Pulmonary fungal infection in patients with acute exacerbation of chronic obstructive pulmonary disease

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Background Pulmonary fungal infection (PFI) is increasing among patients with chronic obstructive pulmonary disease (COPD). Survival depends on rapid diagnosis and early treatment.

Aims To assess the prevalence of PFI in acute exacerbation of chronic obstructive pulmonary disease (AECOPD), and to investigate the clinical, demographic, and radiological findings related to PFI in COPD patients.

Patients and methods This observational cross-sectional study was conducted on 80 patients with AECOPD. High-resolution computed tomography, fiberoptic bronchoscopy with bronchoalveolar lavage, spirometry, sputum and bronchoalveolar lavage fungal culture and measurements of serum 1, 3 beta-D-glucan (BDG) were done for all patients. They were classified into possible PFI and probable PFI based on the Bulpa and colleagues criteria.

Results Among the 80 studied patients, 19 patients had possible PFI, and 61 patients had probable PFI; of them 12 patients had positive BDG and 49 had negative BDG. The use of either systemic steroids and/or antibiotics in the last 3 months was higher in patients with probable PFI than those with possible PFI (P=0.003). The daily dose (mg/kg) and duration of systemic steroids were higher in patients with probable PFI (P=0.001). The use of inhaled corticosteroids (ICS), its dose, and its duration did not differ between both groups.

Conclusion Probable PFI is prevalent among patients with AECOPD 61 (76.3%); of them 19.7% was invasive form. PFI in AECOPD is related to the use, dose, and duration of systemic steroids and antibiotic use in the last 3 months. Therefore, a lower dose or interrupted course of systemic steroid must be considered in COPD patients.

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Introduction

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) is defined as 'an acute worsening of respiratory symptoms that warrant changes in patient's usual medications' [1]. The triggering factors of AECOPD include infectious and noninfectious precipitants [2]. Typically, infections cause 75% or more of the exacerbations [3]. The potential role of fungal infection in the pathogenesis of chronic obstructive pulmonary disease (COPD) is poorly understood. *Aspergillus* spp. is the most common fungal genus to cause pulmonary fungal infections (PFIs) in COPD patients [4].

COPD is characterized by significant variability in local immune balance that impacts the patient's ability to contain invasive fungal challenges over time. Additionally, the intrinsic progression of the disease associated with an increasing rate of microbial colonization, the exacerbations of viral and bacterial origins, the repetitive use of antibiotics, the necessity of occasional admissions in the ICU with the requirement for invasive procedures, the steroid-induced immunomodulation, and the sepsis-related cycling fluctuations of immune status from hyper-to-anti-inflammatory phases that can confine to immunoparalysis in extreme cases create favorable conditions for the development of opportunistic invasive PFI [5]. Additionally, ciliary activity impairment plays a role in the development of invasive PFI [6].

Some infections caused by fungi may take months to years to cause symptoms, slowly and progressively growing worse and disseminating throughout the body, causing night sweats, chest pain, weight loss, and enlarged lymph nodes. Others may progress rapidly, causing pneumonia and/or septicemia. Fungal lung infections are more likely to be severe in people who have underlying lung disease and/or a compromised immune system such as those with HIV/AIDS [7]. Outcomes of these infections are significantly improved if the diagnosis is established early and antifungal therapy is begun promptly [8].

Unfortunately, cultures of blood and other body fluids for many of these pathogens are not often positive, and invasive procedures to establish a tissue diagnosis are complicated by the frequent presence of thrombocytopenia and neutropenia in patients at risk for infection with these pathogens. Thus, extensive efforts have been undertaken to establish nonculture-based methods for the diagnosis of invasive mycoses [8]. There are two commercially available biomarker assays useful for the detection of the invasive PFI, the galactomannan and 1, 3 beta-D-glucan (BDG). BDG is positive for not only *Aspergillus* and *Candida* spp., but several other clinically relevant fungal pathogens as well. Adoption of these assays into clinical practice has led to reduced need to perform invasive procedures to obtain deep tissue to establish the diagnosis of invasive fungal infections [9]. A main challenge in COPD patients remains the demarcation between colonization and infection when faced with a positive respiratory culture for fungus [10].

Fungal infections in COPD patients are always classified according to the Bulpa *et al.* [4] criteria. (a) The proven cases require histopathological confirmation. (b) Probable cases require host factors (patient with COPD usually treated with corticosteroids, GOLD stage III or IV, with a recent exacerbation of dyspnea and suggestive radiological findings) plus microbiological factors (isolation of Aspergillus in lower respiratory tract (LRT) samples or positive BDG). (c) Possible cases require host factors but without Aspergillus spp. isolation or serology. (d) Colonization was defined as an asymptomatic isolation of Aspergillus spp. in LRT samples. All the invasive PFI cases described in the literature have been associated with a fatal outcome. Therefore, it seems worthwhile to investigate the diagnostic procedures for nonhematological patients in a prospective manner [11]. Therefore, this study was carried out to assess the prevalence of PFI in AECOPD, and to investigate the clinical, demographic, and radiological findings related to PFI in COPD patients.

Patients and methods

Ethical consideration

The study was conducted after approval of the study protocol by the ethics review committee of the Chest Diseases Department and Faculty of Medicine for Girls Al Azhar University, Cairo, Egypt. All data were anonymous and coded to assure confidentiality of the participants. Ethical issue: the study protocol was approved by the institutional review board and ethics committee of Faculty of Medicine for Girls, Al-Azhar University and all participants gave informed consent before inclusion in the study.

This observational cross-sectional study was conducted at the Chest Diseases Department, Al-Zahraa University Hospital, Cairo, Egypt. It was conducted during the period April 2016–April 2018.

Inclusion criteria

Eighty patients with AECOPD were included in the study. They were diagnosed based on GOLD [12] guidelines. They were included only if they had symptoms and signs of AECOPD according to the Anthonisen *et al.* [13] criteria.

Exclusion criteria

Patients with the following disorders were excluded from the study: malignancies, neutropenia, HIV/AIDS, chronic renal failure, liver cell failure, and chest diseases other than COPD. Additionally, patients treated by cytotoxic or immunosuppressive drugs other than corticosteroids were also excluded from the study.

Demographic data including age, sex, smoking habits, and BMI were reported. A detailed medical history and clinical examination was done to diagnose AECOPD and to assess its severity according to the Anthonisen *et al.* [13] criteria.

Spirometry was carried out on MEDISOFT-HYPERAIR compact+flow meter pulmonary function Testing-Belgium. Spirometry was performed before and after the inhalation of short-acting B_2-agonist.

Forced expiratory volume in the 1 s (FEV_1%), forced vital capacity%, FEV_1/forced vital capacity ratio, and forced expiratory volume in 25–75% of vital capacity were measured. Spirometric indices were calculated using the best out of three technically acceptable performances in accordance with the recommendations of the European Respiratory Society [14].

High-resolution computed tomography (HRCT) chest was done to detect any findings suggestive of PFI (e.g. reticulonodular infiltrations, nodules, cavitation, enlarged lymph nodes, and consolidations). The scan was done by using a multidetector scanner (160 detectors) (Toshiba, Prime Aquilion, Japan).

Bronchoscopy and bronchoalveolar lavage

All bronchoscopies and bronchoalveolar lavage (BAL) were performed by the pulmonologist authors who had

10 years' experience in performing diagnostic fiberoptic bronchoscopy using FB 1T 160 (Olympus, Tokyo, Japan. Supplemental oxygen, pulse oximetry, sphygmomanometer, and equipment for resuscitation including an endotracheal tube were available at the time of the procedure. The procedure was explained to the patients in full detail. Oxygen was administered by a nasal cannula and flows were adjusted upward from 2 l/min to keep the oxygen saturation more than 90%. The patients were sedated with intravenous Midazolam (2.5–5 mg), if not contraindicated.

The patient was placed in a semisupine position. After the topical anesthetic has taken effect, the bronchoscope was introduced through the nose. The vocal cords were examined for abduction and adduction. The bronchoscope was passed through the vocal cords, and a complete airway inspection was performed. Fiberoptic bronchoscopy was gently impacted or 'wedged' into either the bronchus of the involved lobe guided by HRCT or the middle lobe and lingual bronchus as bronchoscopy is usually performed with the patient lying supine; the anteriorly projected location of these segments allows gravity to assist with maximal BAL [15]. BAL was obtained by aspiration of any secretion and instillation of five aliquots of 20 ml of sterile isotonic saline solution, followed by immediate aspiration by suction into a plastic specimen trap. Aspiration was performed by applying gentle suction. Too forceful suction was avoided as it can cause collapse of the distal airways, and therefore, reduces the volume of the recovered BAL fluid. The BAL fluid generally was transported to the laboratory and processed in less than 1 h [16].

Sputum and bronchoalveolar lavage fungal culture

After preparation of sputum and BAL samples, they were streaked on the surface of ordinary media (blood and MacConkey's agar media) and two plates of Sabouraud's dextrose agar containing 0.05 mg/ml of plates were incubated at 25–37° for 3–4 days. The growth on Sabouraud's agar was isolated, purified, stored, and maintained to be identified.

Measurement of serum BDG level uses enzyme-linked immune sorbent assay based on the biotin double antibody sandwich technology.

Our patients were classified according to the Bulpa *et al.* [4] criteria; however, all our patients were symptomatic as they had AECOPD. Therefore, no colonization cases were reported. Also, because it is not possible to perform lung biopsy in COPD patients, no proven cases were demonstrated. Therefore, our patients were classified as having either probable or possible PFI.

Statistical analysis

The data was analyzed using statistical package for the social sciences program on Windows 7, version 17.0 (SPSS Inc., Chicago, Illinois, USA). The results were expressed as mean±SD for quantitative variables, and as percentages for qualitative variables. Comparisons to assess the difference between groups were done using the χ^2 test for qualitative data and Student's t test for quantitative data. Statistical significance was considered at a P value less than 0.05 (with a confidence limit at 95%).

Results

Table 1 shows that among the 80 studied AECOPD patients, 19 (23.8%) had possible PFI and 61 (76.2%) had probable PFI; of them 12 (19.7%) patients had positive BDG and 49 (80.3%) had negative BDG. The demographic data, Anthonisen criteria, type of COPD exacerbation, COPD severity (Table 2), and spirometric indices (Table 3) were nonsignificantly differed between probable PFI cases and possible PFI cases ($P>0.05$). Hemoptysis and chest pain were significantly common in patients with probable PFI ($P=0.04$, 0.015) (Table 2). Table 4 demonstrates that there was no significant difference in HRCT findings between both groups ($P>0.05$). Table 5 shows that the use of either systemic steroids and/or antibiotics in the last 3 months was higher in patients with probable PFI than those with possible PFI ($P=0.003$). Moreover, the daily dose (mg/kg) and duration of systemic steroids were higher in patients with probable PFI ($P=0.001$). The use of inhaled corticosteroids (ICS), its dose, and duration did not differ between both groups ($P>0.05$). Table 6 shows that sputum fungal culture did not differ between both groups ($P>0.05$).

Discussion

Assessing the incidence of PFI in relatively less immunocompromised patients (e.g. AECOPD) is not easy because of the lack of a consistent case

Table 1 Classification of the studied cases according to the types based on symptoms, radiology, and fungal culture

Classification types of PFI	$N=80$ [n (%)]
Possible PFI	19 (23.8)
Probable PFI	61 (76.2)
Probable PFI with positive BDG	12 (19.7)
Probable IPF with negative BDG	49 (80.3)

BDG, 1, 3 beta-D-glucan; PFI, pulmonary fungal infection.

Table 2 Comparison of Anthonisen criteria, type of acute exacerbation of chronic obstructive pulmonary disease, and other presenting symptoms between cases with possible pulmonary fungal infection and cases with probable pulmonary fungal infection

Items	Possible PFI (*N*=19) [*n* (%)]	Probable PFI (*N*=61) [*n* (%)]	Test value	*P* value
Demographic data				
Age (years) (mean±SD)	57.7±3.2	58.36±5.01	–0.50	0.61
Sex: male (female)	17 (89.5) [2 (10.5)]	49 (80.3) [12 (19.7)]	0.83	0.36
Smokers (nonsmokers)	18 (94.7) [1 (5.3)]	56 (91.8) [5 (8.2)]	0.18	0.67
Smoking (pack/year) (mean±SD)	20.7±11.9	22.1±12.6	–0.42	0.67
BMI (mean±SD)	28.19±3.9	28±3.8	0.19	0.84
Anthonisen criteria				
Increased dyspnea	16 (84.2)	54 (88.5)	0.24	0.62
Increased sputum volume	7 (36.8)	27 (44.3)	0.32	0.56
Increased sputum purulence	13 (68.4)	48 (78.7)	0.84	0.35
Cough	19 (100.0)	60 (98.4)	0.31	0.57
Wheezes	19 (100.0)	61 (100.0)	NA	NA
Fever	1 (5.3)	5 (8.2)	0.18	0.67
URTI in the last 5 days	2 (10.5)	9 (14.8)	0.21	0.64
Increased RR >20%	10 (52.6)	21 (34.4)	2.02	0.15
Increased HR >20%	6 (31.6)	12 (19.7)	1.17	0.27
Anthonisen criteria (type of AECOPD)				
Severe AECOPD	5 (26.3)	20 (32.8)	0.28	0.86
Moderate AECOPD	7 (36.8)	21 (34.4)		
Mild AECOPD	7 (36.8)	20 (32.8)		
Chest pain	0 (0.0)	6 (9.8)	7.02	0.015
Cyanosis	4 (21.1)	19 (31.1)	0.72	0.39
Hemoptysis	0 (0.0)	11 (18.0)	3.97	0.04
COPD severity				
Moderate	11 (57.9)	36 (59.0)	4.02	0.13
Severe	8 (42.1)	16 (26.2)		
Very severe	0 (0.0)	9 (14.8)		

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; COPD, chronic obstructive pulmonary disease; HR, heart rate; PFI, pulmonary fungal infection; RR, respiratory rate; URTI, upper respiratory tract infection.

Table 3 Comparison of spirometric indices between cases with possible pulmonary fungal infection and cases with probable pulmonary fungal infection

Items	Possible PFI (*N*=19) (mean ±SD)	Probable PFI (*N*=61) (mean ±SD)	Test value	*P* value
FEV_1/FVC ratio	53.3±11.1	50.6±11.4	0.89	0.37
FEV_1%	53.7±7.6	50.5± 11.9	1.07	0.28
FVC%	48.1±10.4	44.2±9.9	1.50	0.13
VC%	51.4±9.6	47.5±9.4	1.57	0.11
$FEF_{25–75\%}$	34.1±17.2	30.6±14.7	0.85	0.39

$FEF_{25–75\%}$, forced expiratory volume in 25–75% of vital capacity; FEV_1, forced expiratory volume in the 1 s; FVC, forced vital capacity; PFI, pulmonary fungal infection; VC, vital capacity.

Table 4 Comparison of computed chest tomography between cases with possible pulmonary fungal infection and cases with probable pulmonary fungal infection

Findings	Possible PFI (*N*=19) [*n* (%)]	Probable PFI (*N*=61) [*n* (%)]	Test value	*P* –value
Reticulonodular	8 (42.1)	36 (59.0)	1.6	0.19
Cavities	0 (0.0)	1 (1.6)	0.31	0.57
Nodules	4 (21.1)	20 (32.8)	0.950	0.33
Lymphadenopathy	1 (5.3)	14 (23.0)	2.97	0.08
Consolidation	0 (0.0)	3 (4.9)	0.97	0.32

PFI, pulmonary fungal infection.

definition and the absence of a perfect surveillance system [17].

The main findings of the current study are that PFI is prevalent among COPD patients as 19 (23.8%) had possible PFI and 61 (76.2%) patients had probable PFI, of them 12 (19.7%) patients had elevated serum BDG (invasive PFI), while 49 (80.3%) had normal BDG. *Candida* spp. was the most common identified species constituting 63.9%, while *Aspergillus* spp. constitutes 36.1%. Although, COPD patients have normal pulmonary defense mechanisms against *Aspergillus* spp. such as the ingestion of spores by pulmonary macrophages and killing of hyphae by neutrophils. However, there are many factors that predispose to colonization and infection with *Aspergillus* spp., including structural changes with the formation of bullae, and the common use of long-term steroid treatment increases host susceptibility by reducing oxidative killing of the organism by macrophages

Table 5 Comparison of use of systemic steroids and systemic antibiotic in the last 3 months and use of inhaled steroids between chronic obstructive pulmonary disease cases with possible pulmonary fungal infection and chronic obstructive pulmonary disease cases with probable pulmonary fungal infection

Items	Possible PFI (*N*=19) [*n* (%)]	Probable PFI (*N*=61) [*n* (%)]	Test value	*P* value
Systemic steroids in last 3 months				
Status				
Positive	1 (5.3)	26 (42.6)	9.04	0.003
Negative	18 (94.7)	35 (57.4)		
Dose (mg/kg) (mean±SD)	0.02±0.08	0.29±0.3	3.94	0.001
Duration/days (mean±SD)	0.21±0.92	4.07±3.94	4.21	0.001
Antibiotics in last 3 months				
Status				
Positive	2 (10.5)	23 (37.7)	4.98	0.026
Negative	17 (89.5)	38 (62.3)		
Types				
Amoxicillin	1 (5.3)	12 (19.7)	4.98	0.08
Ciprofloxacin	1 (5.3)	11 (18.0)		
Duration/days [median (IQR)]	0 (0–0)	0 (0–5)	–2.05	0.040
Inhaled corticosteroids				
Status				
Positive	18 (94.7)	53 (86.9)	0.89	0.34
Negative	1 (5.3)	8 (13.1)		
Daily dose/μg [median (IQR)]	320 (300–320)	320 (300–640)	0.55	0.57
Duration/days [median (IQR)]	365 (36–1460)	720 (30–1460)	0.09	0.92
Type				
Budesonide	14 (73.7)	44 (72.1)	1.15	0.56
Beclomethasone dipropionate	4 (21.1)	9 (14.8)		

IQR, interquartile range; PFI, pulmonary fungal infection.

Table 6 Comparison of sputum bacterial culture, sputum fungal culture, bronchoalveolar lavage bacterial culture, bronchoalveolar lavage fungal culture, and 1, 3 beta-D-glucan between cases with possible pulmonary fungal infection and cases with probable pulmonary fungal infection

Items	Possible PFI (*N*=19) [*n* (%)]	Probable PFI (*N*=61) [*n* (%)]	Test value	*P* value
Sputum fungal culture				
Positive	3 (15.8)	7 (11.5)	0.24	0.62
Negative	16 (84.2)	54 (88.5)		
BAL fungal culture				
No growth	19 (100.0)	0 (0.0)	80.0	0.001
Aspergillus spp. growth	0 (0.0)	22 (36.1)		
Candida spp. growth	0 (0.0)	39 (63.9)		
BAL fungal sensitivities				
No sensitivities	19 (100.0)	2 (3.3)	70.0	0.001
Ketoconazole+amphotericin B+itraconazole	0 (0.0)	38 (62.3)		
Amphotericin B+terbinafine	0 (0.0)	21 (34.4)		
Serum BDG (pg/ml) [median (IQR)]	9.9 (7.7–11.7)	10.2 (8.5–22.6)	–1.02	0.30

BAL, bronchoalveolar lavage; BDG, 1, 3 beta-D-glucan; IQR, interquartile range; PFI, pulmonary fungal infection.

and increases its linear growth by 30–40% [18]. Same results were reported by Mohamed *et al.* [18]. They found that the prevalence of invasive and probable PFI were significantly higher in COPD patients with comorbidities than COPD patients without comorbidities. *Candida* spp. and *Aspergillus* spp. were the predominant fungal species detected in both groups. Bafadhel *et al.* [19] reported that fungus was isolated in 49% (63/128) of COPD patients. Guinea *et al.* [20] reported that invasive pulmonary aspergillosis affected about 22.1% of patients with COPD. Lower incidence of PFI in AECOPD patients (1.91%) was reported by Gao *et al.* [17]. In contrast to our findings, many different studies concluded that *Aspergillus* spp. is the most common fungal genus to cause PFI in COPD [4,10,19,21]. This disparity between studies regarding the true incidence of PFI in COPD patients may be attributed to disparities in comorbidities, the variable durations of exposure, multiple clinical presentations which require a high degree of suspicion, and the fact that, despite improvement in diagnostic procedures, serological tests

still have a low sensitivity. There are also disparities between studies regarding the incidence of COPD among patients with PFI; Lin *et al.* [22] reported that among 1941 studied patients with PFI, 26 (1.3%) had COPD. In another report, disseminated aspergillosis was documented in six patients who underwent autopsy; five (2.7%) had COPD [23]. COPD is present in 2% of patients dying of invasive PFI [10]. The rate of proven or probable aspergillosis was 3.7% in patients admitted to a medical ICU of a large teaching hospital; ~50% of them had COPD [24]. Rodrigues *et al.* [25] reported that COPD patients constituted 1% of all cases of invasive PFI.

Regarding the value of serological markers in the diagnosis of invasive PFI, our study revealed that serum BDG was positive in 12/61 (19.7%) patients with probable PFI, which indicate that invasive PFI was found in 15% of total studied COPD cases. In contrast, Tutar *et al.* [26] found that BDG was examined in five patients and was positive in three (60%) of them.

Another important finding of our study is that the use of either systemic steroids and/or antibiotics during the last 3 months were the only risk factors for PFI (P=0.003), not only the use of systemic steroids but also its daily dose (0.29±0.3 mg/kg) and duration (4.07 ±3.94 days) were a determinant factors for PFI (P=0.001). It is well known that corticosteroids impair immune function, especially the activity of tissue macrophages, which are responsible for the monocyte-mediated damage to fungal hyphae. Moreover, corticosteroids promote the in-vitro growth of *Aspergillus fumigatus* [27]. Growth rate is likely to be a key determinant of pathogenicity, and this effect was shown to be dose dependent [28]. Similar results were reported by many other investigators, as corticosteroid therapy was a major risk factor for PFI in COPD patients with comorbidities [18] and COPD patients admitted to the ICU [11]. Conesa *et al.* [29] concluded that patients with COPD requiring corticosteroids seem to be at special risk for *Aspergillus* spp. infections. However, the minimum required steroids dose to be at risk for fungal pneumonia is difficult to quantify [21]. By pooling data from 71 controlled clinical trials, it has been evidenced that the rate of infections was not increased in patients given a daily dose lower than 10 mg/day or a cumulative dose of B/700 mg of prednisone [30]. In a revision of autopsy-proven cases of opportunistic pneumonia in patients on chronic corticosteroids treatment, the overall prednisone equivalent dose at the time of admission was 349 mg/d [25]. Similarly, it has been shown that corticosteroid use plays a significant role in terms of increasing the rate of invasive PFI in COPD patients [20]. In a retrospective study, it was shown that steroid use of over 700 mg in total within the last 3 months in COPD patients increased the risk for invasive pulmonary aspergillosis (IPA) [31].

Similarly, Muquim *et al.* [32] and He *et al.* [33] reported that using three or more antibiotics for 10 days was a risk factor for invasive PFI in COPD. Another study found that four cases had used antibiotics in the last 3 months and a history of antibiotic use was the only risk factor for PFI in one case [21]. In another study on 1209 patients with a positive respiratory culture for *Aspergillus* spp. showed that COPD, corticosteroid use, and diabetes mellitus were the three main risk factors for fungal colonization [34].

In our study the use of ICS, and its dose and duration were not risk factors for PFI. Different results regarding ICS use had been reported by Leav *et al.* [35], as cases of invasive PFI have been reported with high-potency ICS. It has been speculated that patients with COPD are particularly at risk for developing fungal pneumonia when receiving high or repetitive doses of steroids [21]. Garnacho-Montero *et al.* [36] in a multicenter prospective study including patients with an ICU stay longer than 7 days, evidenced that both treatment with steroids and COPD were significantly associated with *Aspergillus* spp. isolation in respiratory secretions. Gao *et al.* [17] reported that four patients with proven and probable IPA had been treated with systemic or inhaled steroid before hospitalization. Bafadhel *et al.* [19] reported that patients with *A. fumigatus* were on a higher ICS dose compared with those who were culture negative.

In our study the clinical and radiological findings, types of acute exacerbation, spirometric indices, and COPD severity were not significantly differed between patients with possible PFI and patients with probable PFI. Similarly, Meersseman *et al.* [24] and Agusti *et al.* [21] have found that the characteristic clinical and radiological findings are usually prominent in neutropenic patients but not helpful in the diagnosis of aspergillosis in COPD patients. Bafadhel *et al.* [19] concluded that there were no differences in health status, exacerbation frequency, or FEV_1% in COPD patients who were *Aspergillus* spp. culture-positive compared with those who were *Aspergillus* spp. culture negative. Symptoms of chronic necrotizing pulmonary aspergillosis in COPD patients are similar to those of pneumonia that is unresponsive to antibacterial agents and these progress to include cavitation and pleural involvement

[37]. Gao *et al.* [17] reported that the typical symptoms and diagnostic signs of IPA were relatively less common in four COPD patients with proven and probable PFI.

Conclusion

Probable PFI are prevalent among patients with AECOPD [61 (76.3%) patients], of them 12 (19.7%) patients had elevated serum BDG (invasive form). PFI in AECOPD patients was related to the use, daily dose, and duration of systemic steroids and antibiotic use in the last 3 months. Therefore, a lower dose or interrupted course of systemic steroids must be considered in COPD patients. Clinical and radiological characteristics of IPA are often nonspecific and a high index of clinical suspicion is required for the early diagnosis.

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Conflicts of interest

There are no conflicts of interest.

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