



# Affective Comorbidity Associated with Symptoms, Lung Function, and Differences Between Patients with COPD for Biomass and Tobacco Smoke Exposure

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## Abstract

Anxiety and depression are common entities in patients diagnosed with Chronic Obstructive Pulmonary Disease (COPD). This study aimed to determine the prevalence of affective comorbidity (depression and anxiety) associated with lung function, functional capacity, dyspnea, and quality of life; as well as the differences between groups of patients diagnosed with COPD associated with biomass (COPD-BE) and patients with COPD secondary to tobacco (COPD-TS). Comparative cross-sectional observational study. Multiple hierarchical regression models, analysis of variance, and covariance were carried out. A total of 291 COPD patients were evaluated, symptoms of depression were found to be higher in patients with COPD-BE than in patients with COPD-TS ( $5.3 \pm 4.2$  versus  $4.2 \pm 4$ ,  $1$ ,  $p = 0.016$ ), as well as anxiety complications ( $4.1 \pm 3.8$  versus  $3.8 \pm 3.3$ ,  $p = 0.095$ ), although with anxiety it was not statistically significant, being adjusted for age and FEV1. Patients with COPD-BE had higher prevalence of depression, compared to COPD-TS (41.2% versus 27.7%,  $p = 0.028$ ). In the multivariate regression models, the variables of dyspnea and quality of life were associated with depression and anxiety, explaining 25% and 24% of the variability, respectively. Depression is higher in COPD-BE patients compared to COPD-TS patients, it is necessary to consider affective comorbidity in routine evaluation and provide a comprehensive intervention to prevent the effects on other clinical conditions of the disease.

**Keywords** Depression · Anxiety · Comorbidity · Chronic obstructive pulmonary disease

## Introduction

Currently, 64 million persons suffer from Chronic Obstructive Pulmonary Disease (COPD) and 3 million individuals die from it each year. It is estimated that, by the year 2030, it will have become the third cause of death worldwide. Projective figures reported by the World Health Organization (WHO) regarding the increase in COPD affirm that these

will remain the main causes of death worldwide until the year 2030 (*Chronic respiratory diseases*, n.d.).

Additionally, COPD is a disease with multiple comorbidities. Among the commonest of these found in the European SCA-3/MJD Initiative (ESMI) study are psychological disorders, anxiety (18.3%), or depression (15%), associated with risk of death (Almagro et al., 2015). The Global Initiative for Chronic Obstructive Lung Disease (GOLD, 2020) (*Gold Reports for Personal Use*, n.d.) recognizes that patients frequently presented depression or anxiety as comorbidities and that both caused a negatively impact on the disease course, the control of symptoms, and Health-Related Quality of Life (HRQOL). In a systematic review, COPD patients with anxiety experienced their first hospitalization earlier compared with COPD patients without anxiety; the former also have higher rates of mortality and hospital re-admission after an exacerbation (Atlantis et al., 2013). It is known that the QOL of a chronic COPD patient can be especially complicated by depression, which can lead the patient to a vicious circle:

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depressed mood will decrease the capacity needed to cope with chronic illness, physical symptoms will be less tolerable, and the exhausting effect of the disease may be related with depressed mood (Atlantis et al., 2013; Mewes et al., 2016). It has also been reported that depression doubles the risk of COPD emergency care, regardless of disease severity, or physical comorbidity (Blakemore et al., 2019). A recent meta-analysis, which was based on five eligible case–control studies, found that persons with history of COPD are more likely to commit suicide (Odds Ratio [OR] 1.90; 95% Confidence Interval [95% CI] 1.272.48;  $p=0.002$ ) (Sampaio et al., 2019).

Especially in developing countries, COPD is associated with exposure to biomass smoke both in rural and urban areas (Camp et al., 2014; Pathak et al., 2020; Ramírez-Venegas et al., 2018) COPD due to Biomass (smoke) Exposure (COPD-BE) manifests with less emphysema but more air trapping, and also with more symptoms, more impact in activities and quality of life, and lower oxygen saturation at rest and during exercise compared to women with COPD due to exposure to tobacco smoke (COPD-TS) (Camp et al., 2014). However, we are unaware of studies of depression and anxiety in COPD-BE, likely to be, as in COPD-TS, a negative factor that adversely affected the disease course.

Therefore, the aim of this study was to determine the prevalence of affective comorbidity (depression, anxiety) and their relationship with lung function, dyspnea, and QOL in patients with COPD-BE in comparison with COPD-TS.

## Materials and Methods

### Design

This was an observational, cross-sectional study conducted in patients diagnosed with COPD-BE and in patients with COPD-TS, performed at the National Institute of Respiratory Diseases (INER), a public referral center for respiratory diseases mostly for uninsured and the economically deprived population of Metropolitan Mexico City.

### Participants

A total of 291 patients were recruited from a cohort of patients from the INER COPD Clinic during their usual consultation. Eligible participants were aged between 60 and 85 years, with diagnosis of COPD according to American Thoracic Society/European Respiratory Society standards for diagnosis and treatment of patients with COPD, stable and without exacerbations in the last 6 weeks. Patients with COPD-BE were never smokers, who cooked with a biomass stove for at least 6 months and

who had at least 100 h-years of exposure (the product of the number of years cooking with wood stoves multiplied by the average number of hours spent daily in the kitchen) (Pérez-Padilla et al., 2012; Ramírez-Venegas et al., 2018), whereas patients with COPD-TS were never exposed to biomass smoke during cooking and had at least 10 pack-years of cumulative smoking. We excluded patients with additional clinical diagnosis of sleep apnea, other chronic respiratory diseases (bronchiectasis, lung cancer, cystic fibrosis), or any acute or chronic condition that would limit the patient's ability to participate in the study. We used Mexican standard reference equations for predicted (pred) values of Forced Expiratory Volume in the first second ( $FEV_1$ ) and for Forced Vital Capacity (FVC), which are similar to the third National Health and Nutrition Examination Survey values for Mexican-Americans (Pérez-Padilla et al., 2001).

### Measures

To determine the prevalence of anxiety and depression, we applied the Hospital Anxiety and Depression Scale (HADS) validated in Mexican population, (Orozco et al., 2013) which is composed of 14 questions for the anxiety subscale and seven for the depression subscale (Zigmond & Snaith, 1983) The questions refer to the subject's well-being during the previous two weeks. Required short time (2 to 5 min) to complete the scale. Each question has four responses rated on a scale of 0–3, with a maximal score of 21 for each subscale (indicating a high level of depression and anxiety symptoms). Previous studies have suggested the limit for the depression subscale of 6 and of 8 for the anxiety subscale, which could produce a sensitivity of 0.82 (95% CI 0.73–80) and a specificity of 0.74 (95% CI 0.60–0.84) (Brennan et al., 2010; Snaith, 2003) Following standardized procedures by trained interviewers, a face-to-face evaluation was carried out by a Specialist Psychologist.

For each patient, the following information was collected: social demographics; biomass smoke exposure history; tobacco smoke exposure history; exacerbations in the previous year, and healthcare resource utilization during last 12 months. The level of dyspnea was measured using the modified scale of the Medical Research Council (mMRC) (Bestall et al., 1999). The COPD Assessment Test (CAT) was employed to evaluate the impact of the disease and symptoms, with scores of  $\geq 10$  indicating a very symptomatic patient (Jones et al., 2009). Each participant completed a 6-min walking test (6MWT) and the distance walked (6MWD) was calculated. We measured Oxygen Saturation ( $SpO_2$ ) and heart rate using a pulse oximeter, at rest and at the end of the 6MWT.

## Ethics Approval and Informed Consent

All patients signed an informed consent form, and the study was approved by the Ethics and Research Committee of the National Institute of Respiratory Diseases “Ismael Cosío Villegas” of Mexico City, with reference approval number C-2217.

## Data Analysis

Statistical analysis was conducted by using SPSS ver. 19.0 statistical software (SPSS, Chicago, IL, USA). Normality distribution was tested by the Shapiro–Wilk test for numeric variables. Categorical variables were described by frequencies and percentages, while continuous variables with normal distribution were described using means and Standard Deviations (SD). We utilized ANalysis Of VAriance (ANOVA) and ANalysis of COVAriance (ANCOVA) or the Chi2 test to compare groups. We compared affective comorbidity symptoms (anxiety and depression) between COPD-BE and COPD-TS (women and men), using multiple regression lineal analysis, adjusted for age, sex, and FEV<sub>1</sub>, which are likely confounders for anxiety and depression scores. Finally, the association was evaluated with Pearson correlations and multiple hierarchical regression models to determine the main effects and interactions with anxiety and depression.

## Results

A total of 291 patients with COPD were evaluated. There were 207 patients with COPD-TS and 84 patients with COPD-BE. The patients had a mean age of  $72.8 \pm 9.1$  years, 55% (161) were male, a mean FEV<sub>1</sub> of  $58 \pm 24$  (percentage of predicted FEV<sub>1</sub>), CAT of  $9.6 \pm 6.9$ , mMRC of  $1.8 \pm 1.1$ , and 6MWD of  $382.4 \pm 105.7$  m. The prevalence of depression was 30.9% and there was one of 11.3% for anxiety in the total study population ( $n = 291$ ) (Table 1).

Table 2 presents the results of the comparison of demographic data and lung function, and the symptoms, quality of life, and 6MWD between COPD-BE ( $n = 85$ ), COPD-TS women ( $n = 47$ ), and men COPD-TS ( $n = 159$ ). Statistically significant differences between groups were found in age, height, and weight, lung function (FEV<sub>1</sub>% pred, FEV<sub>1</sub>/FVC), and 6MWD.

The prevalence of depression was 41.2% in patients with COPD-BE vs. 27.7% in patients with COPD-TS women and 26.4% in COPD-TS men ( $p < 0.05$ ). After being adjusted for age, sex, and FEV<sub>1</sub>% pred, we observed that the prevalence of depression and score was also higher in COPD-BE compared with other groups ( $p < 0.05$ ). No difference was found in terms of anxiety among the groups (Table 3).

**Table 1** General characteristics

	All patients $n = 291$
Exposures, $n$ (%)	
Biomass exposure	84 (28.9)
Hour-years	$314.5 \pm 287.8$
Tobacco exposure	207 (71.1)
Packs/year	$43.8 \pm 32.7$
Demographic data	
Age, (years)	$72.8 \pm 9.1$
Male $n$ (%)	161 (55)
Height (cm)	$157.4 \pm 11.2$
Weight (kg)	$64.7 \pm 17.1$
BMI ( $\text{kg}/\text{m}^2$ )	$26 \pm 5.8$
Lung function	
Post-bronchodilator	
FEV <sub>1</sub> % pred	$58.0 \pm 24$
FEV <sub>1</sub> /FVC	$52.8 \pm 16.1$
SaO <sub>2</sub> %	$87.8 \pm 5.1$
Symptoms, quality of life, and 6MWD	
mMRC score	$1.8 \pm 1.1$
CAT score	$9.6 \pm 6.9$
6MWD distance (m)	$382.4 \pm 105.7$
Affective comorbidity	
Depression $\geq 6$ prevalence $n$ (%)	90 (30.9)
Score	$4.3 \pm 3.9$
Anxiety $\geq 8$ prevalence $n$ (%)	33 (11.3)
Score	$3.6 \pm 3.4$

Data are presented as mean  $\pm$  Standard Deviation (SD)

*BMI* Body Mass Index; *FEV<sub>1</sub>* Forced Expiratory Volume in 1 Second; *FVC* Forced Vital Capacity, % *pred* percentage predicted; *SaO<sub>2</sub>* Oxygen Saturation; *mMRC* modified Medical Research Council dyspnea scale; *CAT* COPD Assessment Test; *6MWD* 6-min walking test

We also analyzed the association between depression and anxiety and sociodemographic and clinical variables. Table 4 depicts the correlations and linear regression analysis of the study variables ( $n = 291$ ), CAT scores correlated best with the depression score ( $r = 0.459$ ;  $p < 0.01$ ) and the anxiety score ( $r = 0.436$ ;  $p < 0.01$ ). The depression score also had a significant association with mMRC ( $\beta = 1.48$ ; 95% CI 1.06–2.07;  $p = 0.021$ ) and CAT ( $\beta = 1.09$ ; 95% CI 1.0–1.15;  $p = 0.000$ ) in the multiple linear analysis. Anxiety was associated with CAT ( $\beta = 1.12$ ; 95% CI 1.06–1.20;  $p = 0.000$ ) and FEV<sub>1</sub>% ( $\beta = 1.02$ ; 95% CI 1.00–1.04;  $p = 0.040$ ). On adjusting for age, post-bronchodilator FEV<sub>1</sub>% did not alter these results.

Table 5 depicts the results of hierarchical multiple regression equation to determine the main and interaction effects of sociodemographic and clinical variables for predicting depression and anxiety. In the models to predict

**Table 2** Comparison between the COPD-BE and COPD-TS groups

	COPD-BE		COPD-TS		<i>p</i> value
	Women		Women	Men	
	<i>n</i> = 85		<i>n</i> = 47	<i>n</i> = 159	
Demographic data					
Age, years	76 ± 7.5		71.2 ± 8.7	71.6 ± 9.6	0.001*
Biomass smoke exposure hours/years	298.5 ± 176.1		–	–	–
Tobacco smoke exposure pack/years	–		38.6 ± 24.8	45 ± 34.5	–
Height cm	145 ± 6.4		155.2 ± 7.7	164.6 ± 7.3	0.000*
Weight kg	54.9 ± 12.5		64.4 ± 19.9	70 ± 16.1	0.004
BMI kg/m <sup>2</sup>	26.1 ± 5.4		26.6 ± 7.7	25.8 ± 5.4	0.666
Lung function					
Post-bronchodilator					
FEV <sub>1</sub> % pred	69.8 ± 22.7		54.7 ± 20.4	52.6 ± 23.7	0.000*
FEV <sub>1</sub> /FVC	57.2 ± 11		52.5 ± 12.4	48.1 ± 13.5	0.000*
SaO <sub>2</sub> %	87.5 ± 5.1		88 ± 6.1	88 ± 4.8	0.79
Symptoms, quality of life, and 6MWD					
mMRC score	1.6 ± 1.0		1.9 ± 1.3	1.8 ± 1.1	0.433
CAT score	8.7 ± 6.7		11.4 ± 7.9	9.6 ± 6.7	0.097
6MWD distance (m)	338 ± 88.6		353.9 ± 110.3	413.1 ± 102.5	0.000*

The relationship is significant if  $p \leq 0.05$ . One-way ANOVA for continuous variables and chi-squared for categorical variables. Data are presented as mean ± Standard Deviation (SD)

ANOVA ANalysis Of VAriance; BMI Body Mass Index; FEV<sub>1</sub> Forced Expiratory Volume in 1 Second; FVC Forced Vital Capacity; % pred percentage predicted; SaO<sub>2</sub> Oxygen Saturation; mMRC modified Medical Research Council dyspnea scale; CAT COPD Assessment Test; 6MWD 6-min walking test

\*Statistically significant difference between groups

**Table 3** Results of the affective comorbidity in groups

Affective comorbidity	COPD-BE	COPD-TS		Crude <i>p</i> value	Adjusted <i>p</i> value
	Women <i>n</i> = 85	Women <i>n</i> = 47	Men <i>n</i> = 159		
Depression ≥ 6 prevalence % ( <i>n</i> )	35 (41.2)	13 (27.7)	42 (26.4)	0.052	0.028*
Score	5.3 ± 4.2	4.2 ± 4.1	3.9 ± 3.6	0.024	0.016*
Anxiety ≥ 8 prevalence % ( <i>n</i> )	13 (15.3)	5 (10.6)	15 (9.4)	0.383	0.192
Score	4.1 ± 3.8	3.8 ± 3.3	3.2 ± 3.1	0.158	0.095

Data are presented as mean ± Standard Deviation (SD) or percent of prevalence (%). Crude *p* value of ANOVA; Chi-square as appropriate. Adjusted *p* value of ANCOVA corrected for age and FEV<sub>1</sub>%

ANOVA ANalysis Of VAriance; ANCOVA ANalysis of COVAriance

\*Statistically significant difference between groups

the depression and anxiety scores, first, sociodemographic variables age and sex were introduced to control their possible effects. Then, the clinical variables (mMRC, 6MWD, CAT, and FEV<sub>1</sub>% pred) were introduced. In the multivariate analysis, age and sex alone explained 3% and 1%, respectively, of the anxiety and depression variance, and mMRC and CAT were significantly associated with anxiety and depression scores and explained 25% and 24%, respectively, of the variability.

## Discussion

We described (for the first time, to our knowledge) the high prevalence in depression and anxiety comorbidities in COPD associated with biomass smoke. The prevalence of depression in COPD-BE was nearly twice that of COPD-TS (women and men). COPD-BE exhibited better lung function, but also presented a worse Quality-Of Life (QOL) measurement by the CAT questionnaire compared

**Table 4** Pearson correlations and linear regression analysis of affective comorbidity with all variables

Variables	Depression			Anxiety		
	<i>r</i>	<i>p</i> value	$\beta$ (95% CI), <i>p</i> value	<i>r</i>	<i>p</i> value	$\beta$ (95% CI), <i>p</i> value
Age	0.06	0.306	1.00 (0.96, 1.03), 0.896	−0.09	0.14	0.99 (0.93, 1.04), 0.745
mMRC	0.365	0	1.48 (1.06, 2.07), 0.021*	0.222	0	1.31 (0.78, 2.18), 0.296
CAT	0.459	0	1.09 (1.04, 1.15), 0.000*	0.436	0	1.12 (1.06, 1.20), 0.000*
FEV <sub>1</sub> % pred	−0.03	0.654	1.00 (0.98, 1.01), 0.592	0.009	0.873	1.02 (1.00, 1.04), 0.040*
6MWD	−0.25	0	0.99 (0.99, 1.00), 0.589	−0.01	0.876	1.00 (1.00, 1.01), 0.070

*r*, Pearson correlation; *p* value, Statistical Significance

mMRC modified Medical Research Council dyspnea scale; CAT COPD Assessment Test; FEV<sub>1</sub> Forced Expiratory Volume in 1 Second; % pred percentage predicted; 6MWD 6-min walking test

\*Statistically significant

**Table 5** Hierarchy multiple regression analysis

Step and variables	Anxiety		Depression	
	$\beta$ step 1	$\beta$ step 2	$\beta$ step 1	$\beta$ step 2
Control variables	−0.09	−0.07	−0.03	−0.03
Age (years)	−0.160*	−0.185**	−0.145***	−0.113*
Male				
Main effects		0.136*		0.347**
mMRC		0.122*		0.109
FEV <sub>1</sub> %		0.197**		−0.03
6MWD		0.438**		0.347**
CAT				
<i>R</i>	0.173	0.503	0.153	0.507
<i>R</i> <sup>2</sup>	0.03	0.253	0.016	0.24

$\beta$  values correspond to standardized regression coefficients

mMRC modified Medical Research Council dyspnea scale; FEV<sub>1</sub> Forced Expiratory Volume in 1 Second; % pred percentage predicted; 6MWD 6-min walking test; CAT COPD Assessment Test

\**p* < 0.05; \*\**p* < 0.01

with COPD-TS. In a previous study, on matching for age and severity of airflow obstruction, women exposed to biomass smoke had a lower QOL and more hypoxemia than smokers (Camp et al., 2014).

Women with COPD have been reported to have higher negative affective comorbidity than men. Women had higher susceptibility to the negative effects of COPD on health status (SGRQ total and impact scores) (Antonelli-Incalzi et al., 2003), and appear to be more susceptible to psychological impairment, which correlates with some specific symptomatic aspects of the disease, such as dyspnea (Di Marco et al., 2006).

It was surprising for us to observe the high prevalence of depression in COPD-BE compared with COPD-TE (women and men) in our cohort. Usually, women with COPD-BE are unaware of the damage caused by the use of wood for cooking, but also that they present depression or anxiety. In addition, they tend to delay medical consultation until their

symptoms are severe, or until they experience a moderate to severe exacerbation. Women with COPD-BE needed to resolve other priorities, not mood alterations to such a great extent, and are unaware of depressive and anxiety terms. Even we asked them, they tended to deny symptoms. On asking about specific depressive or anxiety symptoms by employing a questionnaire such as the HADS, we can identify that these women suffer from depression and anxiety. A hypothesis of underreporting in anxiety and depression symptoms could come from the contextual situation in Mexico, being a population with low economic resources and a lower educational level.

The great majority of information on the prevalence of affective comorbidity in COPD has derived from patients with COPD-TS; the interaction of depression and anxiety in patients with COPD-BE was unknown. Therefore, it was very relevant to evaluate the effective comorbidity in this vulnerable group, which also requires interventions adapted to socioeconomic conditions, in that these variables can interact as mediators or moderators in anxiety and depression. In addition, considering that the presence of anxiety and depression as comorbidities in COPD contribute to a substantial burden of COPD-related morbidity by impairing QOL and reducing treatment adherence (Hanania & O'Donnell, 2019; Khmour et al., 2012; Miravittles et al., 2017; Pooler & Beech, 2014; Yohannes et al., 2018) In particular, depression has been identified as an independent risk factor for frequent exacerbations (Deng et al., 2020). The results we obtained indicate that it is justified to identify people with the symptoms of anxiety and depression (particularly occurring simultaneously) to provide them with additional psychological and therapeutic support in order not to further exacerbate the disorder but to reduce and eliminate it. The mental health and public health implications of these results are necessary to prioritize routine psychological evaluation in COPD patients, not only the tobacco-related phenotype, but also in patients with the biomass phenotype, being a vulnerable population in the social sense and psychological, it is important to provide the patient with tools

that will allow him to live with the disease in the best possible way and avoid its psychological effects.

We assessed the relationship between affective comorbidity (anxiety, depression) with pulmonary function, dyspnea, exercise capacity, and health-related QOL in these populations. The multivariate model developed with all of the study variables study demonstrated the association of affective comorbidity scores and the usual characteristics of COPD severity (degree of dyspnea, symptoms, and exercise capacity 6MWD). This model explains up to 25.3% of anxiety variability and 24.0% of depression variability. Our results coincide with those reported in other investigations of associations of affective comorbidity and clinical variables (Hanania & O'Donnell, 2019; Mathew et al., 2019; Mewes et al., 2016; Pascal et al., 2017; Yohannes et al., 2018).

In our population, anxiety and depression were associated with higher CAT and dyspnea, scores reflecting poorer QOL and also increased breathlessness. Other studies had reported similar results. Dua et al. (2018), in an observational, prospective, multicenter study of 128 patients with and without psychiatric comorbidities, both baseline dyspnea scores of mMRC ( $p=0.002$ ) and CCQ scores for QOL ( $p<0.001$ ) were significantly higher in patients with psychiatric comorbidity. Ramírez-Venegas et al. (2018) showed that in COPD-BE, the prevalence of cough, phlegm, and wheezing are higher but, on the other hand, lung function was more preserved than in COPD-TS (Ramírez-Venegas et al., 2006; Regalado et al., 2006).

Finally, more recent evidence highlighted the effect of inflammation on the mood of COPD (Ding et al., 2021; Long et al., 2020). Systemic inflammation runs through the COPD patient's entire life cycle because of the disease, from the airways to the target organs and tissues throughout the body and may be related to its comorbidities such as anxiety and depression. Hence, it is necessary to find how these inflammatory markers change in COPD during acute exacerbation, and whether there are some potential associations with depression and/or anxiety, deserve further research. Which contributes to highlighting the importance of promoting coping skills and developing resilience to reduce effective comorbidity.

## Limitations

Our analysis is only cross-sectional survey and temporal sequence of COPD, and the affective symptoms or the impact on exacerbations cannot be determined. The analysis of depressive and anxiety symptoms should be considered from a proximal perspective, at the present time, it would be worth evaluating longitudinally, which allows a long-term analysis in these variables. Poverty is associated with biomass smoke exposure and is also a marker of access to healthcare, nutrition, and vaccination, impacting general

health and the risk for COPD and may also exert an effect on affective comorbidity. The women who were recruited to participate in this study were seen at the national hospital for low-income residents; thus, current socioeconomic status between the groups was probably similar. Nevertheless, we cannot assess the impact of other factors that can mediate or moderate anxiety and depression, such as social support, emotional regulation, or personality characteristics.

## Conclusion

Women with COPD-BE, common in developing countries, have a high prevalence of affective comorbidity. It is very relevant to assess affective comorbidity and intervene early in a routine manner in these patients. Failure to intervene in this comorbidity renders these women with COPD-BE more susceptible to having more exacerbations and a worse quality of life. As recommended for COPD, comorbidities should be identified, including psychological comorbidities, and comprehensive care should be offered to patients by an interdisciplinary team.

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**Author Contributions** AH collected the data and drafted the manuscript. RP and IV revised the manuscript for submission. AH and AR completed the analysis and assisted in drafting paper. BM provided overall guidance on paper structure and content and revised early drafts. All authors read and approved the final manuscript.

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## Declarations

**Conflict of interest** The authors declare that they have no competing interests.

**Research Involving Human and Animal Rights** All Procedures performed in studies involving human participants were in accordance with the ethical standards of National Institute of Respiratory Diseases Ismael Cosío Villegas Mexico and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by the authors.

**Informed Consent** Informed consent was obtained from all individual participants included in the study.

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