PCT levels. Levels of TNF-α, IL-1, IL-6, IL-8 and IL-10 were measured using a microtiter plate with coated wells and antibodies; TNF-α/IL-6 and IL-1/IL-8/IL-10 were determined using the Medgenix and PerSeptive commercial enzyme immunoassay, respectively.

Statistical analysis

Analyses were carried out using a statistical software package (SPSS 17 for Windows). Normality of the data distribution was determined with the Shapiro–Wilk. Results were expressed as mean ± standard deviation (SD) or as median (25th -75th percentiles) for continuous variables, and frequency (percentage) for categorical variables.

Differences in continuous variables were analyzed using an independent two-tailed *t* test or the nonparametric Mann–Whitney U or Kruskal–Wallis as appropriate. Categorical variables were examined using the X^2-test or Fisher's exact test.

In order to define predictors of readmission in a period of 30 days, a univariate and a stepwise multivariate logistic regression model were performed with clinical and inflammatory data assessed at admission, during hospital stay and at discharge. In a univariate analysis a p value < 0.10 was used to determine which variable entered into the multivariate analysis. A Hosmer-Lemeshow goodness of fit test was performed to evaluate calibration of regression models. Cut-offs for continuous variables that best differentiated non-readmitted and readmitted patients were determined by receiver operating curve (ROC) analysis. For all analyses, a p value of <0.05 was considered to be statistically significant.

Results

Baseline variables

After a follow-up period of 30 days the discharge from the index hospitalization a total of 125 patients admitted to two Spanish university hospitals for an acute exacerbation of COPD (AECOPD) were considered for our study (see the study flow diagram in Figure 1); of these, 96 patients (77%) required no new hospitalization, while 29 (23%) were readmitted for a new AECOPD. Table 1 compares the baseline characteristics of the readmitted and non-readmitted patients.

Readmitted patients had a higher rate of exacerbations requiring antibiotic (2.27 versus 1.09, $p < 0.001$) and requiring hospitalization for exacerbations (1.93 versus 0.83, $p < 0.001$) in the preceding year. Moreover, a greater prevalence of patients with ≥ 2 and ≥ 4 events/previous year (48% versus 24%, $p = 0.017$ and 31% versus 4%, $p < 0.001$, respectively) was also found in readmitted patients. Prevalence of diabetes, as a co-morbidity associated with COPD, was higher in readmitted patients (28% versus 9%, $p = 0.008$): a similar distribution was found between patients with non-insulin dependent (NIDDM) and insulin-dependent diabetes mellitus (IDDM). All the other baseline characteristics did not distinguish readmitted from non-readmitted patients.

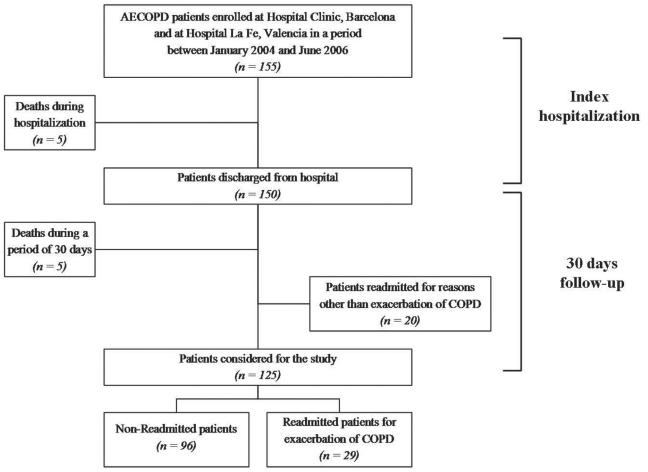

Figure 1. Study flow diagram.

Admission and hospitalization variables

Of the clinical variables evaluated at admission (Table 2), the only distinguishing feature was a slightly lower PaO_2/FiO_2 (median, 242 (201-262) versus 258 (228-281); $p = 0.046$) in readmitted patients. Readmitted patients received more intense treatment of their exacerbation, as indicated by a longer duration, in days, of antibiotic treatment (median, 8 (6-12) versus 7 (5-9); $p = 0.017$) and a greater prevalence of patients using systemic steroids during clinical course (100% versus 86%, $p = 0.023$).

Laboratory values

Conventional serum laboratory data measured at hospitalization (Table 3) did not differentiate between non-readmitted and readmitted patients.

Systemic Inflammatory response

Assessment of systemic inflammatory response (Figure 2) performed at admission, at day 3 and at discharge showed higher serum levels of CRP (median, 20.5 (6.5–49.0) versus 3.5 (1.0–14.7) mg/L; $p < 0.001$) and IL-6 (median, 28.5 (7.5–61) versus 10.5 (4.5–26.5) pg/mL; $p < 0.05$) at discharge in readmitted than in non-readmitted patients. The remaining inflammatory biomarkers (PCT, TNF-α, IL-1, IL-8 and IL-10) were similar between the two groups at all 3 time points.

Multivariate regression analysis

Variables with a p value < 0.10 in the comparison between readmitted and non-readmitted patients (CRP and IL-6 both at discharge, number of co-morbidities,

Table 1. General characteristics of enrolled patients

Variables	All patients	Non-Readmitted Patients	Readmitted Patients	*p*
No (%)	125 (100)	96 (76.8)	29 (23.2)	–
Age, y	69.2 ± 9.8	68.6 ± 10.1	71.0 ± 8.6	0.318
Male, %	93.6	92.7	96.5	0.108
Smoking habit				
Current/former, %	28/72	29.2/70.8	24.1/75.9	0.459
FEV_1, litres	1.12 (0.88–1.48)	1.12 (0.89–1.62)	1.08 (0.87–1.36)	0.629
FEV_1, % predicted	45.9 (34.8–55.2)	46 (36–60)	47 (33.7–52.4)	0.209
FEV_1/FVC, %	46.5 ± 12.0	47.3 ± 12.3	44.0 ± 11.0	0.219
COPD-GOLD stage				
Mild/moderate/severe/very severe, %	0.9/35.5/35.5/28	1.2/39.5/33.3/25.9	0/23.1/42.3/34.6	0.384
LTOT, %	18.4	17.7	20.7	0.833
MRC dyspnea score† ≥ 2, %	85.6	85.4	86.2	0.880
Exacerbations in the preceding year				
Patients with ≥ 2 events, %	29.7	24.2	48.1	**0.017**
Patients with ≥ 4 events, %	10.4	4.1	31	**<0.001**
Rate (events/patients)				
Requiring antibiotics	1.36	1.09	2.27	**<0.001**
Requiring hospitalizations	1.08	0.83	1.93	**<0.001**
Chronic co-morbidities				
Congestive heart failure	27 (21.6)	21 (21.8)	6 (20.7)	0.988
Chronic renal failure	1 (0.8)	1 (1)	0 (0)	0.433
Diabetes	17 (13.6)	9 (9.3)	8 (27.6)	**0.008**
NIDDM/IDDM	7/10	4/5	3/5	1.000
Non-cirrhotic liver disease	3 (2.4)	2 (2)	1 (3.4)	0.676
Neurologic disease	8 (6.4)	6 (6.2)	2 (6.9)	0.939
Non-active cancer	12 (9.6)	7 (7.2)	5 (17.2)	0.117
Use of inhaled bronchodilators				
SABA	84 (67.2)	61 (63.5)	23 (79.3)	0.177
Salbutamol/terbutaline	79/5	58/3	21/2	0.670
LABA	77 (61.6)	61 (63.5)	16 (55.2)	0.428
Formoterolo/salmeterol	25/52	19/42	6/10	0.656
Anticholinergics	84 (67.2)	64 (66.7)	20 (69)	0.811
Ipatropium/tiotropium	33/51	24/40	9/11	0.649
Use of inhaled corticosteroids	74 (59.2)	56 (58.3)	18 (62.1)	0.890
Budesonide/fluticasone	32/42	26/30	6/12	0.498
Use of theophylline	9 (7.2)	6 (6.2)	3 (10.3)	0.451

Values are reported as mean ± SD, as median (25th -75th percentiles) or as frequency (%).
†: evaluated at baseline.
Abbreviations: FEV_1 indicates forced expiratory volume in the 1st second; FEV_1/FVC, ratio of FEV_1 to forced vital capacity (FVC); GOLD, global initiative for chronic obstructive lung disease guidelines; LTOT, long-term oxygen therapy; MRC, medical research council dyspnea score; NIDDM and IDDM, non and insulin-dependent diabetes mellitus; SABA, short action β_2 agonist; LABA, long action β_2 agonist.

diabetes, prior hospitalization for AECOPD, PaO_2/FiO_2, duration of antibiotics treatment) were entered into a multivariate regression analysis with readmission in a period of 30 days as the dependent variable (Table 4). Prior hospitalization for AECOPD (≥1 versus 0), higher levels of CRP at discharge and the presence of diabetes were independent predictors of increased risk of readmission in the stepwise multivariate analysis.

ROC analysis of serum CRP values at discharge demonstrated the maximum area under the curve-AUC (AUC 0.708; SE 0.59; 95%CI 0.593 to 0.823; $p = 0.002$) with a cut-off of 7.6 mg/L.

Ability to discriminate between readmitted and non-readmitted patients for each of these predictive factors individually and combination of 2 or 3 factors is shown in Table 5: a perfect positive and negative predicted

Table 2. Clinical and microbiological variables evaluated at admission and outcomes

Variables	Non-Readmitted Patients	Readmitted Patients	*p*
Fever,* %	40.6	34.5	0.549
Chills, %	28.1	31	0.770
Cough, %	83.3	75.9	0.260
Characteristics of sputum Absence/mucoid/purulent/rusty, %	28.1/54.2/15.6/2.1	34.5/58.6/6.9/0	0.391
Classification of AECOPD according to Anthonisen criteria, % Type I/Type II/Type III	41.8/29.7/28.6	34.5/31/34.5	
pH	7.40 (7.37–7.43)	7.41 (7.36–7.44)	0.374
PCO_2, mmHg	47 (41.1–56)	47 (41.3–54.5)	0.547
PaO_2/FiO_2	257.1 (227.6–280.9)	241.9 (201.4–262.3)	**0.046**
HCO_3 , mmol/L	28 (25.3–31.2)	29.3 (27–34.1)	0.082
BE, mmol/L	3 (1–5.9)	4 (2.7–7)	0.087
Confirmed bacterial etiology, n/n total of patients for each group in whom sputum was provided (%)	38/91 (41.7)	10/27 (37.0)	0.661
Gram-positive bacteria			
Streptococcus pneumoniae	4 (10.5)	1 (10)	1.000
Streptococcus viridans	6 (15.8)	1 (10)	1.000
Staphylococcus aureus	4 (10.5)	0 (0)	0.572
Gram-negative bacteria			
Haemophilus influenzae	9 (23.7)	3 (30)	1.000
Haemophilus parainfluenzae	4 (10.5)	0 (0)	0.572
Pseudomonas aeruginosa	6 (15.8)	3 (30)	0.432
Moraxella catarrhalis	1 (2.6)	0 (0)	1.000
Chlamydia pneumoniae	1 (2.6)	0 (0)	1.000
Enterobacteriaceae‡	2 (5.3)	1 (10)	0.550
Legionella pneumophila	0 (0)	1 (10)	0.232
Neisseria spp.	1 (2.6)	0 (0)	1.000
LOS, days	7 (5–10)	8 (6-13)	0.368
Use of systemic corticosteroids, %	86.5	100	**0.023**
Total doses of systemic corticosteroids, mg	300 (216–406)	332 (220–600)	0.214
Use of antibiotics, %	78.1	86.2	0.476
Duration of antibiotics treatment, days	7 (5–9)	8 (6–12)	**0.017**
Number of classes of antibiotics used , % Only one class/two classes§	77.3/22.7	72/28	0.767
Classes of antibiotics used§			
Penicillins	39 (48.1)	11 (42.3)	0.795
Fluoroquinolones	36 (44.4)	13 (50)	0.479
Macrolides	10 (12.3)	3 (11.5)	1.000
Cephalosporins	15 (18.5)	5 (19.2)	0.780
Carbapenems	1 (1.2)	1 (3.8)	0.412
Use of both systemic corticosteroids and antibiotics, %	80.2	89.7	0.241
Require of NIMV, %	14.5	13.8	0.732
Mental status alteration, %	7.2	13.8	0.290
Admission to ICU, %	3.1	3.4	0.860

Values are reported as median (25th–75th percentiles) or as frequency (%). For microbiological data values are reported as frequency and percentage (%) related to the number of patients with etiological diagnosis in each group. ‡Including *Escherichia coli* and *Proteus mirabilis*. §Calculated on patients with use of antibiotics only.
Abbreviations: $PaCO_2$ indicates partial arterial carbon dioxide pressure; PaO_2/FiO_2, ratio of partial arterial oxygen pressure to the fraction of inspired oxygen; HCO_3, serum bicarbonate; BE, base excess; LOS, length of hospital stay; NIMV, non-invasive mechanical ventilation; ICU, intensive care unit.

Table 3. Serum laboratory data measured at admission

Parameters	*n*	Non-Readmitted Patients	Readmitted Patients	*p*
Total leukocytes, counts × 10^9/L	*n* = 125	10.15 (7.7–12.8)	9.1 (7.5–13.5)	0.670
Hematocrit, %	*n* = 125	45 (42–49)	45 (41–48.1)	0.529
Glucose, mg/dL	*n* = 125	118 (104.2–150.2)	132.7 (109–161.5)	0.262
Creatinine, mg/dL	*n* = 125	0.9 (0.7–1.1)	1.1 (0.8–1.2)	0.081
Sodium, mmol/L	*n* = 125	136.8 (134.2–139)	137 (135–140)	0.480
Potassium, mEq/L	*n* = 124	4.4 (4–4.7)	4.5 (4.1–4.7)	0.529
Aspartate transaminase-AST, IU/L	*n* = 108	22 (18–30)	22 (19–29)	0.847
Alanine transaminase-ALT, IU/L	*n* = 110	19 (14–27.5)	17 (14–24.8)	0.785
Total bilirubin, mg/dL	*n* = 103	0.8 (0.6–1.1)	0.9 (0.7–1.3)	0.167
Creatine phosphokinase-CPK, mcg/L	*n* = 100	72.5 (44.5–110)	70.5 (35–128.9)	0.756
Lactate dehydrogenase-LDH, IU/L	*n* = 107	351 (274–460)	331 (244–460)	0.702

Values are reported as median (25th-75th percentiles).

value (1.000; 95% CI, 1.00-1.00) was obtained when all 3 risk factors were present.

Discussion

Because of its clinical and economic impact, there is a strong interest in predicting and preventing readmission for COPD patients. Previous studies have identified several clinical and conventional laboratory parameters during an AECOPD that are associated with higher rates of readmission; these include lung function and dyspnea perception (14–17, 24, 25), levels of oxygenation (14, 16, 18), carbon dioxide (19) and serum magnesium (26) as well as co-morbidities (16, 23, 24), physical capacity (14), global and respiratory muscle weakness (18, 20), previous hospitalizations (14, 16, 19, 23), socio-economic status and health related quality of life (15, 19, 21, 24, 25), cured meat consumption (22), and use of anticholinergic drugs (14).

Our prospective observational study confirms that clinical variables obtained at admission to hospital (presence of diabetes mellitus and presence of ≥1 episode of

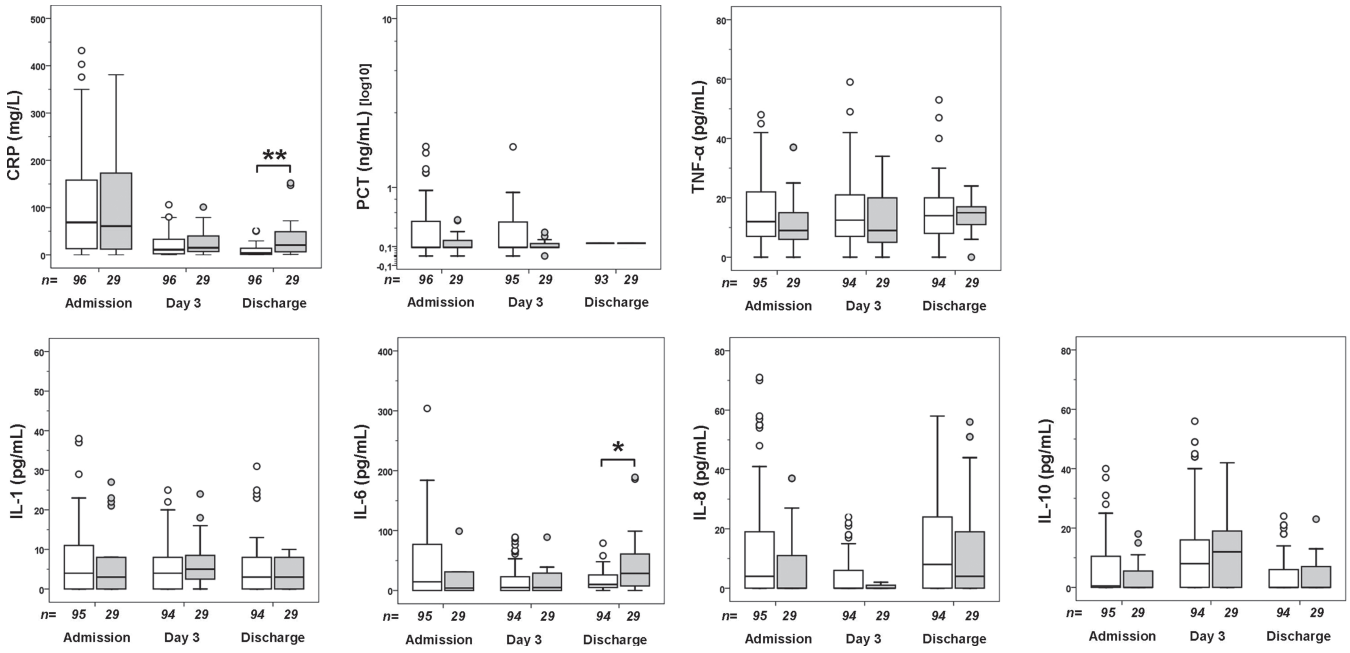

Figure 2. Panel of inflammatory response collected at admission, at day 3 and at discharge. White and grey boxplots represent non-readmitted and readmitted AECOPD patients, respectively. CRP indicates C-reactive protein; PCT, procalcitonin; TNF-α, tumour necrosis factor-alpha; IL, interleukin. The horizontal bar and box length represent the median and the 25th–75th percentiles, respectively. Circles indicate outliers. * and **: p value <0.05 and 0.001 between groups, respectively.

Table 4. Logistic regression analysis

	Univariate logistic regression				Stepwise multivariate logistic regression			
Risk factors	OR	SE	95% CI	*p*	OR	SE	95% CI	*p*
CRP at discharge†, ≥7.6 mg/L	4.68	0.52	1.68 to 13.06	**0.003**	7.41	0.87	1.34 to 40.91	**0.022**
IL-6 at discharge†, ≥19.5 pg/mL	3.27	0.48	1.26 to 8.43	**0.014**	4.84	0.82	0.95 to 24.51	0.056
Number of co-morbidities	1.38	0.19	0.95 to 2.02	**0.086**	1.34	0.23	0.84 to 2.14	0.215
Diabetes, presence	3.64	0.54	1.25 to 10.56	**0.017**	11.03	0.93	1.77 to 68.54	**0.010**
Hospitalization for AECOPD†‡, ≥1 events	4.70	0.54	1.62 to 13.57	**0.004**	8.04	0.82	1.61 to 40.17	**0.011**
PaO_2/FiO_2	0.99	0.00	0.98 to 1.00	**0.075**	0.98	0.00	0.97 to 0.99	0.135
Duration of antibiotics treatment, days	1.10	0.03	1.02 to 1.19	**0.011**	1.08	0.06	0.96 to 1.22	0.186

Dependent variable: readmission to hospital in a period of 30 days.
Hosmer and Lemeshow Tests: X^2 10.47 $p = 0.863$.
†Cut-offs obtained by receiver operating characteristic (ROC) analysis.
‡Data evaluated during the preceding year.
Abbreviations: OR indicates odds ratio; SE, standard error; CI, confidence interval; CRP, C-reactive protein; IL, interleukin.

hospitalization for AECOPD in the preceding year) are important in predicting readmission, and for the first time shows that a readily obtained serum biomarker of inflammation, CRP at discharge can be very useful in predicting readmission. Moreover, the integration of these three risk factors provides excellent predictive ability with a positive predictive value of 1.00 and a negative predictive value of 1.00 that makes it possible to discriminate perfectly which patients will be readmitted to hospital; this ability in our model, however, can be confirmed only on a limited number of patients ($n = 24$, prevalence = 0.208) in whom the three risk factors were present at the same time.

Our findings that previous hospitalizations for AECOPD predict readmission confirm the results of previous prospective studies (14, 16, 19) and a retrospective study (23). However, in three of these previous studies, the timing of readmission was established in a longer period of up to 1 year after the index hospitalization (14, 19, 23). Almagro et al. (16) did use a 30-day period from discharge for, the evaluation of readmission, as was the case in our study. Clearly, patients with a previous history of hospitalization for AECOPD should receive careful attention at and following discharge from the hospital to prevent readmission. This should include not only management of COPD, but also management of comorbidities, social and mental health issues.

Whether diabetes predicts readmission has been an inconsistent finding in previous studies (16, 23). Although a prospective study demonstrated that diabetes increased risk of readmission (16), McGhan et al. (23) found diabetes to be associated with a decreased risk of re-hospitalization at 1 year. However, the McGhan study used a retrospective administrative database with non-confirmed definitions of chronic conditions associated with COPD, which may play a role in this discrepancy.

Table 5. Analysis of predicted values, likelihood ratios values, sensitivity and specificity for risk factors

Risk factors	*n*	True Prevalence	PPV (95% CI)	NPV (95% CI)	Sensitivity	Specificity	LR+†	LR-†
CRP at discharge ≥7.6 mg/L	$n = 125$	0.226	0.360 (0.292 to 0.427)	0.892 (0.850 to 0.933)	0.750	0.609	1.91/0.56	0.41/0.11
Presence of diabetes	$n = 125$	0.233	0.470 (0.348 to 0.591)	0.803 (0.764 to 0.841)	0.275	0.905	2.89/0.87	0.80/0.24
≥1 hospitalization for AECOPD during previous year	$n = 125$	0.226	0.333 (0.273 to 0.392)	0.903 (0.861 to 0.944)	0.807	0.528	1.70/0.49	0.36/0.10
CRP at discharge ≥7.6 mg/L *and* Presence of diabetes	$n = 56$	0.196	0.750 (0.596 to 0.903)	0.895 (0.850 to 0.939)	0.545	0.955	12.11/2.95	0.47/0.11
CRP at discharge ≥7.6 mg/L *and* ≥1 hospitalization for AECOPD during previous year	$n = 42$	0.381	0.714 (0.615 to 0.812)	0.952 (0.905 to 0.998)	0.937	0.769	4.05/2.49	0.08/0.05
Presence of diabetes *and* ≥1 hospitalization for AECOPD during previous year	$n = 56$	0.160	0.667 (0.509 to 0.824)	0.936 (0.900 to 0.971)	0.667	0.936	10.42/1.98	0.35/0.06
CRP at discharge ≥7.6 mg/L *and* Presence of diabetes *and* ≥1 hospitalization for AECOPD during previous year	$n = 24$	0.208	1.000 (1.000 to 1.000)	1.000 (1.000 to 1.000)	1.000	1.000	∞/∞	0.00/0.00

Abbreviations: PPV and NPV indicate positive and negative predictive values, respectively; LR+ and LR- indicate positive and negative likelihood ratios, respectively; CRP, C-reactive protein.
†Data reported as conventional and weighted for prevalence.

Biological plausibility that diabetes would increase the risk of readmission is provided by the demonstration that diabetic patients have elevated levels of pro-inflammatory cytokines such as TNF-α and IL-6, which induce insulin resistance (30); moreover, lung function (31) and gas transfer impairments (due to microangiopathy (32)) are found in patients with diabetes.

Hyperglycemia increases susceptibility to infection, and infections are a major cause of exacerbation. In addition, systemic corticosteroid use for AECOPD, especially if used in large doses for long periods of time, is associated, through a decrease of β-cell insulin production and insulin resistance, with an increased risk of hyperglycemia in patients without known diabetes mellitus (induction of diabetes) and worsened glycemic control in diabetic patients (aggravation of diabetes) (33). The pro-inflammatory and hyperglycemic states associated with diabetes likely explain its role in readmissions in COPD.

Perera et al., have shown that a higher serum CRP level at day 14 of an exacerbation event (34), in outpatients was predictive of a recurrent exacerbation event within 50 days of the index exacerbation. We confirm and extended their observation to inpatients with COPD, using serum CRP at discharge and for prediction of readmission within 30 days. In our study, the high levels of CRP at discharge were not related to any of the clinical, severity and therapeutic variables included. Elevated CRP levels are seen with bacterial exacerbation, and remain elevated in patients with non-resolving exacerbations (35).

We speculate that residual bacterial infection or a super-infection during treatment could underlie enhanced CRP levels after treatment of an exacerbation. This persistent or recurrent infection could then cause the next exacerbation event and readmission. Another potential explanation of the observed association between CRP and exacerbation relapse is that these patients have a higher baseline systemic inflammation in the stable phase of their COPD. Such elevated systemic inflammation in COPD has been associated with poor clinical outcomes (34, 36–38); including susceptibility to developing future exacerbations (36, 39). Further prospective studies are needed to determine the precise mechanism of increased systemic inflammation following treatment of an AECOPD, as specific interventions for this phenomenon could impact readmission and relapses.

The major strengths of our study were the prospective design, exclusion of patients with CAP and heart failure, the systematic analysis of serum inflammatory biomarkers. Limitations include the modest sample size and limited number of sites for data collection. Though our predictive model could be easily applied to clinical practice, validation in a large and international cohort of AECOPD patients is desirable. Another limitation of our study is the lack of information about the specific cause of the exacerbation of readmitted patients and their outcomes.

Conclusion

Our prospective study demonstrates that, in hospitalized AECOPD patients, high values of CRP at discharge, diabetes, and one or more hospitalizations during previous year can predict who will be admitted soon after discharge. Moreover, the integration of these risk factors makes it possible to significantly discriminate readmitted patients. This aspect generate the hypothesis that a greater attention to these selected patients by a more careful pre-discharge clinical evaluation and close post-discharge follow-up (eg, early clinic visits, home care) might modify the rate of readmission in these patients and, consequently, the natural history of COPD (3,6) and COPD-related health care costs (13).

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Declaration of Interest Statement

The authors declare that they have no competing interests. The authors alone are responsible for the content and writing of the paper as follows: Study concept and design: EC, AH, MG, NS, AT; Data collection: RMe, AH, MG, RMa, NS; Data analysis and data interpretation: EC, AT, AH, MG, RMa, NS, SS, RoMe; Writing the article: EC, AT, AH, MG, RMa, NS, SS; Critical revision of the manuscript: AT, SS, RoMe; and Final approval of the manuscript: AT, SS.

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