Original Article

Incidence and profile of severe exacerbations of chronic obstructive pulmonary disease due to biomass smoke or tobacco

Rafael Golpe, Nagore Blanco-Cid, David Dacal-Rivas, Irene Martín-Robles, Iria Veiga, Indhira Guzmán-Peralta, Olalla Castro-Añón, Luis A. Pérez-de-Llano

Pneumology Service, University Hospital Lucus Augusti, Lugo, Spain

Address for correspondence:
Dr. Rafael Golpe, Servicio de Neumología, Unidad Administrativa 4-A, Hospital Universitario Lucus Augusti, C/Dr Ulises Romero, 1. 27002 Lugo, Spain.
E-mail: rafagolpe@gmail.com

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Abstract:

INTRODUCTION AND OBJECTIVES: Stable chronic obstructive pulmonary disease (COPD) caused by biomass smoke (B-COPD) has some differences from tobacco-induced-COPD (T-COPD), but acute exacerbations (AECOPD) have not been well characterized in B-COPD.

OBJECTIVE: To compare the incidence, characteristics and outcomes of AECOPD in B-COPD with those of T-COPD.

METHODS: A retrospective observational study that included consecutive patients seen at a specialized COPD clinic (2008–2021). The incidence of severe AECOPD that required hospital admission was studied. For the first AECOPD, the following variables were recorded: fever, coexistence of pneumonia, purulent sputum, eosinophil count, neutrophil to lymphocyte ratio, hypercapnia, and respiratory acidosis. Outcome variables were intensive care unit (ICU) admission, length of hospital stay, and mortality within 1 month of hospital admission.

RESULTS: Of 1060 subjects, 195 (18.4%) belonged to the B-COPD group and 865 (81.6%) to the T-COPD group. During a follow-up of 67.9 (37.8–98.8) months, 75 (38.4%) patients in the B-COPD group and 319 (36.8%) in the T-COPD group suffered at least one severe AECOPD. The only difference between groups was in a higher risk of ICU admission for the T-COPD group. The incidence, characteristics, and the rest of the outcomes of AECOPD were similar for both groups.

CONCLUSION: AECOPD are similar events for B-COPD and T-COPD and should be managed similarly.

Keywords:

Biomarkers, biomass, chronic obstructive, prognosis, pulmonary disease, tobacco, exacerbation

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of mortality and morbidity worldwide. Although smoking is recognized as the leading cause of COPD, there is growing evidence to suggest that biomass smoke is also a notable etiology for the disease.[1] COPD caused by biomass smoke (B-COPD) has been described mainly in low-income countries, but it is also reported in industrialized countries.[2,3] Patients with B-COPD are usually excluded from clinical trials and, consequently, there is a remarkable lack of knowledge about the optimal therapeutic approach for B-COPD.

There are differences in clinical phenotypes between B-COPD and tobacco-induced-COPD (T-COPD),[3,4] Probably reflecting differences in pathophysiologic mechanisms. For example, the inflammatory profile could be different

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for both types of noxious agents.[5,6] Acute exacerbations are cardinal events in the evolution of COPD patients. Exacerbations are not homogeneous, and the biologic response to the agents that cause them varies from one patient to another, leading to different phenotypes.[7] Some phenotypic traits are associated with a different response to specific therapies for the management of exacerbations (e.g., Blood eosinophilia and systemic corticosteroids).[8] Therefore, it is highly desirable to characterize acute exacerbations of COPD (AECOPD) and analyze the variables that can influence its incidence, clinical presentation and evolution. To date, few studies have been published on the subject of acute exacerbations of B-COPD compared with T-COPD, focusing especially on the risk of exacerbation.[9,10]

Our hypothesis was that there would be differences in the incidence, clinical profile, or mortality of AECOPD of patients with B-COPD and T-COPD. The objective of the present study was to test this hypothesis in a cohort of patients followed up in a University Hospital.

Methods

Setting

The study was carried out in the specialized COPD clinic of a second-level University Hospital that provides community health services to 221,441 people who live mainly in rural areas, where biomass fuels (wood smoke) have traditionally been used for cooking and heating home.

Study design and subjects

This was retrospective observational study. All consecutive patients seen at the COPD clinic between January 2008 and January 2021 were considered for study recruitment. Subjects were selected from a prospectively collected database of COPD patients maintained for clinical purposes. Medical records are fully computerized and include information from both the hospital and primary care settings, which allows reliable information to be obtained. Inclusion criteria were age a40 years and COPD diagnosis according to the Global Initiative for Chronic Obstructive Lung Disease.[11] Exclusion criteria were alpha-1-antitrypsin deficiency, human immunodeficiency virus infection and concomitant diagnosis of other major respiratory diseases (e.g., interstitial lung disease and pneumoconiosis).

Study variables

The index date was the date of the first visit to the COPD clinic. Cumulative smoke exposure was recorded using the pack-year index and the years of biomass smoke exposure.[3] Patients were classified into two groups: T-COPD (history of smoking, with a pack-year index >10) and B-COPD (history of at least 20 years of exposure to biomass smoke that began in youth age, in never smokers).[3] The following variables were recorded on the index date: age, sex, body mass index (BMI), Charlson comorbidity index,[12] dyspnea (measured by the modified Medical Research Council scale), number of severe AECOPD in the previous 2 years (exacerbations that required hospital admission), spirometric variables, and oxygen saturation when breathing room air (measured with a finger pulse oximeter). The BMI, obstruction, dyspnea, and exacerbations (BODEX) index was calculated for each patient at this visit.[13]

We recorded the prescribed treatments for the management of COPD on the index date.

We recorded all hospital admissions because of AECOPD after the index date. For the purposes of this study, we included pneumonia in the concept of AECOPD. This is a controversial issue, but episodes of lower respiratory tract infection are the most common causes of severe decompensation in COPD and can be difficult to differentiate from pneumonia. Pulmonary infiltrates are demonstrated in up to 60% of AECOPD when computed tomography (CT) scans are systematically performed.[14] In fact, the dyspnea, eosinopenia, consolidation, acidemia, and atrial fibrillation score, used to predict the prognosis of AECOPD, includes pulmonary infiltrates among the prognostic variables.[15] We thought it was of interest to determine if the pneumonia rate was different for B-COPD and T-COPD.

We calculated the admission rate/year by dividing the number of hospital admissions after the index date by the years of follow-up. We recorded the time from the index date to the first hospital admission. The following variables were obtained at the first admission: diagnosis of pneumonia (defined according to clinical diagnosis, confirmed with infiltrates on chest X-ray or CT); presence of fever (defined as ≥two temperature measurements >37.5°C separated by at least 24 h, or ≥one measurement >38°C); presence of purulent sputum reported by the patient (as recorded in medical records); presence of potentially pathogenic microorganisms in sputum culture; hypercapnia (pCO2 >45 mmHg in arterial blood gas analysis obtained in the emergency room or at any time during admission); respiratory acidosis (pH <7.35 in hypercapnic patients, after excluding metabolic acidosis); admission to the intensive care unit (ICU); use of systemic corticosteroids or antibiotics to treat the exacerbation; days of hospital stay; neutrophil, eosinophil and lymphocyte counts in the first blood test obtained in the emergency room before starting treatment for the exacerbation, expressed both in cells/mm^3 and in percentages. The neutrophil to lymphocyte ratio (NLR) was calculated as the number or

neutrophils divided by the number of lymphocytes/mm^3. Regarding the eosinophil count, it was verified whether the patient had received systemic corticosteroids in the 4 weeks prior to hospital admission.[16] These patients were excluded from the eosinophil blood count analysis. We recorded all-cause deaths that occurred within 30 days of the hospital admission date.

Statistical analysis

The normal distribution of data was evaluated using the Kolmogorov–Smirnov test. Data were reported as percentages for categorical variables and as mean ± standard deviation or median (interquartile range [IQR]) for quantitative variables, depending on whether they followed a normal distribution or not, respectively. For quantitative variables, comparisons between groups were made using Student's *t*-test or Mann–Whitney *U*-test, as appropriate. For categorical variables, the Chi-squared test was used. Kaplan–Meier curves were obtained to compare survival within 1 month from hospital admission for patients with T-COPD and B-COPD. In addition, a multivariable Cox-proportional hazards survival analysis was performed to look for differences in the occurrence of death within 1 month after hospital admission between both study groups, considering possible confounding factors. All variables with biological plausibility were simultaneously entered into the model, without verification. The following potential confounders were included as covariates: age, sex, BODEX index value, nonage adjusted Charlson index value, hypercapnia on admission, respiratory acidosis on admission, pneumonia diagnosis, NLR, blood eosinophil value, and oxygen saturation on the index date. Age was coded in 1-year increments. NLR, blood eosinophils, Charlson and BODEX indices and oxygen saturation were coded in one-unit increments. The rest of the variables were coded dichotomously (present/absent). Since the selected variables are commonly obtained in the management of severe COPD exacerbations, there were few missing data (97.2% of patients had recorded all the study variables). Therefore, the risk of bias was considered low, imputation techniques were not considered necessary and complete case analysis was carried out.[17] Statistical package used was MedCalc statistical software, Version 13.3.3.0 (MedCalc Software bvba, Ostend, Belgium). All effects were considered significant at a $P < 0.05$.

Compliance with ethical standards

This is an analysis of a project aimed to search for clinical differences between B-COPD and T-COPD and authorized by our ethical committee (Comité Ético de Investigación Clínica de Galicia. Registry number: 2012/132). The data were de-identified for analysis. Informed consent was waived for this analysis due to the retrospective and noninterventional design of the study and the use of anonymous clinical data for the analysis.

Results

A total of 1060 subjects were included in the study. Of these, 195 (18.4%) belonged to the B-COPD group and 865 (81.6%) to the T-COPD group. The median pack-year index for the T-COPD group was 50 (40–80). Two hundred and forty-two subjects (27.9% of the T-COPD group) were current smokers. Exposure to biomass for the B-COPD group was 60 (20.2–68.0) years. Table 1 shows the main characteristics of the study subjects. Patients in the B-COPD group were older, more frequently female, had more preserved lung function variables and a higher BMI. Table 2 shows the treatments prescribed on the index date. Triple therapy with long-acting beta-agonist (LABA) plus long-acting muscarinic agent (LAMA) plus inhaled corticosteroid (IC) was the more frequently prescribed treatment in both groups, followed by LABA/LAMA in the T-COPD group and LABA/IC in the B-COPD group.

Follow-up time from the index date was 67.9 (37.8–98.8) months. During this time, 75 (38.4%) patients in the B-COPD group and 319 (36.8%) in the T-COPD group suffered at least one severe AECOPD that required hospital admission ($P = 0.73$). The median number of admissions per year of follow-up was 0.00 (IQR: 0.00–0.25) for the B-COPD and 0.00 (0.00–0.29) for the T-COPD group ($P = 0.96$). The time from the index date to first admission was the 31.1 (11.4–56.0) months

Table 1: Main characteristics of the study subjects

Variable	B-COPD (*n*=195)	T-COPD (*n*=865)	*P*
Age (years)	75.6 (70.2-79.2)	68 (60.9-75.5)	<0.0001
Male sex, *n* (%)	85 (43.6)	762 (88.1)	<0.0001
FEV_1%	55 (45-65)	50 (37-64)	0.001
FVC%	71 (62-82)	75 (64-87)	0.001
FEV_1/FVC %	54 (47-63)	50 (39-60)	<0.0001
BMI (kg/m^2)	29 (25.4-32.4)	28 (24.6-31.8)	0.01
Charlson index* >1, *n* (%)	85 (43.6)	413 (47.7)	0.33
BODEx index, *n* (%)			
0-2	124 (63.5)	485 (56.0)	0.03
3-4	54 (27.6)	238 (27.5)	
5-6	16 (8.2)	110 (12.7)	
7-9	1 (0.5)	32 (3.6)	
SpO_2 (%)	94 (93-96.7)	94 (92-96)	0.16
Chronic bronchitis, *n* (%)	100 (51.3)	418 (48.3)	0.50
Patients with at least 1 previous exacerbation†, *n* (%)	37 (18.9)	208 (24.0)	0.15

*Nonage-adjusted, †At least 1 exacerbation that required hospital admission within the 2 years previous to the index date. B-COPD=Biomass-caused chronic obstructive pulmonary disease, T-COPD=Tobacco-caused COPD, FEV_1=Forced expiratory volume in the 1 s, FVC=Forced vital capacity, BMI=Body mass index, BODEx=Biomass, obstruction, dyspnea, exacerbations, SpO_2=Oxygen saturation by pulse oximetry

for the B-COPD group versus 25.5 (11.3–50.0) for T-COPD (P = 0.36).

Systemic steroids were prescribed during admission to 66 (88.0%) of the B-COPD subjects and to 278 (87.1%) of the T-COPD group (P = 0.99). Antibiotics were used, respectively, in 63 (84.0%) and 275 (86.2%) of the cases (P = 0.75).

Table 3 shows the characteristics of the first hospital admission. The only significant difference between both study groups was that none of those in the B-COPD group required ICU admission, while it was necessary for 8.8% of the T-COPD group. Figure 1 shows the Kaplan–Meier survival curves for T-COPD and B-COPD. There were no significant differences between groups (P = 0.64). Table 4 shows the results of the Cox analysis. The variables significantly associated with death within 1 month from hospital admission in the Cox analysis were age (Hazard ratio [HR]: 1.09, confidence interval [CI]: 1.00–1.19, P = 0.03), and the BODEX index (HR: 1.64, CI: 1.10–2.45, P = 0.01). The rest of the variables were not significantly associated with an increased risk of death. There were no differences in this regard between both study groups: HR for biomass exposure was 1.47, CI: 0.23–9.35, P = 0.67.

Table 2: Treatments prescribed on the index date

Treatment	B-COPD (*n*=195), *n* (%)	T-COPD (*n*=865), *n* (%)	*P*
LABA	8 (4.1)	10 (1.1)	0.007
LAMA	26 (13.3)	145 (16.7)	0.28
LABA/LAMA	35 (17.9)	295 (34.1)	<0.001
LABA/IC	37 (18.9)	54 (6.2)	<0.001
LABA/LAMA/IC	86 (44.1)	332 (38.3)	0.15
Only SABA o SAMA as needed	2 (1.0)	27 (3.1)	0.16
Only nebulized SABA, SAMA or IC	1 (0.5)	2 (0.2)	0.97
Oxygen	13 (6.6)	70 (8.0)	0.60
Roflumilast	4 (2.0)	37 (4.2)	0.21
Theophylline	5 (2.5)	47 (5.4)	0.12
Azithromycin	0	11 (1.2)	0.25

B-COPD=Biomass-caused chronic obstructive pulmonary disease, T-COPD=Tobacco-caused COPD, LABA=Long-acting beta-agonist, LAMA=Long-acting muscarinic agent, IC=Inhaled corticosteroid, SABA=Short-acting beta-agonist, SAMA=Short-acting muscarinic agent

Discussion

The present study did not find significant differences in the incidence, characteristics, or outcomes of severe COPD exacerbations caused by tobacco or by biomass smoke exposure, except for a higher risk of ICU admission for the T-COPD group.

It is not clear what the global health burden of B-COPD is, but an estimated 3 billion people are exposed to

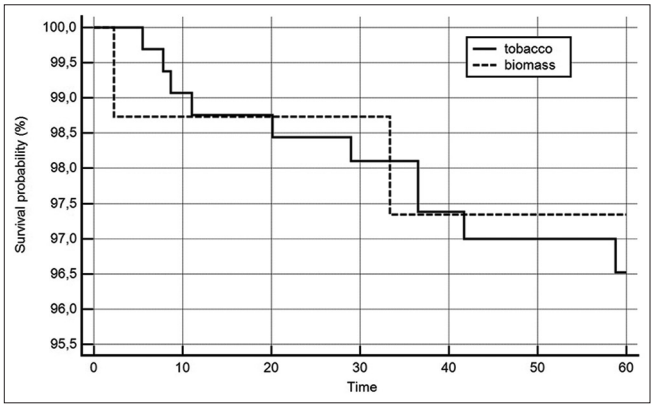

Figure 1: Kaplan–Meier survival curves for mortality within 1 month from hospital admission

Table 3: Characteristics of the first hospital admission

Variable	B-COPD (*n*=75), *n* (%)	T-COPD (*n*=319), *n* (%)	*P*
Neumonía	21 (28.0)	66 (20.7)	0.22
Fever	42 (56.0)	156 (48.9)	0.32
Purulent sputum	30 (40.0)	132 (41.4)	0.92
Sputum culture obtained	22 (29.3)	130 (40.7)	0.09
Positive sputum culture	4 (5.3)	33 (10.4)	0.14
Neutrophil count (cells/mm^3)	8400 (5700-12,200)	8700 (6300-12,200)	0.41
Neutrophil count (%)	80 (72-86)	80 (72-85)	0.91
Eosinophil count (cells/mm^3)*	50 (0-100)	100 (0-100)	0.55
Eosinophil count (%)*	0.15 (0.00-1.40)	0.50 (0.00-1.30)	0.77
Lymphocyte count (cells/mm^3)	1000 (700-1500)	1100 (700-1600)	0.84
Lymphocyte count (%)	10.3 (5.9-13.9)	10.0 (5.9-16.0)	0.83
NLR	7.5 (5.3-14.3)	8.1 (4.6-15.2)	0.83
Hypercapnia	30 (40.0)	145 (45.5)	0.46
Respiratory acidosis	8 (10.7)	64 (20.1)	0.08
Duration of admission (days)	5 (3-7)	6 (4-8)	0.09
ICU admission	0	29 (8.8)	0.01
Deaths within 30 days of admission	2 (2.5)	12 (3.6)	0.88

*Only for patients who had not received steroids before the first analysis (biomass=56, tobacco=242). NLR=Neutrophil to lymphocyte ratio, ICU=Intensive care unit, B-COPD=Biomass-caused chronic obstructive pulmonary disease, T-COPD=Tobacco-caused COPD

Table 4: Results of the Cox proportional hazards analysis for mortality risk within 1 month from hospital admission

Variable	*P*	HR	95% CI
Age	0.03	1.09	1.00-1.19
Male sex	0.81	1.34	0.12-14.95
BODEx index	0.01	1.64	1.10-2.45
Charlson index	0.14	1.33	0.90-1.96
Hypercapnia	0.06	8.48	0.88-81.00
Respiratory acidosis	0.08	3.01	0.87-10.33
Pneumonia	0.60	1.54	0.29-8.08
NLR	0.44	1.01	0.98-1.04
Eosinophil count	0.90	0.98	0.71-1.34
Biomass exposure	0.67	1.47	0.23-9.35
SpO_2	0.11	0.92	0.83-1.01

HR=Hazard ratio, CI=Confidence interval, BODEx=Biomass, obstruction, dyspnea, exacerbations, SpO_2=Oxygen saturation by pulse oximetry, NLR=Neutrophil to lymphocyte ratio

indoor air pollution from biomass smoke and therefore it has been suggested that it could be comparable, if not greater than, human health threat than T-COPD.[1] B-COPD is a particular concern in low-income countries but biomass fuels are also used in developed countries, where the disease is also diagnosed.[2,3,18] Clinical research is less developed for B-COPD than for T-COPD, and there are many unknowns regarding its pathogenesis and treatment. One of the areas where more research is needed is with regard to exacerbations of B-COPD. The prevention and treatment of these events are a central element in the management of COPD because they have a great impact on quality of life, disease progression, and survival. Therefore, obtaining information on the incidence, pathogenesis, and outcomes of B-COPD exacerbations is of great clinical importance.

We found a similar incidence of severe exacerbations in patients with B-COPD and T-COPD. Few studies have previously evaluated this question. A study carried out in Mexico, which included 481 patients followed for 7 years, found no differences between T-COPD and B-COPD in the global number of exacerbations, or in the number of admissions to the emergency room or hospital ward.[19] Consistent with this finding and with the present study, a Korean study that enrolled 1033 patients followed for 3 years found a similar risk of exacerbations for B-COPD and T-COPD.[10] In contrast, another multicenter study conducted in India found a higher rate of exacerbations, emergency room visits and hospitalizations in nonsmoking COPD patients (most of whom were women exposed to biomass smoke) than in T-COPD.[9] However, in that study, exposure to biomass smoke was not independently associated with a high risk of exacerbations (odd ratio [OR: 1.02 [0.85–1.22]).[9]

We are not aware of any studies that compare the characteristics of exacerbations of COPD caused by biomass smoke exposure with those related to smoking. Several studies confirm that there are phenotypic differences between B-COPD and T-COPD. Emphysema is more frequent in T-COPD, while B-COPD is associated with a predominant airway phenotype.[4,5,20] Furthermore, asthma-COPD overlap might be more frequent in B-COPD.[3] As a consequence, it is plausible that AECOPD might have a different biological behavior for diseases caused by both types of noxious agents. AECOPD are heterogeneous events with respect to their inflammatory profile,[7] and in the era of precision medicine, in which we aspire to tailor interventions to the individual patient, it is a matter of interest to investigate whether there are different phenotypic traits in exacerbations of B-COPD and T-COPD. We have looked for differences in clinically relevant biomarkers. Blood eosinophil count is a particularly valuable biomarker in AECOPD since it can predict response to systemic corticosteroids, allowing personalized recommendations on the treatment of exacerbation.[8] Purulent sputum is commonly accepted as a reliable marker of bacterial exacerbation,[21] although its specificity may be lower when reported by patients.[22] NLR is a simple biomarker that is associated with significant clinical outcomes both in stable COPD and in AECOPD, and it seems to be a good indicator of the inflammatory status in this disease.[23] The present study has found no differences between B-COPD and T-COPD in any of these biomarkers, nor in the incidence of fever or pneumonia.

The only difference found in the outcomes of AECOPD caused by both types of fumes was an increased risk of ICU admission for the T-COPD group. The incidence of hypercapnia or respiratory acidosis, length of hospital stay and, most importantly, the short-term mortality, were not significantly different for both study groups. No other study has evaluated this aspect in AECOPD to date. However, previous research suggests that the overall mortality of B-COPD is similar to T-COPD.[19,24] Given the recognized influence of AECOPD on the survival of these patients, this finding is consistent with the results of the present study.

Some limitations of our study should be recognized: Due to its design, it is vulnerable to selection and information biases. There were few missing study variables, but the study setting (a single-center COPD clinic) raises concerns about the generalizability of the results to other scenarios. We have only studied severe AECOPD that required hospital admission, and the results might not be extrapolated to mild or moderate exacerbations. The biomass fuel used in our area was almost exclusively wood, and there is evidence that other types of biomass (e.g., Cow dung) can elicit different inflammatory responses.[25] Therefore, our results might not be comparable with areas where other biomass fuels

are used. The treatments prescribed for the long-term management of COPD were only recorded on the index date, and therefore we were unable to reliably assess their influence on the incidence of hospital admissions. Given the differences found in pharmacological treatment at steady state between both study groups, this is an important limitation. We cannot totally exclude the possibility of a Type-II error for negative results, caused by a possible low statistical power of the study. Finally, all of our patients were Caucasian. There may be ethnic differences in the biological response to biomass smoke and, as a consequence, our results may not be applicable to other countries/ethnic groups.[26]

Conclusion

We have only found minor differences in AECOPD between patients with B-COPD and with tobacco-related disease. Therefore, the clinical importance of these events is similar for both types of the disease, and our results do not support the need for a different management of AECOPD in patients exposed to biomass smoke, compared with T-COPD.

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Conflicts of interest
There are no conflicts of interest.

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