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Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: a case control study from China

H. Xu[1], L. Li[1], W.-J. Huang[1], L.-X. Wang[2], W.-F. Li[1] and W.-F. Yuan[1]

1) *Respiratory Medicine and* 2) *Clinical Laboratory, Guangzhou General Hospital of Guangzhou Military Command, Guangzhou, China*

Abstract

Patients with severe chronic obstructive pulmonary disease (COPD) are at higher risk of developing invasive pulmonary aspergillosis (IPA). However, there are limited data for this disease. To evaluate risk factors and the clinical characteristics of IPA in COPD patients, we conducted a hospital-based, retrospective case-control study of 30 COPD patients with IPA and 60 COPD control patients without IPA. Patients in the case group were significantly more likely to have concurrent co-morbidities than controls. Of the IPA patients, 65.4% had worsening radiological findings vs. 11.4% in the control group ($p < 0.001$). IPA in COPD was associated with a higher proportion of mechanical ventilation (43.3% vs. 5%; $p < 0.001$), a longer hospital stay duration (45.8 ± 39.1 days vs. 18.4 ± 11.8 days; $p < 0.001$), and higher mortality (43.3% vs. 11.4%; $p < 0.001$). Systemic use of steroids in the stable phase, treatment with three or more antibiotics during hospitalization and antibiotic treatment longer than 10 days were independent risk factors associated with IPA. COPD patients with obvious dyspnoea, antibiotic-resistant lower respiratory tract infection and repeated detection of *Aspergillus* in sputum should be considered for the possibility of IPA.

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Corresponding author: W.-J. Huang, Respiratory Medicine, Guangzhou General Hospital of Guangzhou Military Command, No. 111 Liuhua Rd, Guangzhou, China
E-mail: huangyelu1029@vip.163.com

Introduction

Invasive pulmonary aspergillosis (IPA) is a life-threatening pneumonia characterized by lung parenchyma invasion with vasculature erosion and necrosis that is caused by opportunistic fungi belonging to the species *Aspergillus*. There is growing evidence to suggest that the incidence of IPA in the context of chronic obstructive pulmonary disease (COPD) is increasing [1–3]. However, the clinical characteristics, risk factors and pathogenesis of this disease are limited, as most of the relevant data have come from case/series reports. Here, we investigated the clinical conditions and risk factors of IPA in COPD patients using a case-control study that compared COPD patients with and without IPA.

Materials and Methods

Study population and case definitions

This retrospective study enrolled 992 patients in the 2000-bed Guangzhou General Hospital of Guangzhou Military Command, Guangzhou, China, from January 2006 to December 2009. Ethics committee approval and patient consent statements were waived due to the retrospective design.

A diagnosis of COPD was based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [4]. The diagnostic criteria for IPA in COPD patients suggested by Bulpa *et al.* [5] were used as a modified reference in this study, and IPA in COPD patients was carefully monitored in our hospital. Proven cases required histopathological or cytopathological confirmation. Probable cases required both host factors (COPD patient, had recent exacerbation of dyspnoea and suggestive chest imaging, and typically had poor response to conventional treatment) and microbiological factors (isolation of *Aspergillus* in the lower respiratory track (LRT) samples, or two consecutive positive serum galactomannan (GM) tests). Possible cases required host

factors, but without microbiological proof. Colonization was defined as asymptomatic and isolation of *Aspergillus* in LRT samples. Possible patients were excluded from this study. Because we could not guarantee that all the patients had a chest X-ray every 3 months, we only compared chest imaging with the final results before admission for some patients. We did not restrict patients to those with COPD stage III or IV.

Inclusion and exclusion criteria

Case group patients were admitted to the hospital with an initial diagnosis of acute exacerbations of COPD (AECOPD), and were diagnosed as 'probable IPA' after relevant examinations. Control group patients met the following conditions: (i) had a primary discharge diagnosis of COPD (International Classification of Diseases, tenth revision (ICD-10) codes J44.0, J44.1, J44.9); (ii) had exacerbations of baseline symptoms of COPD, such as dyspnoea, cough and/or sputum, at admission; (iii) had an aetiology examination with LRT samples more than twice and *Aspergillus* was negative; and (iv) did not receive any antifungal therapy during hospital stay. Patients were excluded for: (i) concurrent malignant tumour; (ii) concurrent haematological system diseases; (iii) organ transplantation; (iv) apparent immunodeficiency (e.g. AIDS or immunosuppressive drugs); and (v) long-term use of glucocorticoid for reasons other than COPD.

Laboratory procedures

A sputum sample with >25 polymorphonuclear leukocytes and <10 squamous epithelial cells per low-power field was defined as a valid sputum sample representative of the lower airways. All samples were cultured on conventional media, including blood agar, chocolate agar, MacConkey agar and Sabouraud's Dextrose agar. Bacterial infection was defined as a colony count $\geq 10^5$ cfu/mL. *Aspergillus* isolates were identified using microculture and standard morphological procedures. GM antigen levels in serum were determined with Platelia GM-EIA kits (Bio-Rad, Marnes-la-Coquette, France). A cut-off of index ≥1 was used to define a positive result.

Data collection

Electronic medical records of all the cases were searched from our medical records centre. Variables included demographic factors, body mass index (BMI), smoking history, co-morbidities, pulmonary function, medication history, clinical manifestations, laboratory test results, imaging findings, mechanical ventilation, antibiotics and steroid therapy, length of hospital stay, and outcome.

Statistical analysis

Results were given as means ± SDs or number of positive results. Categorical variables were compared using chi-square or Fisher's exact tests; continuous variables were compared using *t*-test or the Mann-Whitney *U*-test. Multivariate logistic regression was performed in a stepwise manner to search for risk factors associated with IPA in COPD patients. Variables with a level of significance <0.2 in the univariate analysis were included in the model. The level of significance was set at 0.05. Statistical analysis used SPSS, version 11.5.

Results

Patients

Our hospital had 992 AECOPD admissions, of which 298 (30.0%) had LRT sample examinations at least twice. Amongst these, 58 had isolates of *Aspergillus* from LRT samples, with 19 cases diagnosed as colonization according to the criteria described in 'Materials and methods'. Thirty-nine (3.9%) were diagnosed with IPA, but only 30 were included in the case group. Excluded cases had other concurrent conditions: four had malignant tumours; two had haematological system diseases; and three used immunosuppressive drugs for rheumatoid arthritis. We were not able to perform biopsies, so all cases were classified as probable IPA. Of the 240 patients with *Aspergillus*-negative LRT samples, 15 had received antifungal therapy, 11 had concurrent tumours, two had concurrent haematological system diseases, and six used glucocorticoids for a long time for reasons other than COPD. Of the remaining 206 patients, we randomly selected 60 cases as the control group.

In the case group, 29 were identified as having *Aspergillus fumigatus*, and one had *Aspergillus flavus*. GM testing was performed only for serum: 16 cases had the test once and six of these were positive; three cases had the test at least twice and all results were positive. The GM antigen positive rate in the case group was 47.4%. IPA was diagnosed within 5–30 days. The average diagnosis time was 11.5 ± 5.1 days for those who survived and 15.0 ± 8.1 days for those who died (p 0.19).

Baseline characteristics

Cases and controls did not differ significantly regarding sex, age, BMI or smoking history. Based on the GOLD criteria for COPD severity, 83.3% of the case group patients had stage III or IV disease, which was higher than in the control group (68.3%), although not significantly different (p 0.13). Co-morbidities were more common in the case group.

Pre-hospital treatments for the two groups were also significantly different, particularly the use of broad-spectrum antibiotics during the previous 3 months (83.3% in the case group vs. 30% in the control group; p <0.001; Table 1).

Clinical characteristics

The main clinical manifestations and treatments are shown in Table 2. Dyspnoea was the most common complaint of IPA patients (93.3%), and 80% experienced wheezing. Radiological signs for each group are listed in Table 2. The proportions with initial abnormal imaging findings in the two groups were not significantly different (p 0.64 for chest X-rays, p 0.92 for computerized tomography (CT) scans). However, for dynamic observations, 65.4% of the IPA patients had progressing lung lesions, while only 11.4% in the control group had these features (p <0.001).

The detection rates for other pathogens (e.g. *Acinetobacter baumannii, Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Staphylococcus aureus*, and others) were significantly different between the two groups (70% vs. 31.7%; p 0.001).All case group patients were treated with broad-spectrum antibiotics, and 73.3% had received three or more kinds of antibodies compared with 8.3% in the control group (p <0.001).

The proportions receiving inhaled corticosteroid treatments were not significantly different between the groups. However, a significantly higher proportion of systemic corticosteroid use was observed in the case group (66.7% vs. 40%; p 0.017); further, more than one-quarter of IPA cases were treated with an accumulated steroid dose of >700 mg prednisone or its equivalent (26.7% vs. 3.3%; p 0.002).

TABLE 1. Baseline characteristics of patients with and without invasive pulmonary aspergillosis[a]

Characteristics	IPA group (*n* = 30)	Control group (*n* = 60)	p
Total	30	60	
Male	25 (83.3)	53 (88.3)	0.51
Female	5 (16.7)	7 (11.7)	
Age, years	77.2 ± 7.2	76.4 ± 8.3	0.65
BMI, kg/m^2	21.6 ± 2.8	21.1 ± 3.5	0.51
Smoking history			
Yes	23 (76.7)	42 (70.0)	0.51
>40, pack years	12 (40.0)	20 (33.3)	0.53
Co-morbidities			
Diabetes mellitus	9 (30.0)	4 (6.7)	0.008
Cardiovascular diseases[b]	25 (83.3)	36 (60.0)	0.026
Chronic renal insufficiency[c]	4 (13.3)	1 (1.7)	0.041
Pulmonary function stage			
GOLD stage III or IV	25 (83.3)	41 (68.3)	0.13
FEV1%	36.9 ± 15.4	41.5 ± 16.8	0.21
Steroid treatment			
Inhaled	15 (50.0)	16 (26.7)	0.028
Systemic use	4 (13.3)	2 (3.3)	0.093
Recent use of antibiotics[d]	25 (83.3)	18 (30.0)	<0.001

BMI, body mass index; FEV1, forced expiratory volume in 1 s.
[a]Data are presented as mean ± SD or No. (%).
[b]Primary hypertension, coronary atherosclerotic heart disease and chronic heart insufficiency were included.
[c]Creatinine >133 μM.
[d]In the 3 months prior to admission.

TABLE 2. Clinical characteristics of patients with and without invasive pulmonary aspergillosis[a]

Characteristics	IPA group (*n* = 30)	Control group (*n* = 60)	p
Clinical signs[b]			
Fever (>38°C)	3 (10.0)	14 (23.3)	0.16
Dyspnoea	28 (93.3)	38 (63.3)	0.002
Sputum increase	12 (40.0)	43 (71.7)	0.004
Wheezing	24 (80.0)	35 (58.3)	0.041
Radiological data			
Chest radiograph abnormal[c]			0.64
Infiltrates	9 (34.6)[d]	9 (25.7)[e]	
Nodules	3 (11.5)[d]	1 (2.9)[e]	
Cavitations	1 (3.8)[d]	0 (0)[e]	
Consolidations	2 (7.7)[d]	2 (5.7)[e]	
CT scan abnormal			0.92
Halo sign	1 (5.9)[f]	0[g]	
Infiltrates	12 (70.6)[f]	8 (53.3)[g]	
Nodules	4 (23.5)[f]	2 (13.3)[g]	
Cavitations	3 (17.6)[f]	1 (6.7)[g]	
Consolidations	3 (17.6)[f]	2 (13.3)[g]	
Worsening radiological sign[h]	17 (65.4)[d]	4 (11.4)[e]	<0.001
Other pathogens positive	21 (70.0)	19 (31.7)	0.001
Mechanical ventilation	13 (43.3)	3 (5.0)	<0.001
Antibiotic treatment			
Three or more kinds	22 (73.3)	5 (8.3)	<0.001
Duration >10 days	27 (90.0)	29 (48.3)	<0.001
Carbapenem[i]	13 (43.3)	6 (10.0)	<0.001
Steroid treatment			
Inhaled	21 (70.0)	32 (53.3)	0.13
Systemic use	20 (66.7)	24 (40.0)	0.017
>700 mg	8 (26.7)	2 (3.3)	0.002
Hospital stay	45.8 ± 39.1	18.4 ± 11.8	<0.001
Mortality in hospital	13 (43.3)	4 (11.4)	<0.001

CT, computed tomography.
[a]Data are presented as mean ± SD or No. (%).
[b]The clinical features were considered at hospital admission.
[c]The first chest radiograph results were included.
[d]*n* = 26 (only 26 cases had chest radiograph examination in the case group).
[e]*n* = 35 (only 35 cases had chest radiograph examination in the control group).
[f]*n* = 17 (only 17 cases had a CT scan).
[g]*n* = 15 (only 15 cases had a CT scan).
[h]New images of infection appeared or old lesions worsened in comparison with previous chest radiographs.
[i]Carbapenem medicines included Imipenem and cilastatin, Meropenem, and Ertapenem.

The results of biological variables in the two groups are shown in Table 3. Although no significant differences were found between the groups in blood gas analysis, the proportion with hypoxemia in the case group was still higher, and nearly half of these IPA cases received mechanical ventilation (43.3% vs. 5%; p <0.001); only one of them survived.

Multivariate logistic regression analysis

Variables with a p-value <0.2 in the univariate analyses were included in logistic regression analysis. These results are shown in Table 4. Use of systemic steroids before admission, treatment with three or more antibiotics during hospitalization and duration of antibiotic treatment longer than 10 days, were independent risk factors associated with IPA.

TABLE 3. Biological parameters of the two groups at admission[a]

Parameters	IPA group (n = 30)	Control group (n = 60)	p
Leucocyte count, 10^3/mL	11.7 ± 7.7	9.1 ± 4.1	0.19
Eosinophil count, cells/mL	189 ± 201	148 ± 175	0.32
Haemoglobin, g/dL	12.6 ± 2.1	13.7 ± 1.9	0.015
Platelets, 10^3/mL	194.9 ± 75.5	201.7 ± 82.3	0.71
Albumin, g/dL	38.8 ± 9.4	38.0 ± 3.5	0.99
Urea nitrogen, mM	7.9 ± 4.4	5.8 ± 2.4	0.016
Creatinine, μM	107.6 ± 100.1	76.9 ± 22.8	0.17
Blood gas analysis			
PaO_2 < 60 mmHg	15 (57.7)[b]	16 (36.4)[c]	0.083
$PaCO_2$ > 45 mmHg	16 (61.5)[b]	25 (56.8)[c]	0.70
SaO_2 < 90%	14 (53.8)[b]	14 (31.8)[c]	0.069

[a]Data are presented as mean ± SD or No. (%).
[b]n = 26 (only 26 cases had a blood gas test in the case group).
[c]n = 44 (only 44 cases had a blood gas test in the control group).

TABLE 4. Multivariate logistic regression analysis of risk factors for invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease

Variable	Wald	OR	95% CI	p
Systemic use of steroids in stable phase	6.592	37.84	2.36–606.98	0.01
Three or more kinds of antibiotics[a]	16.297	46.90	7.24–303.78	0.000
Duration of antibiotic use >10 days[a]	5.763	13.41	1.61–111.72	0.016
Pulmonary function stage* Recent use of antibiotics[b]	10.649	20.26	3.33–123.47	0.001

[a]During admission.
[b]In the 3 months prior to admission.

In addition, recent use of antibiotics and the pulmonary function stage had an interactive effect in this model. Broad-spectrum antibiotics during the 3 months prior to admission significantly increased the probability of IPA in patients with GOLD stage III or IV (Table 5).

Antifungal treatments and outcomes

In the case group, 26 patients had antifungal treatments: voriconazole (13); caspofungin (6); itraconazole (6); and voriconazole combined with caspofungin (1). Among these, nine cases died during their hospital stay. In addition, four subjects in the case group who declined antifungal therapy also died. We followed-up 17 survivors for 6 months; three died of AECOPD during this period.

TABLE 5. Interaction of pulmonary function stage and recent use of antibiotics in multivariate model[a]

	Pulmonary function stage I or II			Pulmonary function stage III or IV		
IPA	Without antibiotics[b]	With antibiotics[c]	Total	Without antibiotics[b]	With antibiotics[c]	Total
No	11 (84.6)	8 (72.7)	19	31 (91.2)	10 (31.3)	41
Yes	2 (15.4)	3 (27.3)	5	3 (8.8)	22 (68.8)	25
Total	13	11	24	34	32	66

IPA, invasive pulmonary aspergillosis.
[a]Data are presented as No. (%).
[b]Without use of antibiotics in the 3 months prior to admission.
[c]Use of antibiotics in the 3 months prior to admission.

Discussion

This study showed that COPD patients with concurrent IPA are more likely to be in a critical condition. Compared with non-IPA patients, COPD patients with concurrent IPA had a higher proportion receiving mechanical ventilation, longer hospital stays, and higher mortality.

Aspergillosis in patients without classical predisposing factors has been consistently reported [6–9]. A multicentre prospective study showed that COPD was one of most important predisposing factors for *Aspergillus spp*. colonization/infection in critically ill patients [10]. However, the frequency of IPA in COPD patients has been poorly documented. In one large study, Guinea *et al.* [11] reported that 1.63% of COPD admissions had isolates of *Aspergillus* from their LRT samples and, of these, 22.1% had probable IPA. In our study, the incidence of COPD complicated with Aspergillosis was 3.9%, which was significantly higher than in other reports [12–14]. This discrepancy may be due, at least partially, to different diagnostic criteria used, regional climates, living conditions, and racial differences.

There are no standard diagnostic criteria for IPA in COPD patients. In 2007, Bulpa *et al.* [5] proposed definitions of IPA in COPD. By these definitions, in terms of classification criteria, patients must have COPD classified as GOLD stage III or IV. Because there are no indications that IPA does not occur in moderately severe COPD patients, it seems inappropriate to exclude those patients only because their lung function does not meet the criteria. In our case group, five patients were GOLD stage II. They were all treated with systemic steroids during hospitalization and three of them had received inhaled corticosteroids in the stable phase (although this was inappropriate). Because of repeated detections of *Aspergillus* in sputum and antibiotic-resistant lower respiratory tract infections in these patients, the diagnosis of IPA was approved by clinicians, even without biopsies. Antifungal treatments were selected and the patients' clinical conditions improved.

Previous studies have suggested that COPD patients with IPA have poor lung function [2]. However, the relationship between pulmonary function classification and *Aspergillus* susceptibility remains unclear. In this study, there was no significant difference in the proportions of patients with GOLD

stage III or IV in the two groups. However, in the multivariate model, the lung function stage and recent use of antibiotics showed an interactive effect. The risk of IPA increased 20 times in patients with poor lung function when recently treated with antibiotics (OR 20.26). We suspect that this may indicate more cases of colonization of *Aspergillus* in severe COPD patients.

Steroids are believed to play a role in the emergence of IPA in COPD patients [2,5]. Guinea *et al.* [11] reported that the accumulated doses of corticosteroids (>700 mg) received during the 3 months prior to admission significantly increased the risk of IPA in COPD patients. Some reports suggested that high doses of inhaled corticosteroids might also be a risk factor for IPA [15,16]. In this study, the case group had a higher proportion of inhaled steroid use while stable. However, data on the timing and dose of inhaled corticosteroids were not complete for this study. During their hospital stay, the case group had more systemic use of corticosteroids and higher doses, which might have been related to serious dyspnoea symptoms. However, high-dose systemic steroid use might promote *Aspergillus* airway colonization to develop into IPA.

Co-morbidities were more common in the case group, suggesting that COPD patients with underlying diseases may be more susceptible to *Aspergillus*. An underlying disease might also be partly responsible for more severe clinical conditions. Another prominent feature was that the case group had a higher detection rate for other pathogens and more types of pathogens in their sputum samples than the control group, suggesting that mixed infections are very common in COPD with IPA. Perhaps due to these many reasons, the administration of antibiotics in the case group was significantly increased.

The mortality rate of IPA in COPD patients is very high [5,11,17]. Thus, a prompt diagnosis and treatment are important for improving the outcomes. However, early diagnosis of IPA is always a problem clinically. A CT scan and a serum GM antigen test are the most common methods for an early diagnosis of IPA in immunocompromised hosts. However, typical CT scan features, such as consolidation, 'air-crescent sign' and 'halo sign', are very rare in COPD patients with IPA [2,5,11]. In recent years, nearly all studies that included serum GM antigen tests were limited to immunocompromised hosts. For immunocompetent patients, the positive rate for GM antigen is under 50%, as the GM antigen is susceptible to macrophage clearance [11,18]; this rate is much lower than in immunocompromised hosts (61–71%) [19]. Our report had a similar result (47.4%). Because most of the positive patients had the GM test only once, false-positive results caused by the use of piperacillin-tazobactam and amoxicillin-clavulanate could not be avoided. Therefore, the real positive rate might be lower.

For the retrospective study, bias in the design itself is difficult to avoid. We cannot ask all patients to have sputum examinations at the same time and under similar conditions. Clinicians decide whether or not patients need sputum fungal cultures. Those patients who have no apparent indications of fungal infection would not have sputum fungal cultures. Therefore, this study cannot fully account for positive *Aspergillus* cultures in COPD. However, because this study depended on searching for *Aspergillus* in LRT samples, no proven patient was included in the case group, so the real incidence of IPA in COPD patients could not be determined. The relationship between the use of antibiotics and IPA remains confusing. Although treatment with multiple antibiotics and a longer duration of antibiotic treatment were independent risk factors associated with IPA, it remains difficult with the present data to strongly affirm that these are not just indicators of disease severity.

In summary, COPD patients with IPA are in a very critical condition. A prompt diagnosis is important in order to provide the maximum chance of successful treatment. Dyspnoea and antibiotic-resistant pneumonia are the most prominent clinical manifestations. In this context, positive *Aspergillus* culture from LRT samples should be regarded as an important clue of infection.

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Transparency Declaration

Conflicts of interest: nothing to declare.

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