Respiratory Medicine 204 (2022) 107010

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Original Research

Clinical and microbiological characteristics and inflammatory profile during an exacerbation of COPD due to biomass exposure. A comparison with COPD due to tobacco exposure

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ARTICLE INFO

Keywords:
Acute COPD exacerbation
Non-smokers
Biomass exposure
TH2 cells
Microbiome
Inflammatory biomarkers

ABSTRACT

Background: Patients with biomass exposure-related COPD (BE-COPD) is a prevalent disease in developing countries and requires a detailed study of its clinical and inflammatory characteristics, specifying interventions that may differ from tobacco exposure-related COPD (TE-COPD). The objective was to describe clinical characteristics, biomarkers of inflammation, T-helper cells, and microbiological agents during a COPD exacerbation in BE-COPD in comparison with TE-COPD.

Methods: A prospective observational study in patients with moderate or severe exacerbation was recruited either in the emergency room or the COPD clinic. At enrollment, nasopharyngeal swabs and sputum were collected to identify viral and bacterial pathogens. Blood samples were also collected to measure inflammatory biomarkers and T-helper cells levels. Days of hospitalization and mechanical ventilation requirement was evaluated.

Results: Clinical characteristics, vaccination history, hospitalization, history of exacerbations, and microbiological pattern between BE-COPD and TE-COPD were similar. The Th2 profile was higher in BE-COPD than in TE-COPD (2.10 [range 1.30–3.30] *vs.* 1.40 [range 1.20–1.80], p = 0.001). The Th2/Th1 ratio was higher in BE-COPD than TE-COPD (1.22 [range 0.58–2.57] *vs.* 0.71 [range 0.40–1.15], p = 0.004). The need of mechanical ventilation (MV) was higher in TE-COPD than BE-COPD (13% vs. 31.1%, p = 0.01). Nonvaccination history and high CRP levels were significantly associated with hospitalization [OR 1.48 (CI 95% 1.30–4.61, p = 0.005) and OR 1.17 (CI 95% 1.10–1.24, p = 0.001), respectively].

Conclusions: Clinical characteristics, inflammatory markers, and microbiological isolates were similar in both groups but BE-COPD show a tendency to present higher inflammatory Th2 cells and low requirement MV compared with TE-COPD.

1. Introduction

Biomass exposure-related COPD (BE-COPD) is highly prevalent, particularly among women who live in low-income rural and suburban areas [1–3]. However, information on exacerbations in this group is scarce. BE-COPD is an entity that potentially has a more significant impact than tobacco exposure-related COPD (TE-COPD) since the precarious poverty conditions of rural women increase their susceptibility to recurrent infections and bronchiectasis [4,5].

Despite the fact that progress has been made in the last decade in the

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https://doi.org/10.1016/j.rmed.2022.107010
Received 12 August 2022; Received in revised form 1 October 2022; Accepted 8 October 2022
Available online 12 October 2022

knowledge of the clinical picture and even longitudinally in terms of lung function and survival of this entity [6–9], the clinical biomarkers of inflammation, etiological infectious agents and severity of BE-COPD exacerbations have not yet been studied. Additionally, some researchers have speculated that patients with BE-COPD may experience more exacerbations than TE-COPD because the main damage is in the airway [6,7,10]. In this sense, the inflammatory profile could reflect airway damage during an acute exacerbation of COPD (AECOPD) in BE-COPD. The inflammation profile may be mediated by helper T cells, but with a greater increase in the number of Th2 cells in BE-COPD than in TE-COPD, as has been shown by other investigators [8]. Nevertheless, this information could support a hypothetical trend of greater activity of Th2 cells in BE-COPD during an exacerbation compared with TE-COPD, with higher levels of biomarkers such as sputum eosinophils or peripheral eosinophils [8,9,11–13]. Th17 and IL-17A lymphocytes participate in promoting inflammation by coordinating granulopoiesis and the mobilization of neutrophils, for example, in S. pneumoniae infections [9,11,12,14]. The predominance of Th2 lymphocytes is increased in AECOPD with IL4 and IgE, causing inflammation in the airways [13,15,16]. Our objective was to describe clinical characteristics and biomarkers of inflammation, emphasizing the profile of T cells and microbiological profiles during a COPD exacerbation, comparing BE-COPD to TE-COPD.

2. Materials and methods

This was a cross-sectional comparison of two groups of patients with COPD who had different exposure histories. This single-center cross-sectional study was performed at the National Institute of Respiratory Diseases (INER) in Mexico City. This tertiary care hospital is the referral center for patients with respiratory diseases and mainly provides service to the economically deprived population of Mexico.

The sample was conveniently defined by the duration of the study, which lasted one year, and we included all patients with a diagnosis of COPD based on the American Thoracic Society/European Respiratory Society standards for the diagnosis and treatment of patients with COPD [17]. The inclusion criteria for BE-COPD were a history of daily wood smoke exposure for at least 100 h/year assessed with a standardized questionnaire used locally in our Institution. Cumulative exposure to biomass was expressed as hours/year, calculated by multiplying the number of years of cooking with wood by the average of daily hours spent cooking [5,18]. Inclusion criteria for TE-COPD were defined as a history of tobacco smoking of at least >10 packs/year. In both groups, the FEV_1/FVC ratio had to be less than 70% for inclusion. We excluded patients from the study groups who had both biomass and tobacco exposure, exposure other than wood smoke or a history of other chronic pulmonary conditions, such as asthma, tuberculosis, or bronchiectasis. The study population included patients presenting with an acute exacerbation either as an ambulatory patient requiring at least a short course of oral steroids or antibiotics or hospital admission.

An acute exacerbation was when a patient exhibited increased dyspnea, cough, sputum volume, and/or sputum purulence. A moderate exacerbation occurred when the patient did not require hospitalization and only underwent ambulatory treatment with antibiotics and/or a short course of oral steroids. A severe exacerbation was when the patient required hospitalization [19]. We also evaluated the requirement for mechanical ventilation during hospitalization, and whether it was noninvasive or invasive ventilation.

To identify the possibility of viral infections clinically, patients were asked if, within the 5 days prior to enrollment, they presented some of the following symptoms: fever, dry cough, fatigue, headache, muscle pain, eye symptoms, nasal symptoms (sneezing, drip, and congestion).

At enrollment, nasopharyngeal swabs, sputum, and blood samples were collected. Viral pathogens were identified using the RespiFinder19 and RespiFinder22 kits (which use a multiplex polymerase chain reaction (PCR) to identify respiratory pathogens). Sputum samples for bacterial pathogens were obtained from hospitalized and ambulatory patients; they were processed in the microbiology laboratory and cultured if they met the Murray Washington criteria [20]. Blood samples underwent a complete blood count (UniCel DxH 800 Coulter Cellular Analysis System). C-reactive protein (CRP) was determined by immunoturbidimetry, and PATHFAST™ PCT was used to measure procalcitonin by immunoassay in plasma or serum. Measurements and analysis of the $TCD4^+$ cell subpopulations in mononuclear cells were performed with a FACSAria I (BD, Biosciences) cytometer. The acquisition was controlled by DiVa software (BD, Biosciences), and the collected data were exported to FlowJo software for analysis (Treestar, Ashland, Ore). The clinical and functional data were obtained from hospitalized and ambulatory patients using a standardized questionnaire and lung function from the medical records. The study protocol and informed consent were approved by the Ethics and Research Committee of the National Institute of Respiratory Diseases Ismael Cosío Villegas in Mexico City, Mexico, with approval reference number C-5212. All patients signed informed consent forms. This study was conducted following the tenets of the Declaration of Helsinki.

2.1. Statistical analysis

Comparisons of the characteristics between patients with BE-COPD and TE-COPD were evaluated using the unpaired *t*-test, chi-square test, or Fisher's exact test, as appropriate, for categorical variables and Student's *t*-test for continuous variables. T-cell subsets are expressed as the median and range, and differences in the distribution of T-cell subsets were analyzed with Kruskal–Wallis analysis. For between-group differences, the Mann–Whitney *U* test was used. A logistic regression analysis was performed to determine the independent variables associated with hospitalization and mechanical ventilation between the exposure groups. All statistical models were controlled for age, sex, BMI, and type of exposure (BE or TE). SPSS version 16 software was used.

3. Results

The study patients were enrolled from January 2016 to January 2017. To determine the presence of an exacerbation, 345 patients with TE-COPD and BE-COPD were surveyed with a standard questionnaire during their medical follow-up visits. According to our inclusion criteria, 55 patients with BE-COPD and 94 with TE-COPD were included. Of those, 73 had moderate exacerbation criteria in accordance with the survey, and 76 patients presented with a severe exacerbation and required hospitalization. The demographic and clinical characteristics of both groups are shown in Table 1. In general, both groups were similar. The most significant differences were that the BE-COPD population mainly included women who were significantly older than those in the TE-COPD group ($p < 0.001$). The predicted FEV_1 of the BE-COPD group tended to be higher than that of the TE-COPD group ($p = 0.052$), showing moderate-severe obstruction in both groups. Approximately 50% of the patients in both groups had a vaccination history against pneumococcus and influenza, and their history of exacerbations was similar.

Table 2 shows the characteristics of the severe exacerbations. A history of viral symptoms within 5 days prior the assessment occurred in almost 50% of patients in both groups, and the clinical signs suggesting an acute exacerbation during the assessment affected between 74% and 90% of the patients in both groups. Two-fold more patients in the TE-COPD group required mechanical ventilation than in the BE-COPD group (13% vs. 31.1%, $p = 0.01$), regardless of whether it was invasive or noninvasive. No difference in the number of days of hospitalization was observed between the BE-COPD and TE-COPD groups (10 ± 4 vs. 11 ± 9). Both groups observed similar mortality rates during hospitalization, BE-COPD vs. TE-COPD (4% vs. 8%, $p = 0.65$).

Table 3 shows the levels of biomarkers of inflammation during exacerbations. Leukocyte and neutrophil counts were similar in both

Table 1
Demographic and clinical characteristics in BE-COPD and TE-COPD.

Characteristics	BE-COPD, n = 55	TE-COPD, n = 94	p-value
Age (yr) X±SD	75 ± 10	69 ± 9	0.001
Female n (%)	46 (83.6)	20 (20.9)	<0.0001
Tobacco smoking (packs/years) X ±SD	–	57 ± 32	–
Current smoking n (%)	–	47 (50)	–
Biomass smoke exposure, hour-years X (range)	250 (141–385)	–	–
Pulmonary function Post-bronchodilator			
FEV_1% pred X±SD	51 ± 30	39 ± 23	0.052
FVC % pred X±SD	73 ± 31	65 ± 28	0.233
FEV_1/FVC X±SD	54 ± 16	41 ± 18	0.002
Dyspnea, mMRC X (range)	3 (2–4)	3 (2–4)	0.37
Severity by GOLD			
I	6 (10)	7 (7)	0.006
II	29 (50)	21 (22)	
III	13 (23)	35 (37)	
IV	7 (13)	31 (33)	
Comorbidities n(%)	**43(78.5)**	**61 (64.9)**	**0.063**
Gastroesophageal reflux disease n (%)	10 (18.2)	19 (20.2)	0.47
Arterial Hypertension n (%)	24 (43.6)	35 (37.2)	0.274
Diabetes Mellitus n (%)	10 (18.2)	12 (12.9)	0.261
Cor Pulmonale n (%)	0 (0)	6 (6.4)	0.059
Metabolic syndrome n (%)	3 (5.5)	8 (8.5)	0.367
Medication for COPD n(%)			
*Monotherapy	10 (20.8)	13 (14.0)	0.03
**Double therapy	14 (29.2)	25 (27.9)	0.03
***Triple therapy	24 (50.0)	51 (58.1)	0.03
History of exacerbations			
2 ≥ moderate exacerbations in the preceding year n (%)	32 (52.8)	58 (62.5)	0.37
Exacerbations/year X±SD	1.94 ± 1.81	2.29 ± 1.99	0.32
Hospitalizations in the preceding year n (%)	12 (21.8)	28 (29.8.)	0.19
Immunization in the previous year Pneumococcus n (%)	22 (40.0)	43 (45.7)	0.356
Immunization in the previous year Influenza n (%)	30 (54.5)	50 (53.2)	0.505
Home oxygen therapy n (%)	36 (65.5)	74 (78.7)	0.057

BE-COPD, biomass exposure-related COPD; TE-COPD, tobacco exposure-related COPD; mMRC, modified Medical Research Council. * Monotherapy = LAMA or LABA bronchodilators; ** double therapy = LAMA/LABA or ICS/LABA or LAMA + ICS; +++ triple therapy = LAMA/LABA/ICS.

Table 2
Characteristic of severe exacerbations in BE-COPD and TE-COPD.

Variable	BE-COPD	TE-COPD	p-value
Viral symptoms within 5 days prior assessment			
Fever, n (%)	30 (54.5)	39 (41.5)	0.085
Headache, n (%)	31 (56.4)	47 (50.0)	0.281
Odynophagia, n (%)	19 (34.5)	26 (27.7)	0.242
Arthralgias, n (%)	20 (36.4)	19 (20.2)	0.025
Myalgias, n (%)	26 (47.3)	26 (27.7)	0.013
Epiphora, n (%)	12 (21.8)	9 (9.6)	0.035
Rhinorrhea, n (%)	24 (43.6)	36 (38.3)	0.319
Suspected virus case, n (%)	29 (52.7)	45 (47.8),	0.7
Acute exacerbation assessment at enrollment			
Sputum increased, n (%)	45 (81.1)	85 (90.4)	0.104
Purulent Sputum, n (%)	42 (76.4)	70 (74.5)	0.505
Increased cough, n (%)	50 (90.9	85 (90.4)	0.584
Increased dyspnea, n (%)	48 (87.3)	79 (84.0)	0.389
Characteristics during hospitalization			
Requiring hospitalization n (%)	29 (56)	47 (49.0)	0.26
Mechanic ventilation requirement n (%)	6 (13)	28 (31.1)	0.01
Length of intrahospital stay (days) n (%)	10 ± 4	11 ± 9	0.45
Systemic corticosteroids requirement during hospitalization n (%)	22 (40.0)	43 (45.7)	0.35
Antibiotics requirement during hospitalization n (%)	31 (56.4)	52 (55.3)	0.77
Mortality during hospitalization n (%)	1 (4)	4 (8)	0.65

BE-COPD, biomass exposure-related COPD; TE-COPD, tobacco exposure-related COPD.

groups. Regarding eosinophil counts, the total eosinophil count >300 was higher in BE-COPD but without statistical significance (18.1% vs. 15.9%, p = 0.349). There was no association between the eosinophil count and exacerbation severity in either study group. High CRP levels, which indicate the degree of systemic inflammation associated with exacerbation, were similar in both groups. Procalcitonin levels showed normal values in both groups. A difference between the T helper lymphocyte subpopulations was found in the highest percentage of Th2 subpopulations (median 2.10% [range 1.30–3.30%] vs. median 1.40% [range 1.20–1.80%], p = 0.001) and in the Th2/Th1 ratio (median 1.22% [range 0.58–2.57%] vs. median 0.71% [range 0.40–1.15%], p = 0.004) for BE-COPD compared to TE-COPD.

Fig. 1 presents the microbiological profiles. Viral infection was detected in 36% of patients in the BE-COPD group and 35% of patients in the TE-COPD group (p = 0.5); rhinovirus was the most prevalent virus in both groups. Regarding bacterial cultures, an adequate sample was obtained for the analysis from 80% of the patients in both groups. Twenty percent of patients with BE-COPD had a positive culture, and 34% of patients with TE-COPD had a positive culture. *Streptococcus pneumoniae* was the most prevalent bacteria detected in both groups. Viral and bacterial coinfections were present in 29% of patients with BE-COPD and 15% of patients with TE-COPD (p = 0.02). Negative results for either viral or bacterial tests were recorded for 45% of patients with BE-COPD and 39% with TE-COPD (p = 0.27). The presence of purulent phlegm was associated with 29.9% (n = 32) of the positive bacterial isolates in the cultures, and hyaline phlegm was associated with 11.1% (n = 3) (p = 0.082).

To identify factors associated with hospitalization and mechanical ventilation, as shown in Table 4, we performed a stepwise multivariate logistic regression analysis, and we found that a nonvaccination history and high CRP levels were significantly associated with hospitalization [OR 1.48 (CI 95% 1.30–4.61, p = 0.005) and OR 1.17 (CI 95% 1.10–1.24, p = 0.001), respectively]; virus isolation had a weaker association with hospitalization (OR 0.62 [CI 95% 0.43–0.89], p = 0.03). For MV, nonvaccination was associated with hospitalization (OR 2.85 [CI 95% 1.32–6.17], p = 0.008). A history of biomass or tobacco exposure was not a risk factor associated with hospitalization; however, regarding the probability of needing mechanical ventilation, patients with BE-COPD had a significantly lower risk than patients with tobacco exposure [OR 0.28 (0.08–0.82), p = 0.02].

4. Discussion

In the present study, we found that clinical characteristics, inflammatory markers, and microbiological isolates were similar in BE-COPD and TE-COPD, but BE-COPD had a tendency for an inflammatory pattern with a predominant cell-mediated inflammatory microenvironment with Th2 and eosinophils during exacerbations. This is the first study that characterized the COPD patients induced by biomass exposure, including their clinical profile and their inflammatory and microbiological profile during an exacerbation. It is also the first study to compare exacerbations of COPD associated with tobacco with those

Table 3
Inflammatory biomarkers.

Laboratories findings	BE-COPD n = 55 (%)	TE-COPD n = 94 (%)	p-value
Leukocytes (#10^3/mm3) X±SD	9.96 ± 4.5	10.11 ± 5.2	0.862
Hemoglobin (gr/dl) X±SD	15.1 ± 2.7	15.2 ± 2.8	0.795
Platelets (#10^3/mm3) X±SD	210.2 ± 81.4	218.3 ± 88.1	0.595
Neutrophils n (%)	71.98 ± 19.91	71.24 ± 19.36	0.831
Total Neutrophils (#10^3/mm^3) X±SD	10.65 ± 12.73	9.2 ± 8.8	0.456
Lymphocytes n (%)	17.08 ± 13.49	17.61 ± 13.58	0.741
Total lymphocytes (#10^3/mm3) X±SD	1.555 ± 1.61	1.535 ± 1.07	0.781
Eosinophils n (%)	2.37 ± 2.11	2.00 ± 1.45	0.215
Total Eosinophils (#10^3/mm3) X±SD	221.00 ± 253.96	204.04 ± 236.84	0.693
Eosinophils >2% n (%)	25 (45.4)	42 (44.6)	0.353
Total Eosinophils >200 (#10^3/mm3) n (%)	18 (32.7)	30 (31.9)	0.378
Eosinophils >3% n (%)	16 (29.0)	22 (23.4)	0.189
Total Eosinophils >300 (#10^3/mm^3) n (%)	10 (18.1)	15 (15.9)	0.349
CRP (mg/dl) X±SD	7.08 ± 9.3	5.53 ± 6.7	0.252
Procalcitonin (ng/ml) X±SD	0.56 ± 0.62	0.38 ± 0.39	0.315
T helper lymphocytes			
Treg (%), X±SD	9.10 ± 2.1	8.48 ± 2.07	0.128
Th1 (%), Median [range]	1.70 [1.14–3.80]	1.50 [1.30–2.80]	0.472
Th2 (%), Median [range]	2.10 [1.30–3.30]	1.40 [1.20–1.80]	0.001
Th2/Th1 ratio, Median [range]	1.22 [0.58–2.57]	0.71 [0.40–1.15]	0.004
Th17 (%) Median [range]	7.2 [3.27–10.20]	7.1 [4.45–9.77]	0.516

BE-COPD, biomass exposure-related COPD; TE-COPD, tobacco exposure-related COPD; CRP, C-reactive protein; Treg, T helper lymphocytes; Th2, Lymphocytes Th2; Th17, Lymphocytes Th17.

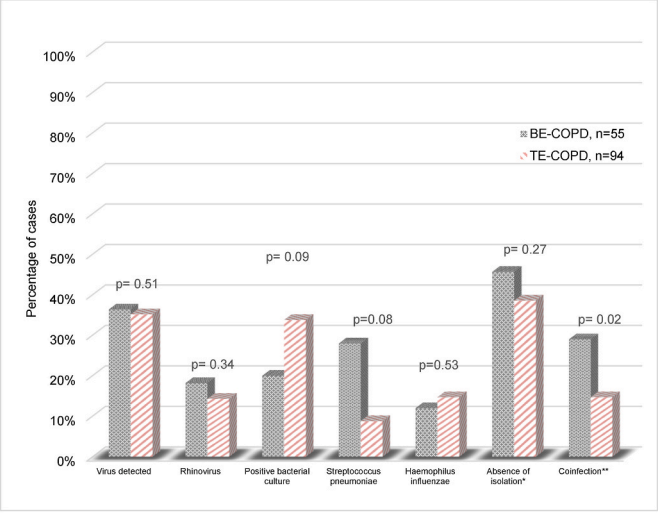

Fig. 1. Microbiological profiles prevalence during exacerbation.
BE-COPD, biomass exposure-related COPD; TE-COPD, tobacco exposure-related COPD.
* No viral or bacterial isolation, ** Viral or bacterial co-infection detected by viral PCR and bacterial culture of sputum.

associated with biomass exposure.

The first finding was that moderate or severe exacerbation characteristics were similar in patients with BE-COPD and TE-COPD. Although the biomass phenotype has a specific characteristic of small airways [10,21] that presumably predisposes the patient to a higher rate of exacerbations, in this study, we showed that when a patient with BE-COPD presented with an exacerbation, their clinical and lung function history, levels of inflammatory biomarkers, etiological agent, use of pharmacological interventions, health resources, severity of the exacerbation, duration of hospitalization and mortality were similar to

Table 4
Risk factors associated with hospitalization or mechanical ventilation.

Variable	OR	CI 95%	p-value
Hospitalization risk factors			
TE-COPD	1.78	[0.75–4.20]	0.18
Age	1.026	[0.994–1059]	0.11
Virus isolation	0.62	[0.43–0.89]	0.03
Non-vaccination	1.48	[1.30–4.61]	0.005
High CPR	1.17	[1.10–1.24]	0.001
Mechanical ventilation risk factors			
BE-COPD	0.28	[0.08–0.82]	0.02
Age	0.953	[0.90–1.02]	0.14
High CRP	1.016	[0.95–1.08]	0.61
Non-vaccination	2.85	[1.32–6.17]	0.008
Virus isolation	0.595	[0.19–1.83]	0.36

BE-COPD, biomass exposure-related COPD; TE-COPD, tobacco exposure-related COPD; CRP, C-reactive protein; OR, Odds Ratio; CI, Confidence interval.

those of the TE-COPD group. These findings are relevant because BE-COPD has been treated as a negligible disease regarding its social burden, costs, and health policies. Considering the high expenses generated during an exacerbation, our findings are highly important. Other researchers have investigated how different the exacerbations are in BE-COPD in comparison with TE-COPD. A study [22] reported that nonsmokers had a higher rate of exacerbations and higher health care resource utilization than smokers. They showed a significantly elevated frequency of acute symptomatic worsening, emergency visits, and hospitalization in the last year relative to nonsmokers. The frequency of exacerbations in the last year has been considered a risk factor for an increasing number of exacerbations. In our study, at least 50% of patients in both groups were considered to have frequent exacerbations, and fifty percent of the patients in both groups were hospitalized due to exacerbations. At least 25% of patients in both groups had experienced one hospitalization related to an exacerbation in the previous year. By using high-resolution computerized tomography (HRCT), we previously reported that BE-COPD have a predominantly bronchial phenotype and a major frequency of bronchiectasis than TE-COPD [10]. However, in the present study, the predominantly bronchial phenotype of BE-COPD was not a factor contributing to a greater number of exacerbations. Although we did not evaluate the patients by HRCT, we infer that the airway damage in these women is similar to those with biomass-induced COPD reported by previous studies [6]. In contrast, the severity of exacerbations in patients with TE-COPD required more support with mechanical ventilation and could be associated with a higher level of emphysema in comparison with BE-COPD [6,10,23,24].

The second finding is that although the inflammatory biomarkers were similar in both types of COPD, there was a tendency for an inflammatory pattern predominant to a cell-mediated inflammatory microenvironment involving Th2 and eosinophils during exacerbations of BE-COPD. In patients with stable BE-COPD, some data on this eosinophilic inflammatory tendency describe the elevation of biomarkers such as the exhaled fraction of nitric oxide, IgE, and sputum eosinophils [9,24–26]. For example, Chong L Ling et al. although they did not observe differences in exacerbations in COPD due to biomass compared with smokers with COPD, observed more allergic symptoms, such as rhinitis and asthma, in their BE-COPD sample [27]. These findings suggest a Th2-mediated profile and this has been corroborated in target organs in patients with chronic bronchitis with a predominance of eosinophilia in the airways during an exacerbation [28]. A possible explanation associated with these Th2 profiles is the hypothesis of immunotoxin mechanisms when subjects are exposed to particulate matter and compounds of organic materials found in wood, particulate matter, or other fuels, such as diesel or kerosene [29–33]. This inflammatory profile may suggest a trait treatable with targeted interventions such as individualized dosing of systemic steroids during AECOPD [34]. In our study, the eosinophil counts were similar between BE-COPD and TE-COPD, and in both groups, only 20% of the patients had eosinophil

counts higher than 300 ml. We did not find a correlation between eosinophil counts and Th2, as other authors have [35], probably because of the small sample size in our study.

The third finding was that patients with BE-COPD are susceptible to developing infectious exacerbations with microbiological patterns similar to those of patients with TE-COPD. We found that the presence of either a respiratory virus or bacteria was isolated from more than 50% of the BE-COPD patients, similar to TE-COPD. The predominant virus was rhinovirus, and the predominant bacteria was pneumococcus. Experimental findings suggest that 1) carbon loading of human alveolar macrophages results in impaired bacterial phagocytosis [36]. 2) In humans with BE, the duration and density of pneumococcal carriage are increased, which predicts pulmonary infection with *Streptococcus pneumoniae* [37]. 3) *Streptococcus pneumoniae* sequencing as part of the oropharyngeal microbiome reveals changes in the upper respiratory airway microbiome following BE. 4) These changes have been shown to occur in the upper respiratory microbiome following BE [38] and may plausibly alter the respiratory mucosal microenvironment sufficiently to produce respiratory infections [39]. 5) A similar association of colonization in the respiratory tract with a reduction in lung function was observed in BE-COPD and TE-COPD, showing that BE is associated with a similar innate immunity defect in patients with TE-COPD [40]. Due to this susceptibility and this study's findings, it is essential to facilitate access to vaccination since we found that nonvaccination was significantly associated with hospitalizations and MV; perhaps the development of new vaccines could also be considered since the COPD population is susceptible to exacerbation after infection by other agents.

5. Conclusions

Exacerbations among the TE-COPD and BE-COPD groups in the Mexican population have similar clinical behavior, microbiology, and severity; however, patients with TE-COPD require mechanical ventilation more frequently, and patients with BE-COPD seem to have an inflammatory pattern mediated by Th2 lymphocytes during an exacerbation.

The limitations of this study are as follows: This study was performed in one center, a local tertiary clinic; therefore, our results might not necessarily be generalizable to other clinical settings. In addition, the sample size looks small; however, in terms of the global prevalence of COPD in Mexico, the number of cases may be appropriate.

The strengths of this study are as follows: This is an observational prospective study, mainly including patients with moderate or severe exacerbation in whom viral and bacteriological samples and biomarkers of inflammation were collected in real-time during the exacerbation event. These assessments make our observations more solid.

CRediT authorship contribution statement

Raúl H. Sansores: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Paulina Paulin-Prado:** Investigation, Writing – review & editing. **Robinson Robles-Hernández:** Data curation, Formal analysis, Validation, Writing – review & editing. **Francisco Montiel-Lopez:** Data curation, Formal analysis, Validation, Writing – review & editing. **Nora Edith Bautista-Félix:** Data curation, Formal analysis, Validation, Writing – review & editing. **Nicolás Eduardo Guzmán-Bouilloud:** Investigation, Writing – review & editing. **Ramcés Falfán-Valencia:** Investigation, Writing – review & editing. **Gloria Pérez-Rubio:** Investigation, Writing – review & editing. **Rafael de Jesús Hernández-Zenteno:** Investigation, Writing – review & editing. **Fernando Flores-Trujillo:** Investigation. **Oliver Pérez-Bautista:** Investigation, Writing – review & editing. **Alejandra Ramírez-Venegas:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Instituto Nacional de Enfermedades Respiratorias reports financial support was provided by chamber of Deputies of Mexico.

Acknowledgments

This work was supported and funded by a non-restricted grant allocated for the care of women with respiratory diseases associated with biomass by the legislature of the Chamber of Deputies of Mexico.

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