Impact of bronchiectasis on outcomes of hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease: A propensity matched analysis

Ernesto Crisafulli1, Mónica Guerrero2, Antonella Ielpo1, Adrian Ceccato3, Arturo Huerta2, Albert Gabarrús2, Néstor Soler2, Alfredo Chetta1 & Antoni Torres2

The coexistence of both Chronic Obstructive Pulmonary Disease (COPD) and bronchiectasis (BE) define an emerging phenotype with a worse prognosis; however, data about these patients do not consider baseline characteristics as confounders. We evaluate the impact of BE on outcomes of hospitalized patients with acute exacerbation of COPD (AECOPD). We prospectively considered AECOPD patients, analysed using a propensity score matching (PSM) method. The outcomes included length of hospital stay, use of non-invasive and invasive mechanical ventilation, intensive care unit admission, and mortality up to 3-years. Out of the 449 patients enrolled, 160 had associated BE. AECOPD with BE were older, had lower body mass index and greater functional impairment and severity of symptoms than AECOPD without BE. After PSM, 91 patients were considered for each group and no significant differences were found for all baseline characteristics. In full cohort, the cumulative mortality rate, the survival time, the Kaplan-Meier survival curves and the risk of death were worse in AECOPD with BE in the follow-up of 6-months, 1-year and 3-years. After PSM, data on mortality were similar between AECOPD with and without BE. In conclusion, in AECOPD patients the presence of BE does not influence mortality in a long-term follow-up.

Chronic Obstructive Pulmonary Disease (COPD) is a non-communicable disease representing the third cause of death worldwide1. During the natural course of COPD many patients experience acute exacerbation (AECOPD) characterized by a deterioration of respiratory signs and symptoms2 and an increase of inflammatory response3. Bronchiectasis (BE) is a chronic respiratory condition related to a dilatation of bronchi and airway wall thickening on imaging of chest computed tomography (CT) scan4; this irreversible alteration may lead to recurrent episodes of bronchial infections, inflammation, airway obstruction and progressive lung destruction5.

In order to define the risk stratification of COPD patients6, specific risk factors (age7, smoking8, sex9), clinical phenotypes (frequent exacerbators10, low body mass index-BMI11, increased dyspnoea12), and measurements of disease severity (forced expiratory volume in the 1st second-FEV113) are associated to worse prognosis. For this reason, these measured baseline characteristics (covariates) may be considered as predictors of mortality7–13.

At present, COPD is not considered a cause of BE and patients who fulfil both diagnostic criteria may be identified in an overlap condition14 having a prevalence between 27% and 69%4,15–18. Although the presence of BE has been reported as an unfavourable feature for COPD15,17,18,21, the role of the baseline covariates7–13 that are different between COPD patients with and without BE16,17,22 have been not entirely evaluated. Although the mortality risk of BE in COPD patients has been evaluated with regression adjustment15,17,18,20, residual confounding factors by unmeasured or inadequately measured baseline covariates may account for the rest of the risk. Comparability between groups should be a requirement in observational studies, avoiding indication bias,

1Department of Medicine and Surgery, Respiratory Disease and Lung Function Unit, University of Parma, Parma, Italy. 2Pneumology Department, Clinic Institute of Thorax (ICT), Hospital Clinic of Barcelona - Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) - University of Barcelona (UB), Barcelona, Spain. Correspondence and requests for materials should be addressed to A.T. (email: ATORRES@clinic.cat)
a specific type of selection bias23; the use of restriction may minimize bias23,24. Propensity score (PS)25 represents the estimated probability of exposure assignment conditional on observed baseline covariates. Propensity score matching (PSM) matches patients in each group based on the similarity of their PS and the distribution of observed baseline covariates will be similar between exposed and unexposed subjects, reducing the effect of confounding variables26.

Our study hypothesis was that potential baseline covariates may influence the clinical impact and prognosis of hospitalized AECOPD patients with BE in a short and long-term follow-up. Using a PSM method and eliminating baseline differences between AECOPD patients with and without BE, we could evaluate the impact of BE that is still lacking in AECOPD patients.

Methods

Study Design. This was a prospective study conducted at the Hospital Clinic of Barcelona (Spain) in a period of 7 years between May 2009 and May 2016. The sampling method was systematic and all AECOPD patients admitted to our Pneumology Department were enrolled in the study.

Patients Selection. The patients included had to meet COPD criteria according to the GOLD document27. Spirometry was performed in the stable phase and at least six months prior admission to hospital and a smoking history of 20 pack/years was considered as a positive habit. Definition of AECOPD was based on worsening of respiratory symptoms compared with preceding days requiring a change in domiciliary therapy27; the hospitalization was based on the severity of AECOPD according to the respiratory signs or symptoms and the presence of potential indicators27.

The presence of BE was detected by a chest CT scan, performed during hospitalization or in a period of at least six months before hospital admission. The radiological features of BE collected regards type (cylindrical, cystic or both), distribution (upper, middle or lower lobes or associated lobes), position (lung right, left or bilateral), and extension (or ≥3 involved lobes). Patients without a chest CT scan available were classified as AECOPD without BE.

Exclusion Criteria. The exclusion criteria concerned patients with a documented history of other concomitant chronic respiratory disease (asthma, cystic fibrosis) and patients in whom an acute heart failure were identified clinically and by chest X-ray or CT scan at admission.

Ethics statement. The Hospital’s Ethics Committee approved the study protocol (CEIC 2008/4106), conducted according to the Good Clinical Practices and the declarations of Helsinki. An informed consent have been obtained from all enrolled patients.

Microbiological Sample collection. On the first day of hospitalization sputum sample was collected from spontaneous cough; if the sample was adequate (a count of more than 25 leukocytes and less than 10 epithelial cells per field) it was processed using Gram stain and sputum culture. In patients without a spontaneous sputum sample an induced sputum production was obtained by an inhalation of a 5% hypertonic saline solution for 5 to 10 minutes delivered via a nebulizer device.

Measurements. Data about demographic variables, body mass index (BMI), smoking habit (current or former) with number of pack/year, number of comorbidities (Charlson index), prevalence of ischemic heart disease and diabetes, dyspnea grade measured by the modified Medical Research Council (mMRC) scale, severity of disease (COPD severity score measured by a COPD-SS questionnaire), and use of long-term oxygen therapy (LTOT) were recorded. Season of occurrence of AECOPD, characteristics and number of previous AECOPD occurring in the preceding year and data on home care medications (inhaled bronchodilators as short-acting β2 agonist [SABA], long-acting β2 agonist [LABA], anticholinergics, inhaled steroids [ICS]) were also recorded.

Vital signs (body temperature, respiratory and heart rate, systolic and diastolic blood pressure) were assessed at admission. At admission and at day 3 we recorded data about gas analysis (pH, partial arterial carbon dioxide pressure [PaCO2], the ratio of partial arterial pressure oxygen to the fraction of inspired oxygen [PaO2/FiO2], serum bicarbonate [HCO3−], and base excess [BE]), systemic response (leukocytes, haematocrit, haemoglobin, C-reactive protein [CRP], glucose, and creatinine). Data on number of patients using systemic corticosteroids and/or antibiotics, duration of antibiotic treatment and classes of antibiotics used were also recorded.

Outcomes. Length of hospital stay (LOS), use of non-invasive and invasive mechanical ventilation (NIMV and IMV), and intensive care unit (ICU) admission were considered as variables of clinical progression. Data on prognosis (cumulative number of deaths for all-causes, estimated time to death) were recorded in a follow-up of 30 days, 6 months, 1 year and 3 years. The date of death was identified by centralized registries.

Statistical analysis. A total sample size of 182 patients (91 patients in the group of AECOPD with BE and 91 patients in the group of AECOPD without BE, according to 1:1 allocation ratio) was estimated to provide at least a 80% power and a two-sided alpha value of 0.05 to detect as statistically significant an absolute difference of 15% in the percentage of 3-years mortality of patients between groups (20% patients with BE vs 5% patients without BE)27.

Data were reported with number and percentage of patients for categorical variables, means ± standard deviation (SD) or medians [1st quartile; 3rd quartile] for continuous variables with normal and non-normal distribution, respectively. Categorical variables were compared using the X2 test or the Fisher exact test while continuous variables with the t test or the non-parametric Mann-Whitney test.
| Variables                                      | AECOPD (Full cohort) (n = 449) | AECOPD (Propensity score matching) (n = 182) |
|------------------------------------------------|-------------------------------|-----------------------------------------------|
|                                               | Without BE (n = 289) | With BE (n = 160) | p-value | Without BE (n = 91) | With BE (n = 91) | p-value |
| Age, years                                    | 70.4 ± 10.2             | 72.7 ± 8.6       | 0.014   | 70.9 ± 9.4          | 71.3 ± 8.6       | 0.761   |
| Male, %                                       | 79                  | 84               | 0.183   | 82                  | 85               | 0.689   |
| BMI, kg/m²                                     | 27.8 ± 5.6            | 26.5 ± 4.9       | 0.022   | 27.4 ± 5.0          | 27.3 ± 5.1       | 0.887   |
| Smoking habit: Current/Former, %               | 47/53                | 26/74            | <0.001  | 35/65               | 30/70            | 0.428   |
| Pack/year                                     | 60 [40; 80]           | 59.5 [40; 80]    | 0.917   | 60 [40; 80]         | 50 [40; 80]      | 0.430   |
| FEV₁, % predicted                             | 48.5 ± 18.9           | 44.6 ± 17.2      | 0.040   | 46.2 ± 17.8         | 47.0 ± 17.7      | 0.758   |
| FEV₁/FVC                                       | 51.2 ± 14.6           | 48.0 ± 15.1      | 0.047   | 50.7 ± 14.2         | 48.9 ± 16.6      | 0.446   |
| GOLD 2017 stages: A/B/C/D,%                   | 31/37/12/21           | 17/33/16/33      | 0.017   | 22/36/19/22         | 21/36/18/24      | 0.991   |
| LTOT, %                                       | 23                  | 36               | 0.004   | 23                  | 24               | 0.861   |
| mMRC dyspnea grade                            | 2 [1; 3]             | 2 [1; 3]         | 0.014   | 2 [1; 3]            | 2 [1; 3]         | 0.670   |
| COPD-SS severity questionnaire                | 12 [7; 17.5]         | 16 [11; 20]      | <0.001  | 14 [9; 17]          | 14 [9; 18]       | 0.798   |
| Charlson index                                 | 2 [1; 3]             | 2 [1; 3]         | 0.174   | 2 [1; 3]            | 2 [1; 4]         | 0.785   |
| Ischemic heart disease, %                     | 9                   | 11               | 0.582   | 8                   | 10               | 0.601   |
| Diabetes, %                                    | 23                  | 22               | 0.866   | 19                  | 20               | 0.851   |
| Season of admission: Winter/Spring/Summer/Autumn, % | 44/14/26/17        | 41/17/28/13      | 0.543   | 41/19/27/13         | 37/18/31/14      | 0.947   |
| Previous AECOPD†                               | 0 [0; 1]             | 1 [0; 2]         | 0.042   | 1 [0; 2]            | 0 [0; 1]         | 0.343   |
| Patients with ≥2 previous AECOPD †, %        | 25                  | 30               | 0.212   | 27                  | 23               | 0.495   |
| Previous AECOPD requiring hospitalization †   | 0 [0; 1]             | 0 [0; 1]         | 0.006   | 0 [0; 1]            | 0 [0; 1]         | 0.717   |
| Patients with ≥1 previous AECOPD requiring hospitalization † | 29 | 41 | 0.037 | 34 | 31 | 0.635 |
| Patients having a chest CT scan*, %           | 73                  | 100              | <0.001  | 100                 | 100              | >0.999  |
| Salbutamol only, %                            | 5                   | 1                | 0.090   | 2                   | 0                | 0.497   |
| Anticholinergic only, %                       | 6                   | 5                | 0.609   | 3                   | 8                | 0.206   |
| LABA + Anticholinergic, %                     | 2                   | 1                | 0.412   | 2                   | 1                | >0.999  |
| LABA + ICS, %                                 | 3                   | 2                | 0.747   | 2                   | 4                | 0.678   |
| Anticholinergic + ICS, %                      | 1                   | 3                | 0.437   | 1                   | 1                | >0.999  |
| LABA + Anticholinergic + ICS, %               | 36                  | 38               | 0.702   | 41                  | 38               | 0.656   |

Table 1. Baseline characteristics of AECOPD patients evaluated in the full cohort and in the propensity score matching sample. Data are shown as number of patients (percentage), means ± standard deviation or medians [1<sup>st</sup> quartile; 3<sup>rd</sup> quartile], unless otherwise stated. Percentages are calculated on non-missing data. Abbreviations: AECOPD indicates acute exacerbation of COPD; BE, bronchiectasis; BMI, body mass index; FEV<sub>1</sub>, forced expiratory volume in the 1<sup>st</sup> second; FVC, forced vital capacity; GOLD, global initiative for chronic obstructive lung disease; LTOT, long-term oxygen therapy; mMRC, modified Medical Research Council; COPD-SS, COPD severity score questionnaire; LABA, long-acting β<sub>2</sub> agonist; ICS, inhaled corticosteroids. LABA includes salmeterol, formoterol and indacaterol; Anticholinergic includes ipratropium and tiotropium; and ICS includes budesonide and fluticasone. *The variables included as covariates in the propensity score matching were: age, body mass index, forced expiratory volume in the 1<sup>st</sup> second; smoking habit, COPD-SS questionnaire, chest CT scan, and patients with ≥2 previous AECOPD. †Previous AECOPD were considered if occurring in a period of the preceding year. ‡The chest CT scan was obtained in a period of six months prior the hospitalization or during the hospitalization.

PS was used to obtain the balance among baseline variables between AECOPD patients with and without BE listed in Table 1. A PSM program<sup>28</sup> was used to match the two cohorts using a 1:1 nearest neighbour matching, without replacement within a caliper width of 0.2. Variables were chosen for inclusion in the PS calculation according to the methods of Brookhart <i>et al</i>.<sup>29</sup> and included variables associated with hospitalized AECOPD patients with BE and outcome (age, BMI, FEV<sub>1</sub>, smoking habit, COPD-SS questionnaire, chest CT scan, and patients with ≥2 previous AECOPD). After matching, an adequate comparability was shown by a decrease to <20% (0.2) of the standardized mean difference<sup>30</sup> between AECOPD with and without BE for all baseline covariates (Fig. 1); moreover, an adequate model fit with discrimination and calibration of the PS was demonstrated by the logistic model including covariates yielded a Goodness-of-Fit p = 0.321.

Time-to event variables were analysed by means of Kaplan-Meier survival curves and a Gehan-Breslow-Wilcoxon test was applied because this test emphasizes early differences<sup>31</sup>. Patients lost to follow-up were censored in the survival analysis. Cox proportional hazard regression models were used in mortality at 30-days, 6-months, 1-year, and 3-years<sup>32</sup>. The hazard ratio (HR) and its 95% confidence intervals (CI) were calculated.

All statistical analyses were performed using IBM SPSS Statistics 24.0 (Armonk, New York, USA). A value of p < 0.05 was considered statistically significant.
Data availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Results
Baseline characteristics. 449 consecutive AECOPD patients (81% men) with a mean age of 72 years were considered; of these, 160 patients (36%) had associated BE. The chest CT scan was available in 330 patients (73%); in the PSM sample only patients having a chest CT scan (n = 182) were considered. Figure 2 shows the study flow diagram.

In full cohort, AECOPD patients with BE were older, with a lower BMI and greater functional impairment, severity of symptoms and questionnaire-reported severity characteristics than AECOPD patients without BE. Moreover, patients with BE were more frequently former smokers, with need for LTOT and had a significant history of AECOPD in the previous year, also requiring hospitalization. After PSM, no significant differences were found in all baseline characteristics (see Table 1).

Concerning the radiological aspects of BE, the cylindrical type (circle A) with a distribution in the lower lobes (circle B), in a bilateral position (circle C) and involving ≤3 lobes (circle D) represent the most prevalent features (86%, 41%, 77%, and 61%, respectively) (Fig. 3).

Clinical, laboratory and microbiological variables. With regard to clinical and laboratory variables (Table 2), AECOPD patients with BE in comparison to patients without BE showed a higher C-reactive protein (CRP) level at day 3 (median 1.7 mg/dL vs 0.9 mg/dL, p = 0.026) in full cohort. In the PSM cohort, at admission lower levels of PaCO2 (42.1 mmHg vs 49.1 mmHg, p = 0.003), HCO3− (26 mmol/L vs 28 mmol/L, p = 0.001), BE (1.4 mmol/L vs 2.7 mmol/L, p = 0.015) and glucose (117 mg/dL vs 129 mg/dL, p = 0.028) were shown in AECOPD patients with BE. The other clinical and laboratory variables presented similar values in the two groups in both full and PSM cohort.

In full cohort, a greater prevalence of *Pseudomonas aeruginosa* (38% vs 19%, p = 0.037) and a lower prevalence of *Haemophilus influenzae* (8% vs 24%, p = 0.049) were shown in AECOPD patients with BE in comparison to patients without BE; after matching, all microbiological variables were similar between groups (Table 3).

Outcomes. In the full cohort, AECOPD with BE in comparison to patients without BE showed a lower prevalence of NIMV (15% vs 25%, p = 0.011) and ICU admission (7% vs 15%, p = 0.016); the PSM cohort confirm data about lower prevalence of ICU admission in AECOPD with BE (6% vs 14%, p = 0.047) (Table 4).

In full cohort, the cumulative mortality rate was significantly higher in AECOPD patients with BE in comparison to patients without BE in the follow-up of 6-months, 1-year and 3-years (17% vs 9%, p = 0.015; 27% vs 16%, p = 0.013; 51% vs 40%, p = 0.045; respectively). Moreover, the mean survival time was lower in AECOPD patients with BE (mean 163.9 days vs 170.5 days, p = 0.016 at 6-months; 304.2 days vs 328.1 days, p = 0.009 at 1-year; 766.8 days vs 852.1 days, p = 0.014 at 3-years) (Table 4). The Kaplan-Meier survival curves (Fig. 4) showed an unfavourable role of AECOPD patients with BE (Gehan-Breslow-Wilcoxon test p = 0.011 in the follow-up of 3 years). In the follow-up of 6-months, 1-year and 3-years, Cox regression (Table 5) showed an increased risk of death for all-causes in AECOPD patients with BE (HR [95% CI] 1.94 [1.12 to 3.36], p = 0.018; 1.73 [1.13 to 2.65],...
After PSM, the mortality rate, the mean survival time, the Kaplan-Meier survival curves, and the risk of death were similar between AECOPD patients with and without BE (Table 4, Fig. 4 and Table 5, respectively).

Figure 2. Study flow chart. Abbreviations: AECOPD stands for acute exacerbation of COPD; BE, bronchiectasis.

Figure 3. Radiological features of AECOPD patients with BE. Circles A, B, C, and D show the number and percentage of patients according to the radiological features (type, distribution, position, and extension, respectively).

p = 0.012; 1.39 [1.02 to 1.89], p = 0.036; respectively). After PSM, the mortality rate, the mean survival time, the Kaplan-Meier survival curves, and the risk of death were similar between AECOPD patients with and without BE (Table 4, Fig. 4 and Table 5, respectively).
Table 2. Clinical and laboratory variables recorded at admission and at day 3. Data are shown as number of patients (percentage), means ± standard deviation or medians [1st quartile; 3rd quartile], unless otherwise stated. Percentages are calculated on non-missing data. Abbreviations: AECOPD indicates acute exacerbation of COPD; BE, bronchiectasis; SBP and DBP, systolic and diastolic blood pressure, respectively; PaCO2, partial arterial carbon dioxide pressure; PaO2/FiO2, ratio of partial arterial oxygen pressure to the fraction of inspired oxygen; HCO3, serum bicarbonate; BE, base excess. Systemic corticosteroids include methylprednisolone; Penicillins includes amoxicillin and amoxicillin/clavulanate; Fluoroquinolones includes ciprofloxacin, moxifloxacin, and levofloxacin; Macrolides includes azithromycin and clarithromycin; Cefalosporins includes ceftriaxone, cefotaxime, cefuroxime and cefepime; and Carbapenems includes meropenem.

Concerning the prevalence of radiological features of BE according to the outcomes (Fig. 5), the only right position in comparison to only left and bilateral was respectively associated to a higher prevalence of NIMV (37%, 9% and 13%, p = 0.027) and survivors at 3-years (69%, 21% and 54%, p = 0.011). Data about type, distribution, and extension of BE had not influenced all outcomes.

In the comparison of baseline covariates between survivors and deaths (Table 6), in full cohort, in the follow-up of 6-months, 1-year and 3-years, deaths were among significantly older patients, former smokers, patients with greater staging severity, needing LTOT, with a higher dyspnoea grade, a greater questionnaire-reported severity and a higher number of previous AECOPD also needing hospitalization. BMI, FEV1, % predicted and Charlson index were respectively worse in deaths at the follow-up of 1-year and 3-years, while prevalence of male gender were higher at 3-year follow-up only. In the PSM cohort, the Charlson index was different among survivors and death in the follow-up of 1-year and 3-years, while age, GOLD 2017 stage, LTOT, mMRC, and COPD-SS questionnaire were different in the follow-up of 3-years.
experience worse prognosis 15,17,19–21; however, data on these patients do not consider several baseline covariates.

Baseline characteristics of our patients with BE were consistent with other reports on age 15,17, low BMI 15–17, smoking habit 15, severe obstruction 16,17,22, greater dyspnoea 16,17, need for oxygen-therapy 17,22 and previous exacerbation events 16,17,22. Concerning our higher prevalence of *Pseudomonas aeruginosa* isolation in patients AECOPD with BE, previous studies on COPD in stable phase confirmed these data 4.16–18,22. The presence of this pathogen, one of the most important PPM - are responsible for the development of BE by an increase in chronic inflammation 36. Surprisingly, the prevalence of *Haemophilus influenzae* in our cohort with a positive sputum culture (n = 16, 17%) was lower in comparison to AECOPD patients in general 6, to BE patients 7, and stable COPD patients 17. However, this prevalence was similar after PSM (n = 5, 16%), to the prevalence of BE having COPD as the aetiology cause in a percentage of 11% 33, lower than previous reports (17%) 38. It is than clear that differences in prevalence of patients having COPD and BE depend on the respective population under consideration.

### Table 3. Microbiological variables. Data are shown as number of patients (percentage).

| BE | Without BE | With BE | p-value |
|----|-------------|---------|---------|
| Patients with positive cultures in sputum* | 53 (18) | 39 (24) | 0.150 |
| *Pseudomonas aeruginosa* | 10 (19) | 15 (38) | 0.037 |
| *Haemophilus influenzae* | 13 (24) | 3 (8) | 0.049 |
| *Streptococcus pneumoniae* | 19 (10) | 8 (20) | 0.844 |
| Staphylococcus spp | 5 (9) | 2 (5) | 0.695 |
| Pasteurella | 0 (0) | 2 (5) | 0.177 |
| Moraxella catarrhalis | 3 (6) | 0 (0) | 0.259 |
| Candida spp | 1 (2) | 1 (3) | 0.999 |
| Aspergillus | 0 (0) | 2 (5) | 0.177 |
| Serratia | 1 (2) | 0 (0) | >0.999 |
| Mycobacterium no-TBC | 0 (0) | 1 (3) | 0.424 |
| Polymicrobial etiology | 10 (18) | 5 (13) | 0.508 |
| Virus-positive patients* | 15 (5) | 7 (4) | 0.714 |
| Influenza B virus | 1 (7) | 1 (14) | >0.999 |
| Respiratory syncytial virus | 6 (40) | 1 (14) | 0.430 |
| Rhinovirus | 2 (13) | 1 (14) | 0.540 |
| Parainfluenza virus type 1 | 2 (13) | 0 (0) | 0.540 |
| Parainfluenza virus type 3 | 2 (13) | 0 (0) | 0.540 |
| Parainfluenza virus type 4 | 0 (0) | 1 (14) | 0.356 |

**Discussion**

The coexistence of both COPD and BE has been recently defined as an emerging phenotype of patients 14 who experience worse prognosis 15,17,19–21; however, data on these patients do not consider several baseline covariates as cofounders. Our prospective study, performed for the first time in hospitalized AECOPD patients and using a PSM method, demonstrated that the presence of BE does not worse the clinical impact at admission, the clinical progression, the rate and the risk of short and long-term mortality.

### Prevalence and characteristics associated to BE.

Although in literature a large prevalence of BE associated to COPD is reported 4,15–18, our prevalence in AECOPD patients was slight higher (36% vs 27%) in comparison with COPD patients in whom a CT scan was performed to phenotype the heterogeneity of disease 4. Recent data on distinctive clinical, functional and microbiological phenotypes of patients with BE have shown the prevalence of BE having COPD as the aetiology cause in a percentage of 11% 33, lower than previous reports (17%) 38. It is than clear that differences in prevalence of patients having COPD and BE depend on the respective population under consideration.

**Clinical impact of BE at admission.**

To our knowledge, we have reported for the first time data on the impact of BE on clinical presentation of AECOPD patients. In clinical practice, it is common belief that BE patients especially if in association with an AECOPD may have a worse impact. However, our findings demonstrate that clinical and laboratory data of AECOPD with and without BE were similar, except for hypoxemia levels with renal compensation, that appear better in AECOPD with BE, as well the prevalence of ICU admission (Tables 2 and 4). Interestingly, also the early inflammatory profile of AECOPD with and without BE was similar. Although COPD patients may have different profiles in response to pneumonic and nonpneumonic exacerbations 39, we demonstrated that the presence of BE in AECOPD does not induce a stronger early inflammatory response.

**Abbreviations:** AECOPD indicates acute exacerbation of COPD; BE, bronchiectasis.
Mortality related to BE. In patients with AECOPD several predictors of mortality have been identified in a short and long-term period\(^4^0\); as well in our data (Table 6), age, BMI, FEV\(_1\), and LTOT predict the worse prognosis of AECOPD\(^4^0\).

There are no published studies evaluating the risk of death based on the presence of BE during an AECOPD, while in COPD patients the association with BE have been reported with\(^{1^5,1^7,1^9,2^0}\) and without\(^^{1^8}\) an impact on mortality. However, studies reporting the worse prognosis, also considered for a recent meta-analysis\(^2^1\), concern preliminary data with very few enrolled patients\(^{1^9}\), studies considering patients with evident baseline covariates, including elderly patients\(^{2^0}\), patients with very severe lung functional impairment\(^^{1^9,2^0}\), and patients with chronic respiratory failure needing oxygen-therapy\(^2^0\). Moreover, the adjustments in regression analysis leading to more striking estimates supported the hypothesis that confounding cannot account for the result\(^1^7\); the role of confounding should always be considered as a possible alternative storyline\(^4^1\).

### Table 4. Study outcomes. Data are shown as number of patients (percentage) or medians [1\(^{\text{st}}\) quartile; 3\(^{\text{rd}}\) quartile], unless otherwise stated. Percentages are calculated on non-missing data. Data for mortality was reported as cumulative. Data for survival time was calculated as mean [95% confidence interval] and reported as days. Abbreviations: AECOPD indicates acute exacerbation of COPD; BE, bronchiectasis; LOS, length of stay in hospital; NIMV and IMV, noninvasive and invasive mechanical ventilation, respectively; ICU, intensive care unit. In the propensity score matching group the survival time for 30-days mortality was not computed because all cases are censored. There is only one valid survival function value per group in at least one stratum.

### Figure 4. Kaplan-Meier survival curves in the follow-up period of 3-years in full cohort and in the propensity score matching cohort. Abbreviations: AECOPD stands for acute exacerbation of COPD; BE, bronchiectasis.
Why a PSM method for our observational data: a comparison with regression adjustment.

Historically, regression adjustment has been used more frequently than PS methods to account for differences in measured baseline characteristics between exposed and unexposed subjects. However, there are several reasons for preferring PS-based methods to regression-based methods for reducing the effects of confounding in observational studies.

First, related to the occurrence of BE and baseline covariates to the outcome, it is simpler to determine whether the PS model rather the regression model has been adequately specified. Diagnostics for PS are based on comparing the distribution of measured baseline covariates, between AECOPD with and without BE in the PSM sample. Goodness-of-fit measures in regression models do not provide a test of whether the outcome model has been correctly specified. Furthermore, goodness-of-fit do not allow one to determine the degree to which the fitted regression model has successfully eliminated systematic differences between AECOPD patients with and without BE.

Second, similarly to a randomized controlled trial (RCT), the PS-based methods allow one to separate the design from the analysis of the study, without any reference to the outcome. However, when using regression adjustment, the outcome is always in sight, and the researcher is faced with the subtle temptation to continually modify the regression model until the desired association has been achieved.

|                  | HR    | 95% CI   | p-value |
|------------------|-------|----------|---------|
| 30-days mortality|       |          |         |
| Crude (full cohort) | 1.28  | 0.40 to 4.04 | 0.669   |
| Propensity score matching | —    | —        | —       |
| 6-months mortality|       |          |         |
| Crude (full cohort) | 1.94  | 1.12 to 3.36 | 0.018   |
| Propensity score matching | 0.97  | 0.24 to 3.91 | 0.977   |
| 1-year mortality  |       |          |         |
| Crude (full cohort) | 1.73  | 1.13 to 2.65 | 0.012   |
| Propensity score matching | 1.14  | 0.45 to 2.90 | 0.771   |
| 3-years mortality |       |          |         |
| Crude (full cohort) | 1.39  | 1.02 to 1.89 | 0.036   |
| Propensity score matching | 0.91  | 0.53 to 1.58 | 0.760   |

Table 5. Cox regression models evaluating the risk of all-causes death for AECOPD with BE. Abbreviations: AECOPD indicates acute exacerbation of COPD; BE, bronchiectasis; HR, hazard ratio; CI, confidence interval. Cox regression for 30-days mortality in the propensity score matching sample cannot compute because all cases are censored.

Figure 5. Prevalence of radiological features of AECOPD patients with BE according to the outcomes. Abbreviations: NIMV stands for non-invasive mechanical ventilation.
Table 6. Comparison of baseline covariates between survivors and deaths, in the full cohort and in the propensity score matching sample, in the follow-up of 6-months, 1-year and 3-years. Data are shown as number of patients (percentage), means ± standard deviation or medians [1st quartile; 3rd quartile], unless otherwise stated. Percentages are calculated on non-missing data. For the full cohort data are calculated on survivors (n = 381, n = 333, and n = 208) and deaths (n = 51, n = 84 and n = 166) in the follow-up of 6-months, 1-year and 3-years, respectively. In the propensity score matching sample data are calculated on survivors (n = 163, n = 144, and n = 97) and deaths (n = 8, n = 18 and n = 52) in the follow-up of 6-months, 1-year and 3-years, respectively. In full cohort, the percentage of lost in AECOPD without and with BE groups was 4% and 4% (p > 0.999), 8% and 6% (p = 0.591), and 19% and 13% (p = 0.130) in the follow-up of 6-months, 1-year and 3-years, respectively. In the propensity score matching sample, the percentage of lost in AECOPD without and with BE groups was 8% and 4% (p = 0.536), 15% and 7% (p = 0.058), and 21% and 15% (p = 0.336) in the follow-up of 6-months, 1-year and 3-years, respectively. Abbreviations: BMI indicates body mass index; FEV₁, forced expiratory volume in the 1st second; GOLD, global initiative for chronic obstructive lung disease; LTOT, long-term oxygen therapy; mMRC, modified Medical Research Council; COPD-SS, COPD severity score questionnaire.

Variable                  | Survivors | Deaths | 6-months | p-value | Survivors | Deaths | 1-year | p-value | Survivors | Deaths | 3-years | p-value |
|--------------------------|-----------|--------|----------|---------|-----------|--------|--------|---------|-----------|--------|---------|---------|
| Age, years               |           |        | 70.6 ± 9.8 | 76.4 ± 7.3 | <0.001 | 70.5 ± 9.7 | 75.2 ± 8.6 | <0.001 | 69.4 ± 10.1 | 75.6 ± 8.2 | <0.001 |
| Propensity score matching|           |        | 70.9 ± 9.0 | 76.8 ± 7.2 | 0.067 | 71.3 ± 8.8 | 71.8 ± 9.2 | 0.831 | 70.3 ± 9.4 | 73.7 ± 7.4 | 0.018 |
| Male, %                  |           |        | 81         | 90       | 0.120 | 82        | 89       | 0.096 | 80        | 92     | 0.002 |
| Propensity score matching|           |        | 81         | 75       | 0.350 | 86        | 89       | >0.999 | 86        | 92     | 0.229 |
| BMI, kg/m²                |           |        | 27.4 ± 5.5 | 26.6 ± 4.2 | 0.451 | 27.7 ± 5.4 | 25.6 ± 4.7 | 0.009 | 28.2 ± 5.6 | 25.9 ± 4.6 | <0.001 |
| Propensity score matching|           |        | 27.3 ± 5.1 | 28.4 ± 4.1 | 0.535 | 27.4 ± 5.1 | 27.6 ± 4.4 | 0.878 | 27.8 ± 5.4 | 26.9 ± 4.3 | 0.315 |
| Smoking habit: Current/Former, % |           |        | 42/58      | 16/84    | <0.001 | 44/56      | 19/81    | <0.001 | 46/54      | 22/78  | <0.001 |
| Charlson index            |           |        | 33/67      | 13/87    | 0.439 | 31/69      | 33/67    | 0.858 | 34/66      | 23/77  | 0.165 |
| FEV₁, % predicted         |           |        | 47.4 ± 18.6 | 42.9 ± 16.8 | 0.150 | 47.8 ± 18.2 | 42.7 ± 17.4 | 0.034 | 48.9 ± 17.8 | 41.8 ± 16.1 | <0.001 |
| Propensity score matching |           |        | 46.3 ± 17.8 | 49.6 ± 16.3 | 0.613 | 46.7 ± 17.5 | 47.2 ± 18.7 | 0.911 | 47.3 ± 17.0 | 43.3 ± 16.4 | 0.170 |
| GOLD 2017 stages: A/B/C/D,% |           |        | 28/37/15/20 | 5/17/0/78 | <0.001 | 30/39/15/16 | 10/26/8/64 | <0.001 | 30/42/16/12 | 12/38/7/43 | <0.001 |
| Propensity score matching |           |        | 24/36/19/21 | 0/0/0/100 | 0.292 | 25/37/20/18 | 25/25/0/50 | 0.132 | 27/38/22/13 | 19/34/9/38 | 0.021 |
| LTOT, %                   |           |        | 22         | 65       | <0.001 | 19         | 57       | <0.001 | 13         | 48     | <0.001 |
| COPD-SS severity questionnaire |           |        | 23         | 25       | >0.999 | 21        | 22       | >0.999 | 13        | 35     | 0.002 |
| mMRC dyspnea grade       |           |        | 2 [1; 3]   | 3 [2; 4] | <0.001 | 2 [1; 3]   | 3 [2; 3] | <0.001 | 2 [1; 3]   | 3 [2; 3] | <0.001 |
| COPD severity score       |           |        | 13 [8; 18] | 19 [16; 22] | <0.001 | 12 [8; 17] | 19 [14; 22] | <0.001 | 11 [7; 2] | 17 [12; 21] | <0.001 |
| Propensity score matching |           |        | 14 [9; 18] | 15 [9; 19] | 0.631 | 13 [9; 16; 7] | 15 [10; 20] | 0.115 | 12 [8; 16] | 15 [12; 20] | <0.001 |
| Charlson index            |           |        | 2 [1; 3]   | 2 [1; 3] | 0.305 | 2 [1; 3]   | 2 [1; 4] | 0.011 | 2 [1; 3]   | 2 [1; 4] | 0.001 |
| Propensity score matching |           |        | 2 [1; 3]   | 2 [1; 3] | 0.960 | 2 [1; 3]   | 3.5 [1; 4.2] | 0.015 | 2 [1; 3]   | 3 [1; 4] | 0.017 |
| Previous AECOPD           |           |        | 0 [0; 1]   | 1 [0; 3] | 0.001 | 0 [0; 1]   | 1 [0; 3] | <0.001 | 0 [0; 1]   | 1 [0; 3] | <0.001 |
| Propensity score matching |           |        | 0 [0; 1]   | 0.5 [0; 1.7] | 0.916 | 0 [0; 1]   | 1 [0; 1.2] | 0.471 | 0 [0; 1]   | 1 [0; 1.7] | 0.166 |
| Patients with ≥ 2 previous AECOPD, % |           |        | 23         | 47       | <0.001 | 20        | 44       | <0.001 | 16         | 34     | <0.001 |
| Propensity score matching |           |        | 23         | 25       | >0.999 | 21        | 22       | >0.999 | 17        | 25     | 0.278 |
| Previous AECOPD requiring hospitalization |           |        | 0 [0; 1]   | 1 [0; 2] | 0.001 | 0 [0; 1]   | 1 [0; 2] | 0.155 | 0 [0; 0]   | 0 [0; 1] | <0.001 |
| Propensity score matching |           |        | 0 [0; 1]   | 0.7 [0; 2] | 0.779 | 0 [0; 1]   | 1 [0; 1] | 0.001 | 0 [0; 1]   | 0 [0; 1] | 0.125 |
| Patients with ≥ 1 previous AECOPD requiring hospitalization, % |           |        | 30         | 51       | 0.002 | 26        | 54       | <0.001 | 24        | 45     | <0.001 |
| Propensity score matching |           |        | 31         | 25       | >0.999 | 28        | 44       | 0.144 | 26        | 38     | 0.108 |
Strength and limitation. The originality of using data about AECOPD patients with BE, the prospective and consecutive nature of the data collection, the large cohort of the patients enrolled, the long-term follow-up, and the statistical method using a PSM are the major strengths of our research. There are however some limitations. First, our study was conducted at a single centre and in only one country; data from international centres are therefore necessary to confirm our findings. Second, we had not chest CT scans for all enrolled patients and we cannot exclude an under estimation of BE. However, in clinical practice at admission to hospital, in an AECOPD patient without a radiological (all patients enrolled had performed a chest X-ray) and a clinical suspicion of BE, the chest CT scan is not performed. We may reasonable hypothesize that really these patients were AECOPD without BE, as we have classified. Moreover, the presence of a chest CT scan has been used as a covariate for the PS model and then all patients considered in PSM cohort (with and without BE) had performed a chest CT scan; this has eliminated the hypothetical bias that patients performing a chest CT scan were worst patients. Finally, the analysis of data excluding patients without a chest CT scan in full cohort (data not shown), after matching of all baseline characteristics produce similar results; however, the total sample size was not adequate to demonstrate the study hypothesis (see statistical analysis). Third, we lack information about the cause of death; in COPD patients, however, the causes of death (respiratory, cardiovascular, others) are not significantly influenced by BE12.

In conclusion, our study supports the hypothesis that in AECOPD patients, the clinical impact and prognosis of BE is influenced by several baseline covariates. After matching, with the elimination of confounding, BE does not directly worsen the prognosis of patients in a period until 3-years.

References
1. Lozano, R. et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 380, 2095–128 (2012).
2. Pavord, I.D., Jones, P.W., Burgeil, R.R., Rabe, K.F. Exacerbations of COPD. Int J Chron Obstruct Pulmon Dis. 11 Spec Iss 21–30 (2016).
3. Hurst, J. R. et al. Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 174, 867–874 (2006).
4. Bafadhel, M. et al. The role of CT scanning in multidimensional phenotyping of COPD. Chest. 140, 634–642 (2011).
5. Pasteur, M. C., Bihon, D. & Hill, A. T. British Thoracic Society Bronchiectasis non-CF Guideline Group. British Thoracic Society guideline for non-CF bronchiectasis. Thorax. 65(Suppl 1), i1–58 (2010).
6. Agusti, A. & Celli, B. Avoiding confusion in COPD: from risk factors to phenotypes to measures of disease characterisation. Eur Respir J. 38, 749–51 (2011).
7. Fuhari, M. A. et al. Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. Lancet. 374, 704–711 (2009).
8. Kohnsral, N. et al. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham Offspring Cohort. Am J Respir Crit Care Med. 180, 3–10 (2009).
9. De Torres, J. P. et al. Sex differences in mortality in patients with COPD. Eur Respir J. 33, 528–535 (2009).
10. Hurst, J. R. et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med. 363, 1128–1138 (2010).
11. Schols, A. M., Broekhuizen, R., Weling-Scheepers, C. A. & Wouters, E. F. Body composition and mortality in chronic obstructive pulmonary disease. Am J Clin Nutr. 82, 53–59 (2005).
12. Nishimura, K., Izuami, T., Tsukino, M. & Oga, T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. Chest. 121, 1434–1440 (2002).
13. Menezes, A. M. et al. EV1 is a better predictor of mortality than FVC: the PLATINO cohort study. Plos One. 9, e90732 (2014).
14. Hurst, J. R., Elborn, J. S. & De Soyza, A. BRONCH-UK Consortium. COPD-bronchiectasis overlap syndrome. Eur Respir J. 45, 310–313 (2015).
15. Mao, B. et al. The existence of bronchiectasis predicts worse prognosis in patients with COPD. Sci Rep. 5, 10961 (2015).
16. Jin, J. et al. Factors associated with bronchiectasis in patients with moderate-severe chronic obstructive pulmonary disease. Medicine (Baltimore). 95, e219 (2016).
17. Martinez-Garcia, M. A. et al. Prognostic value of bronchiectasis in patients with moderate-to-severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 187, 823–831 (2013).
18. Gatheral, T. et al. COPD-related bronchiectasis; independent impact on disease course and outcomes. COPD. 11, 605–614 (2014).
19. Sadigov, A. S. & Akhundov, S. Bronchiectasis associated with COPD: does it increase the mortality rate in patients with severe disease? [abstract]. Am J Respir Crit Care Med. 189, A6257 (2014).
20. Katsura, H., Ogata, M. & Kida, K. Factors determining outcome in elderly patients with severe COPD on long-term domiciliary oxygen therapy. Monaldi Arch Chest Dis. 79, 195–201 (2014).
21. Du, Q., Jin, J., Liu, X. & Sun, Y. Bronchiectasis as a Comorbidity of Chronic Obstructive Pulmonary Disease: A Systemic Review and Meta-Analysis. Plos One. 11, e0150532 (2016).
22. Martinez-Garcia, M. A. et al. Factors associated with bronchiectasis in patients with COPD. Chest. 140, 1130–1137 (2011).
23. Psaty, B. M. & Siscovick, D. S. Minimizing bias due to confounding by indication in comparative effectiveness research: the importance of restriction. JAMA 304, 897–898 (2010).
24. Psaty, B. M. et al. Assessment and control for confounding by indication in observational studies. J Am Geriatr Soc. 47, 749–754 (1999).
25. Rosenbaum, P. R. & Rubin, D. B. The central role of the propensity score in observational studies for causal effects. Biometrika. 70, 41–55 (1983).
26. Austin, P. C. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res. 46, 399–424 (2011).
27. Vogelmeier, C. F. et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report: GOLD Executive Summary. Am J Respir Crit Care Med. 195, S57–S58 (2017).
28. Thoemmes, F. Propensity score matching in SPSS. arXiv:1201.6385 [stat.AP] 2012.
29. Brookhart, M. A. et al. Variable selection for propensity score models. Am J Epidemiol. 163, 1149–1156 (2006).
30. Ho, D. E. et al. Matching as nonparametric preprocessing for reducing model dependence in parametric causal inference. Political Analysis. 15, 199–237 (2007).
31. Mike, V., Stanley, K.E. eds. Statistics in medical research: methods and issues, with applications in cancer research. NY, USA: Wiley, 1982.
32. Collett, D. Modelling survival data in medical research. London: Chapman and Hall, 1994.
33. Alberti, S. et al. Clinical phenotypes in adult patients with bronchiectasis. Eur Respir J. 47, 1113–1122 (2016).
34. Goeminne, P. C., Nawrot, T. S., Rutten, D., Seys, S. & Dupont, L. J. Mortality in non-cystic fibrosis bronchiectasis: a prospective cohort analysis. Respir Med. 108, 287–296 (2014).
35. Patel, I. S. et al. Relationship between bacterial colonisation and the frequency, character, and severity of COPD exacerbations. *Thorax.* **57**, 759–764 (2002).
36. Cole, P. J. Inflammation: a two-edged sword—the model of bronchiectasis. *Eur J Respir Dis Suppl.* **147**, 6–15 (1986).
37. Wilkinson, T. M. A. et al. A prospective, observational cohort study of the seasonal dynamics of airway pathogens in the aetiology of exacerbations in COPD. *Thorax.* **72**, 919–927 (2017).
38. King, P. T., Holdsworth, S. R., Freezer, N. J., Villanueva, E. & Holmes, P. W. Microbiologic follow-up study in adult bronchiectasis. *Respir Med.* **101**, 1633–1638 (2007).
39. Huerta, A. et al. Pneumonic and nonpneumonic exacerbations of COPD: inflammatory response and clinical characteristics. *Chest.* **144**, 1134–1142 (2013).
40. Singanayagam, A., Schembri, S. & Chalmers, J. D. Predictors of mortality in hospitalized adults with acute exacerbation of chronic obstructive pulmonary disease. *Ann Am Thorac Soc.* **10**, 81–89 (2013).
41. Walker, A. M. & Stampfer, M. J. Observational studies of drug safety (editorial). *Lancet.* **348**, 489 (1996).
42. Rubin, D. B. Using propensity scores to help design observational studies: Application to the tobacco litigation. *Health Services & Outcomes Research Methodology.* **2**, 169–188 (2001).
43. Braitman, L. E. & Rosenbaum, P. R. Rare outcomes, common treatments: Analytic strategies using propensity scores. *Ann Intern Med.* **137**, 693–695 (2002).
44. Peduzzi, P., Concato, J., Feinstein, A. R. & Holford, T. R. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. *J Clin Epidemiol.* **48**, 1503–1510 (1995).
45. Peduzzi, P., Concato, J., Kemper, J., Holford, T. R. & Feinstein, A. R. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol.* **49**, 1373–1379 (1996).

**Acknowledgements**

This work was not supported by any financial source.

**Author Contributions**

Conception or design of the work E.C., M.G., A.I., A.G., N.S., A.C., A.T. Acquisition, analysis, or interpretation of data for the work E.C., M.G., A.I., A.C., A.H., A.G., N.S., A.C., A.T. Drafting the work or revising it critically for important intellectual content E.C., M.G., A.I., A.G., A.C., A.T. Final approval of the version submitted for publication A.T. Accountability for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved E.C., A.C., A.T.

**Additional Information**

**Competing Interests:** The authors declare no competing interests.

**Publisher’s note:** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2018