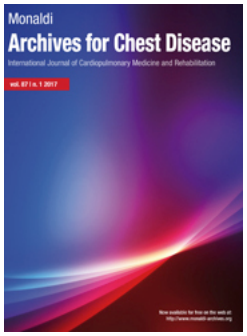

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Prevalence and risk factors for chronic pulmonary aspergillosis in chronic obstructive pulmonary disease patients with acute exacerbations

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Abstract

Chronic obstructive pulmonary disease (COPD) patients often experience acute exacerbations requiring hospitalization. Recently, attention has focused on Aspergillus sensitization in the airways of these COPD patients. This study aimed to assess the prevalence of chronic pulmonary aspergillosis (CPA) in COPD patients with acute exacerbations and identify associated risk factors. A cross-sectional descriptive study was conducted at the Jawaharlal Institute of Postgraduate Medical Education and Research from January 2021 to June 2022. Sixty-one COPD patients presenting with acute exacerbations were included. Demographic details, blood investigations, and sputum examinations were performed for all patients. A high-resolution computed tomography thorax was conducted for eligible patients. The prevalence of CPA among patients with an acute exacerbation of COPD was found to be 9.8%, with chronic cavitary pulmonary aspergillosis being the most common presentation (50%). Among post-tubercular COPD patients, the prevalence of CPA was significantly higher at 22.7%. Hemoptysis ($p<0.001$) and a previous history of tuberculosis ($p=0.008$) were associated with Aspergillus sensitization. This study highlights the substantial prevalence of CPA in COPD patients with acute exacerbations, particularly in those with a history of tuberculosis. Early recognition and targeted management of CPA in COPD patients may improve outcomes and reduce hospitalization rates. Further large-scale multi-center studies are needed to validate these findings and comprehensively address the impact of CPA on all COPD patients.

Key words: ACO, COPD, functional, inflammatory, prevalence, aspergillus colonization.

Introduction

Chronic pulmonary aspergillosis is an emerging infectious disease that affects 3 million individuals worldwide and is expected to have a 5-year survival rate of 15% if left untreated [1]. Pulmonary aspergillosis may range from airway colonization to rapidly invasive and life-threatening disseminated disease depending on the patient's immune status. Simple aspergilloma, chronic cavitary pulmonary aspergillosis (CCPA), chronic fibrosing pulmonary aspergillosis (CFPA), aspergillus nodules, and subacute invasive aspergillosis (SAIA) constitute the spectrum of CPA [1-3]. The risk factors for developing CPA are tuberculosis, non-tuberculous mycobacterial infection, allergic bronchopulmonary aspergillosis (ABPA), previous pneumothorax, and treated lung cancer [2].

Chronic Obstructive Pulmonary Disease (COPD) is characterized by permanent airflow obstruction due to abnormalities of airways, and alveoli and is associated with significant morbidity and mortality [4,5]. The primary causes of COPD exacerbations have been identified as viruses and bacteria. COPD patients with moderate to severe exacerbations may have filamentous fungus as a colonizer. The possible contribution of fungal colonization and infection in the pathogenesis of COPD is still unclear [6]. Literature search demonstrates that patients with severe exacerbation of COPD receiving corticosteroids and antibiotics are at a higher risk of developing invasive pulmonary aspergillosis, which if left untreated, has a mortality rate of 100% [7]. Subacute invasive aspergillosis, an entity of CPA is an indolent form of invasive aspergillosis and can occur in COPD patients receiving corticosteroids. COPD exacerbations affect the quality of life and increase morbidity and mortality. Hence, it is prudent to know the impact of CPA on the same. CPA treatment necessitates the use of antifungals. Identifying a treatable cause for COPD exacerbation will reduce frequent hospital admissions and economic burden in low- and middle-income countries.

Prior studies in Western countries have shown that there is an association between CPA in COPD patients with exacerbations, but the exact prevalence has not been quoted. Our study aimed to assess the prevalence and risk factors contributing to the development of CPA in patients with an acute exacerbation of COPD.

Materials and Methods

This cross-sectional descriptive study was conducted at the Jawaharlal Institute of Postgraduate Medical Education & Research (JIPMER) from January 2021 to June 2022. Patients aged ≥40 years having clinical and spirometry diagnosis of COPD by post-bronchodilator forced expiratory volume in the first second (FEV1) to forced vital capacity (FVC) ratio less than 0.7 and with worsening of baseline symptoms of cough, breathlessness, and sputum production in fourteen days as per GOLD (Global Initiative for Chronic Obstructive Lung Disease) definition for acute exacerbations were recruited from the pulmonary medicine outpatient department or emergency department. Patients with pre-existing diagnoses of asthma, bronchiectasis, interstitial lung disease, lung cancer, chronic kidney diseases, persons living with HIV (PLHIV), hematological malignancies, and those on long-term oral steroids for more than 3 months or immunosuppressants were excluded.

After obtaining ethical clearance and written informed consent from patients, detailed demographic information, smoking status (by National Health Interview Survey conducted by Centers for Disease Control and Prevention), biomass fuel exposure, previous history of exacerbations in the last 1 year, and co-morbidities were recorded in a preformed proforma. Symptomatology of COPD patients was analyzed and recorded based on the St. George Respiratory Questionnaire for COPD patients (SGRQ-C) (used with permission) and modified Medical Research Council (mMRC) dyspnea scale (used with permission). Sputum investigations, including gram stain, pyogenic culture, KOH staining, fungal culture, and acid-fast staining were performed for all recruited COPD patients having an exacerbation. Sputum samples were inoculated onto 5% sheep blood agar and Mac Conkey agar and incubated for 24-48 hours. For fungal pathogens, a 10% KOH mount was prepared, and the remaining portion of the sputum was inoculated into Sabouraud's dextrose agar. Sputum samples were also sent for acid-fast bacilli staining and liquid culture for mycobacterium tuberculosis.

A venous blood sample was taken within 2 hours or before the administration of any treatment in the emergency department. Blood investigations were also performed, for complete blood count with absolute eosinophil count, renal function test, liver function test, and aspergillus specific IgG serology. Aspergillus fumigatus IgG antibodies were analyzed using qualitative immunoenzymatically determination based on the ELISA technique. The manufacturer suggests

that a concentration lower than 5 AU/mL is considered negative, while concentrations between 5 and 10 AU/mL are deemed intermediate, and concentrations equal to or greater than 10 AU/mL are considered positive. Baseline chest X-ray (posterior-anterior view) and high-resolution computed tomography (HRCT) of the thorax in full inspiration were conducted for eligible patients with SIEMEN 6 slice CT placed in department of radio-diagnosis, JIPMER. A single radiologist without blinding evaluated HRCT findings to classify patients under different CPA spectrum and CPA diagnosis was based on the criteria of European society of clinical microbiology and infectious diseases (ESCMID) guidelines [3].

Patients underwent spirometry 6 weeks post-discharge after stabilization (when patients were no longer in respiratory distress, able to complete a full sentence, and not using accessory muscles of respiration) by the Jaeger Masterscreen PFT machine (CareFusion Ltd., Basingstoke, UK). Spirometry results were interpreted according to American Thoracic Society guidelines, and COPD severity was categorized as per GOLD criteria (GOLD stage 1: FEV1>80%, GOLD stage 2: 50%-80%, GOLD stage 3: 30%-49%, GOLD stage 4: <30% [5].

Statistical analysis

Data analysis was performed using SPSS (Statistical Package for the Social Sciences) version 19 software. Categorical variables were presented as numbers and percentages, while continuous variables were expressed as mean with standard deviation or median with interquartile range based on normality of distribution tested by the Shapiro-Wilk test. The association between various categorical variables and CPA status was assessed using the chi-square test or Fisher's exact test. Binary logistic regression analysis was conducted to identify risk factors for CPA. A p-value less than 0.05 was considered statistically significant.

Sample size calculation

The sample size was calculated based on a previous study by Shawki et al. [8], which included 20 patients with an acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Using an absolute precision of 10%, attrition of 10%, and a 95% confidence interval, the calculated sample size was 61 patients.

Results

A total of 98 patients were screened during the study period from December 2020 to June 2022. Thirty-seven patients were excluded from the study as 12 patients could not perform spirometry in follow-up visits,10 patients had coexistent asthma, 7 patients had bronchiectasis on HRCT chest and 8 patients were lost to follow-up. A total of 61 patients were recruited during the study period from December 2020 to June 2022. The demographic characteristics and clinical symptoms of the study participants are summarized. The majority of patients were aged between 51 to 70 years with a mean age of 62±11 and with male preponderance comprising 83.6% of the cohort. Most patients were smokers (72.1%), and nearly half of them had exposure to biomass fuel (49.2%). Dyspnea was the most common symptom reported by all patients (100%) (Table 1).

Among the patients, 29.5% (n=18) showed aspergillus sensitization detected using aspergillus-specific IgG antibody. Hemoptysis was significantly associated with Aspergillus sensitization ($p<0.001$), while other symptoms and comorbidities did not show significant associations. History of previous tuberculosis showed a statistically significant association with Aspergillus sensitization ($p=0.008$). Patients in moderate GOLD stages were more likely to have Aspergillus sensitization ($p<0.01$) (Table 2).

Out of the 61 patients, 6 patients (9.8%) were diagnosed with chronic pulmonary aspergillosis (CPA). The prevalence of CPA was further analyzed based on underlying COPD etiology. Among patients with TB-COPD, the prevalence of CPA was significantly higher at 22.7%. In contrast, COPD patients with bullous emphysema had a lower prevalence of CPA at 2.6%. This difference was statistically significant ($p=0.040$) (Figure 1). Among CPAs, chronic cavitary pulmonary aspergillosis (CCPA) was the most common presentation observed in 3(50%) of the cases (Figure 1).

The microbiological pattern of sputum samples isolated from a subset of patients was analyzed and only 23 patients (37%) showed growth of an organism. Among the patients, 36.1% showed growth in pyogenic culture while fungal culture was identified in one patient with Aspergillus species. (Table 3). The predominant pathogens identified were Gram-negative organisms, including *Pseudomonas aeruginosa, Klebsiella pneumoniae*, *Acinetobacter baumannii*, and Enterobacteriaceae.

Univariate analysis to assess the risk association of CPA based on serum aspergillus-specific IgG antibodies in AECOPD patients showed that diabetes mellitus and hypertension had an increased odds of aspergillus sensitization, although it did not reach statistical significance (Table 4).

Discussion

The prevalence of chronic pulmonary aspergillosis (CPA) in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) has been sparsely explored in the literature, particularly in the Indian subcontinent where the climatic conditions and environment play a role in abetting the growth of these organisms. Previous studies in Western countries have indicated an association between CPA and COPD patients. In our study, we examined 61 patients with AECOPD, with the majority (39.3%) falling within the 51-60 years age group. The mean age of the study participants was 62±10.1 and these findings aligned with previous studies conducted by Shawki et al. and Nguyen et al.in the Egyptian population, where the average age noted was 59±2.3 and 54.9 ±13.9 respectively [8,9]. However, Katsuhiro et al. and Miravitlles et al. noted that the risk of exacerbation in COPD patients increased by 20% for every 10 years of age, making advanced age an independent risk factor for exacerbation[10,11].

The most common symptom of our study participants was dyspnoea followed by cough with phlegm production. Dyspnoea and cough with expectoration may appear several years before the onset of airflow obstruction in pre-COPD patients with a preserved ratio of impaired spirometry (PRISM) and people with these symptoms should be examined to rule out other underlying infections and conditions [12,13]. In our study, all patients had dyspnoea with about 70% experiencing breathlessness of mMRC grade III (Table 1).

Aspergillus sensitized COPD patients had hemoptysis as the most common symptom and this was consistent with the study done by Page et al. [14]. Hemoptysis is considered one of the cardinal symptoms to suspect the various spectrums of chronic pulmonary aspergillosis, as proposed by Denning et al.[3], where there is an absence of a history of uncontrolled asthma. Hence, individuals with COPD who have a history of pulmonary tuberculosis and who present with hemoptysis should be evaluated for CPA (Table 2).

CPA typically arises in patients with underlying lung diseases, yet the burden of CPA in the context of AECOPD remains underexplored. A prior study by Smith et.al has identified pulmonary

tuberculosis infection by mycobacterium tuberculosis (15.3%) and non-tuberculous mycobacterial infection (14.9%) as common underlying conditions of CPA, with COPD accounting for around 9% of CPA cases. (2) Each of these underlying diseases affects the anatomical structure and function of the lung. Our study observed a similar prevalence of CPA (9.8%) in AECOPD patients based on ESCMID criteria. Notably, post-tuberculosis patients were found to have a higher risk of developing CPA, particularly those with residual cavities, underscoring the importance of suspecting CPA in post-tubercular COPD patients with hemoptysis and weight loss.

A twelve-year retrospective study by Molinos-Castro et al. found that out of 75 COPD patients, the prevalence of CPA was found to be around 9.3% [15]. A 5-year prevalence of CPA among post-tuberculosis cases estimated by Aggarwal et al. was calculated as 2,90,147 cases with the estimation of 24 cases of CPA per 1,00,00 tuberculosis patients based on the analysis of crude data [16]. A study by Iqbal et al. analyzed 350 patients with a diagnosis of aspergillosis retrospectively and 67 patients (19.1%) fulfilled the criteria for CPA [17]. Tuberculosis was the underlying cause of CPA in 58 patients (86.6%), while allergic bronchopulmonary aspergillosis (ABPA) was the other cause of CPA found in 8 patients (11.9%). A recent study in 2022 by Denning et al. reported the incidence of CPA was found to be 17.5% out of a total of 3,63,601 cases among active TB cases [18].

In our study, out of 61 patients, 22 patients had undergone treatment for tuberculosis and CPA was found in 5 patients (22.7%) of the same while one patient (2.6%) had bullous emphysema (Figure 1). Tuberculosis leaves a cavity that acts as a residual nidus for the development of CPA, Hence, it is appropriate to suspect CPA in all post-tubercular COPD patients who experience hemoptysis and weight loss besides the differential recurrence of the disease *per se*.

The clinical, radiological, and microbiological evaluation suggested that chronic cavitary pulmonary aspergillosis was the most common spectrum observed in our study, followed by chronic fibrosing pulmonary aspergillosis and aspergilloma. These findings align with a study by Iqbal et al. highlighting the consistency of clinical-radiological patterns across different populations. His study described a clinical spectrum of CPA and the most common types observed in their study were aspergilloma and chronic cavitary pulmonary aspergillosis (CCPA) [17].

We found that 29.5% of the AECOPD patients showed hypersensitivity to aspergillus fumigatus antigen, with most sensitized patients having a history of previously treated pulmonary tuberculosis (Table 2). Bafadhel et al. assessed the aspergillus sensitivity using serum aspergillus-specific IgG antibodies among stable COPD and AECOPD patients [19]. Hypersensitivity to *A. fumigatus* was found in 13% of the AECOPD participants which is lesser compared to our study. In another study done by Aggarwal et al. [20] 17.5% of stable COPD patients showed aspergillus hypersensitivity, tested using a skin prick test which has lower sensitivity and specificity compared to the serological test. Our prevalence of aspergillus sensitization in AECOPD was higher than in the above studies, possibly due to the high burden of tuberculosis in the Indian subcontinent. Due to the endemic nature of tuberculosis in India, TB-related COPD affects a substantial number of patients as sequelae [21].

In our examination of 61 patients experiencing AECOPD, sputum cultures revealed growth in 22 patients (36.1%) (Table 3). The predominant pathogens identified were Gram-negative organisms, including *Pseudomonas aeruginosa, Klebsiella pneumoniae*, *Acinetobacter baumannii*, and Enterobacteriaceae, aligning with the results of a meta-analysis and systematic review conducted by Moghoofei et al. [22]. This comprehensive study encompassed 118 research papers on acute exacerbation of COPD. Aspergillus species were detected in the sputum of only one patient (1.63%).

In contrast, a study by Huerta et al. [23] involving 240 patients with severe AECOPD found a higher prevalence, with 16.6% on admission and 14.1% after one year of follow-up. The disparity in our findings might be attributed to the quality of sputum samples collected for culture, which could have been inadequate. Additionally, not all patients underwent bronchoscopy, which could have affected the detection of Aspergillus species in our study.

Univariate analysis was performed to assess the risk factors associated with aspergillosis. Contrary to expectations, in our study, risk factors of aspergillosis like chronic kidney disease, previous history of exacerbations, and use of inhalational steroids were not associated with a higher odd for COPD patients to develop aspergillosis. This was supported by Tong et al. [24] where there was no relation between previous hospitalization and Aspergillus isolation.

Diabetics and hypertensives had higher odds of acquiring aspergillus sensitization among AECOPD patients though it was not statistically significant: our result aligns with the FUNGI-

COPD study which showed similar inference [23] (Table 4). The lack of association between aspergillus sensitization and severity of lung function which was seen in our study can be attributed to the fact that a significant majority of our participants showing aspergillus sensitization belonged to a moderate group of the GOLD stage classification.

This study has several limitations, the first being that it's a single-center study with a relatively modest sample size. Generalizability may be affected, and hence further large-scale multi-center studies are needed to validate the findings. The absence of bronchoaspirate culture data is notable. However, performing bronchoscopy, particularly in low-income countries like India, poses a financial burden on patients.

Additionally, stable COPD patients were not included, potentially underestimating the overall prevalence of CPA in all COPD patients. To the best of our knowledge, this study is the first to directly estimate the prevalence of CPA in AECOPD patients as a primary diagnosis, with COPD secondary to previous tuberculosis as an underlying disorder. Further research is warranted to elucidate the interplay between AECOPD and CPA, especially in the context of tuberculosis and other comorbidities.

Conclusions

Our study shows that chronic pulmonary aspergillosis is prevalent among AECOPD patients. Hence, aspergillus sensitization and presence of CPA must be evaluated, especially with post-tubercular COPD patients.

Our findings highlight the importance of early recognition and management of CPA in COPD patients with acute exacerbations to improve outcomes and reduce hospitalization rates. Further studies are needed to validate these findings and explore additional risk factors for CPA development in COPD patients.

Summary

This study investigated the prevalence and risk factors for CPA in patients with COPD exacerbations. CPA was present in one-tenth of our study population and important risk factors like prior tuberculosis. and diabetes mellitus were associated with a higher likelihood of

developing aspergillosis, thus highlighting the importance of screening for CPA in AECOPD patients to identify high-risk populations.

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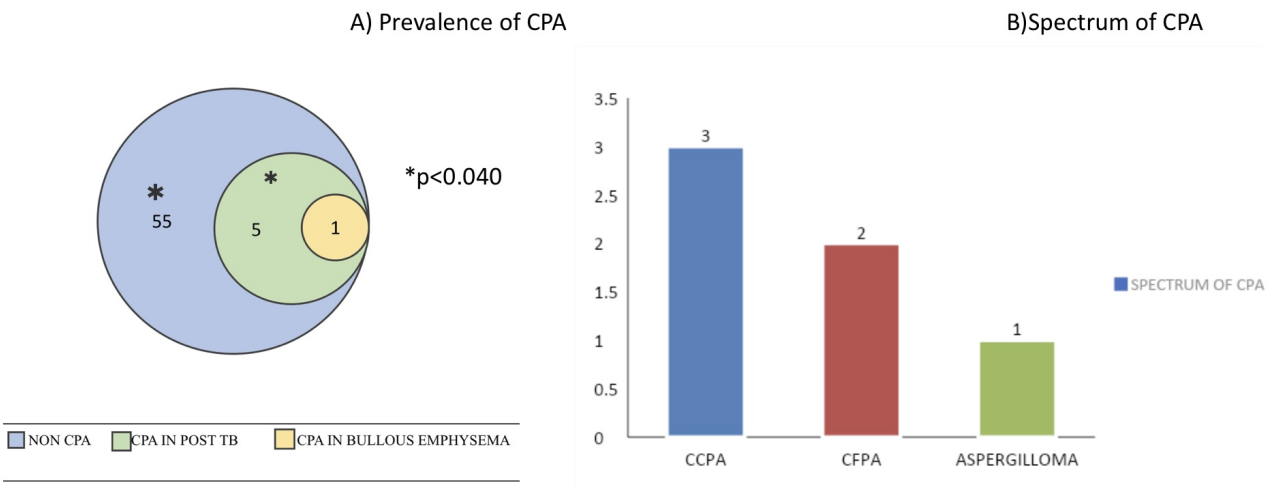

Figure 1. A) Prevalence of chronic pulmonary aspergillosis in patients with acute exacerbation of chronic obstructive pulmonary disease; B) spectrum of chronic pulmonary aspergillosis in patients with acute exacerbation of chronic obstructive pulmonary disease. CPA, chronic pulmonary aspergillosis; TB, tuberculosis; CCPA, chronic cavitatory pulmonary aspergillosis; CFPA, chronic fibrosing pulmonary aspergillosis.

Table 1. Baseline characteristics of acute exacerbation of chronic obstructive pulmonary disease patients.

Variables	Categories	Number of study subjects (n=61)	Percentage (%)
Age	<50	6	9.8
	51-60	24	39.3
	61-70	18	29.5
	≥70	13	21.3
Gender	Male	51	83.6
	Female	10	16.4
Smoking status	Smoker	44	72.1
	Non-Smoker	17	27.9
Biomass-fuel exposure	Present	30	49.2
	Absent	31	50.8
Symptoms	Chest pain	8	31
	Hemoptysis	12	19.7
	Cough	50	82.0
	Sputum expectoration	45	73.8
	Wheeze	42	68.9
	Breathlessness	61	100
Breathlessness	Grade 1	0	0
	Grade 2	3	4.9
	Grade 3	44	72.1
	Grade 4	14	23

Table 2. Baseline characteristics of patients with acute exacerbation of chronic obstructive pulmonary disease based on serum aspergillus specific IgG antibodies positive and negative serology.

	Total	Negative aspergillosis (n=43)	Positive aspergillosis (n=18)	p value
Demographics				
Male gender	51	37(86%)	14(77.8%)	0.509
Female gender	10	6 (14%)	4 (22.2%)	
Smoker	44	32(74.4%)	12(66.7%)	0.664
Biomass fuel exposure	30	20(46.5%)	10(55.6%)	0.36
Symptoms				
Cough	51	33(76.7%)	17(94.4%)	0.101
Breathlessness	61	43(50%)	18(50%)	
Expectoration	45	30(69.8%)	15 (83.3%)	0.272
Chest pain	8	6(14%)	2(11.1%)	0.764
Hemoptysis	12	3(7%)	9(50%)	<0.001
Underlying condition				
Diabetes	29	18(41.9%)	11(61.1%)	0.28
Systemic hypertension	24	15(34.9%)	9(50%)	0.41
Previous tuberculosis	22	11(25.6%)	11(61.1%)	0.008
Stable period treatment				
Use of inhalational steroids	34	26(60.5%)	8(44.4%)	0.251
Previous admission				
COPD exacerbation in previous year ≥1	31	25(80.6%)	6(19.4%)	0.068
Lung function status				
GOLD stage 1	0	0	0	<0.011
GOLD stage 2	18	8(10.7%)	10 (26.7%)	
GOLD stage 3	32	25(50%)	7(40%)	
GOLD stage 4	11	10 (39.3%)	1(33.3%)	

COPD, chronic obstructive pulmonary disease; GOLD, global initiative for obstructive lung disease.

Table 3. Microbiological pattern of sputum sample isolated from patients with acute exacerbation of chronic obstructive pulmonary disease (n=23).

Sputum	Number of study subjects	Percentage (%)
A) Pyogenic isolates	1) Polymicrobial growth (n=5) 2) Monomicrobial growth (n=17)	36.1
B) Fungal isolates	Aspergillus (n=1)	1.6%
C) No organism	n=38	62.2%

Table 4. Univariate analysis to assess risk association of chronic pulmonary aspergillosis based on serum aspergillus specific IgG antibodies in acute exacerbation of chronic obstructive pulmonary disease patients.

Variables	Positive aspergillosis	Negative aspergillosis	OR	CI	p value
Smoker	12	32	0.69	0.21-2.27	0.53
Diabetes mellitus	11	18	2.18	(0.71-6.72)	0.28
Hypertension	9	15	1.87	0.61-5.70	0.41
Use of steroids in last 3 months	8	26	0.52	0.172-1.59	0.254
Previous history of exacerbations in last 1 year	6	12	0.36	0.11-1.14	0.082
GOLD stage 2	10	8	12	(1.30 - 119.3)	0.028
GOLD stage 3	7	25	2.8	(0.30 - 25.77)	0.363

GOLD, global initiative for obstructive lung disease; OR, odds ratio; CI, confidence interval.