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Pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: incidence, risk factors, and outcome

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Abstract

We describe a large series of patients with chronic obstructive pulmonary disease (COPD) and probable invasive pulmonary aspergillosis (IPA), and the risk factors and incidence of the disease in patients with isolation of *Aspergillus* from lower respiratory tract samples. From 2000 to 2007, we retrospectively studied all patients admitted with COPD and isolation of *Aspergillus* (239; 16.3/1000 admissions). Multivariate logistic regression and survival curves were used. Fifty-three patients had probable IPA (3.6 cases of IPA per 1000 COPD admissions). IPA affects at least 22.1% of patients with COPD and isolation of *Aspergillus* in culture. In 33 of the 53 patients with probable IPA, serum galactomannan was determined; in 14 (42.4%) of these, the result was positive. Five variables were independent predictors of IPA with statistical significance: admission to the intensive-care unit, chronic heart failure, antibiotic treatment received in the 3 months prior to admission, the accumulated dosage of corticosteroids equivalent to >700 mg prednisone received in the 3 months prior to admission, and the similar accumulated dosage of corticosteroids received from admission to the first clinical isolation of *Aspergillus*. Multivariate analysis gave an area under the curve of 0.925 (95% CI 0.888–0.962; p <0.001). The overall mean survival of the cohort was 64.1% (28.3% for IPA patients and 75.2% for non-IPA patients). The median number of days of survival was 48 (95% CI 33.07–62.92). However, we found statistically significant differences between patients with IPA (29 days; 95% CI 20.59–37.40) and patients without IPA (86 days; 95% CI 61.13–110.86) (log rank, p <0.001).

Keywords: Aspergillosis, *Aspergillus*, chronic obstructive pulmonary disease, logistic model, mortality, risk factors
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Introduction

Invasive pulmonary aspergillosis (IPA) affects patients with neutropenia, solid organ recipients, and those receiving corticosteroids and other immunosuppressive therapies [1–13]. Patients with severe chronic obstructive pulmonary disease (COPD) who are receiving broad-spectrum antibiotics and corticosteroids are becoming one of the main risk groups for IPA [14–17]. However, data on this disease are limited, fragmented, and usually obtained from case reports, or small collections of cases from different institutions.

Although, in many cases, the isolation of *Aspergillus* from lower respiratory tract (LRT) samples (e.g. sputum, bronchial aspirate, or bronchoalveolar lavage) is the first indication of IPA, the probability of a non-selected risk patient from whom *Aspergillus* has been isolated having IPA was calculated to be 12% [7]. Obviously, this probability depends on the underlying condition of the patients: 72% for patients with neutropenia [18,19], 58% for solid organ transplant recipients [18,19], and 28% for critically ill patients [20]. Unfortunately, the probability for patients with COPD is almost unknown [21].

We describe the clinical condition, risk factors and outcome of a large series of 53 patients with COPD and probable IPA collected in a single institution.

Materials and Methods

Study period and institutional information

This retrospective study (January 2000 to December 2007) was carried out in a 1750-bed tertiary hospital in Madrid, Spain, serving a population that grew from 650 000 to 715 000 inhabitants during the study period. LRT samples from patients admitted with a diagnosis of COPD were submitted for microbiological culture when this was clinically indicated.

IPA is carefully monitored at our hospital, and the usual practice is to follow up every patient with isolation of *Aspergillus* from clinical samples. During the study period, 100 cases of microbiologically documented probable IPA were recorded.

The article does not include a statement of patient consent and the approval of internal review boards, because of its retrospective design.

Microbiology culture and other diagnostic procedures

A total of 429 LRT samples yielded *Aspergillus*. The distribution of samples was as follows: sputum, $n = 240$ (55.9%); bronchial aspirate, $n = 142$ (33.1%); bronchoalveolar lavage, $n = 30$ (7.0%); and other, $n = 17$ (4.0%).

All LRT specimens were cultured on conventional media, including sheep blood agar and chocolate agar. Where appropriate, LRT samples were further cultured on fungal media. Cultures were incubated at 32–37°C for at least 7 days [22]. *Aspergillus* isolates were identified using standard morphological procedures.

The galactomannan level (Platelia; Bio-Rad, Marnes-la-Coquette, France) was determined in serum samples upon request. We used a cut-off of ≥0.5 ng/mL to define positivity. Anti-*Aspergillus* antibodies and precipitins were not measured in samples from these patients.

Patient inclusion criteria and data collected

The individual charts of patients with a discharge diagnosis of COPD and isolation of *Aspergillus* in LRT samples were identified and reviewed, and the following variables were recorded: Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification for COPD patients [23]; McCabe and Charlson scores; chronic heart and renal insufficiency; intensive-care unit (ICU) admission; corticosteroid consumption (accumulated dosage of >700 mg of prednisone or equivalent within the 3 months before admission, and from admission to the first isolation of *Aspergillus*—a cumulative dosage that has already been associated with an increased risk of infection [9]); use of broad-spectrum antibiotics and antifungal agents; analytical data; imaging data; serum galactomannan level; and antifungal treatment.

Definition of IPA

Patients were classified according to the Bulpa criteria [9]. Proven cases required histopathological confirmation. Probable cases required host factors (patient with COPD usually treated with corticosteroids, GOLD stage III or IV, with a recent exacerbation of the dyspnoea and suggestive radiological findings) and microbiological factors (isolation of *Aspergillus* in LRT samples, or two consecutive serum galactomannan determinations). Possible cases required host factors but without *Aspergillus* isolation or serology. Colonization was defined as an asymptomatic isolation of *Aspergillus* in LRT samples. As only patients with positive cultures were included, by definition no possible cases were recorded. Unfortunately, it was not possible to perform histological analysis, and no proven cases were demonstrated. Patients were classified as having IPA (probable cases) or *Aspergillus* colonization.

Number of cases of the disease and distribution of cases over time

We calculated the number of patients with COPD and clinical isolation of *Aspergillus* (with or without IPA), the number of cases of IPA both from overall 1000 hospital admissions and from COPD patient admissions.

Data analysis and risk factors for IPA in patients with COPD and clinical isolation of *Aspergillus*

Categorical variables of patients with and without IPA were described and compared using the chi-square or Fisher exact tests; continuous variables were compared using the *t*-test and the Mann–Whitney *U*-test.

Multivariate logistic regression analysis (SPSS, version 14) was used to study independent variables predictive of IPA. Survival curves for the overall population and for the groups of patients with and without IPA at day 120 after admission were obtained by the Kaplan–Meier method.

Results

Number of patients with *Aspergillus* isolation and IPA

The hospital had 483 176 admissions, of which 14 618 had COPD. The mean number of admissions with COPD per

year (1827) remained stable. Of these, 239 had isolates of *Aspergillus* from the LRT samples (0.49 patients with COPD per 1000 hospital admissions and 16.3 per 1000 COPD admissions).

Only 53 (22.1%) of them had probable IPA (3.6 cases of IPA per 1000 COPD admissions). In recent years, we have detected an increase in the number of cases of IPA in COPD patients (seven per 1000 admissions in 2000 to 13 per 1000 admissions in 2007) (Fig. 1). COPD was the most common predisposing condition for the development of IPA in our hospital, representing 53% of all episodes investigated.

Microbiological and diagnostic procedures

In 33 of the 53 patients with probable IPA, the serum galactomannan level was determined; in 14 (42.4%) of these, the result was positive. We observed false-positive galactomannan results in two patients: one was receiving piperacillin–tazobactam (0.7 ng/mL) and the other was receiving ceftriaxone and parenteral nutrition (0.709 ng/mL) at the time of serum sampling. The overall mean number of positive samples with isolation of *Aspergillus* was 1.8 per patient. Overall, *Aspergillus fumigatus* was involved in 83% of cases of IPA.

Characteristics of the patients evaluated

According to the GOLD criteria for severity of COPD, 32 of the 53 patients with IPA (60.3%) had stage III disease and 21 (39.7%) had stage IV disease.

The demographic and clinical data of patients with COPD with and without IPA are shown in Table 1. Of the 239 patients evaluated, 176 (73.6%) were admitted because of exacerbation of COPD; 45 (84.9% of the patients with IPA) were classified as probably having IPA. Patients with IPA had worse clinical conditions than those without IPA. However, patients with IPA presented non-specific clinical signs that are common in exacerbation episodes: COPD-like dyspnoea (50; 94.3%), fever >38°C (18; 33.9%), haemoptysis (five; 9.4%), and chest pain (nine; 16.9%). In 107 of the 239 patients (44.7%), residual lung lesions were present: 26 (24.2%) had IPA, one had (1%) allergic bronchopulmonary aspergillosis, and six (5.6%) had aspergilloma, which progressed to IPA in three cases.

At the time of the isolation of *Aspergillus*, the infection-specific chest radiography findings were as follows: 107 (44.7%) infiltrates, 31 (12.9%) consolidations, 24 (10.4%) nodules, and 11 (4.6%) cavitations; in the remaining patients, non-specific findings were observed (Table 1). The most frequent radiography findings in patients with COPD and IPA were bilateral infiltrates (29 patients; 54.7%). Worsening radiological findings during admission were observed in 66% of the 53 patients with IPA, as compared with 6.4% of the patients without IPA ($p < 0.0001$). Thirteen (24.5%) patients with probable IPA had a computed tomography (CT) scan, and only three of them showed halo signs; nodules and bilateral infiltration were the most common findings in the patients evaluated (Table 1). The laboratory results revealed an elevated white blood cell count (>12 000 cells/mL) in 31 of 53 patients with IPA. Other parameters, such as lactate dehydrogenase level, also increased in 12 patients with IPA. Anaemia (haemoglobin <12 g/dL), thrombocytopenia (<120 000 platelets/mm^3) and decrease in total protein

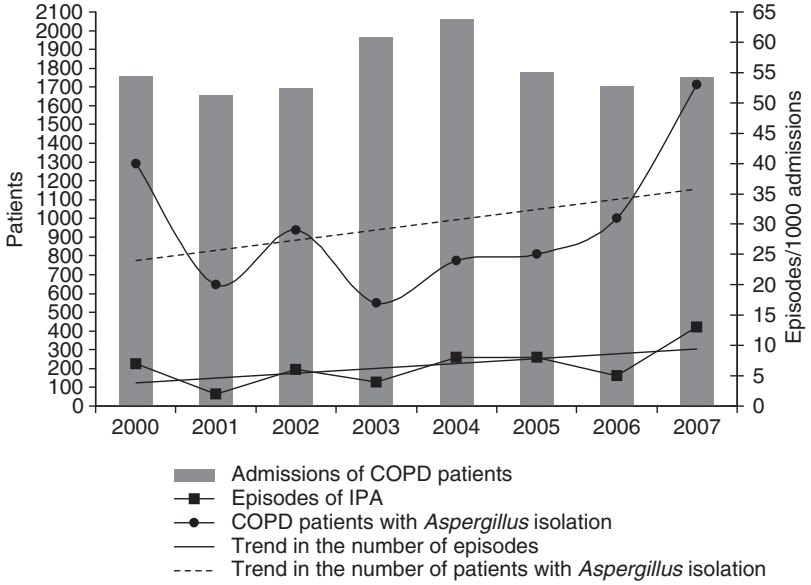

FIG. 1. Number of cases and trend of invasive pulmonary aspergillosis (IPA) episodes. Admissions and number of patients with chronic obstructive pulmonary disease (COPD) with clinical isolation of *Aspergillus* during each year of the study period.

TABLE 1. Summary of clinical and demographic features of the 239 patients with chronic obstructive pulmonary disease (COPD) and clinical isolation of *Aspergillus* included in the study; both groups of patients (with and without invasive pulmonary aspergillosis (IPA)) were compared

Characteristics	IPA	Non-IPA patients	Overall	p
Total, *n* (%)	53 (22.2)	186 (77.8)	239	
Male	43 (81.1)	149 (80.1)	192 (80.3)	
Female	10 (18.8)	37 (19.8)	47 (19.6)	
Mean age (years)[a]	69.97	68.24	68.62	
Days of admission[a]	38.87	29.91	31.90	
ICU admission, *n* (%)[b]	30 (56.6)	51 (27.4)	81 (33.8)	<0.001
Admission by COPD exacerbation, *n* (%)	45 (84.9)	131 (70.4)	176 (73.6)	0.035
GOLD stage, *n* (%)				
I	0	5 (2.6)	5 (2.1)	<0.001
II	0	60 (32.2)	60 (25.1)	
III	32 (60.3)	101 (54.3)	133 (55.6)	
IV	21 (39.6)	20 (10.7)	41 (17.1)	
McCabe score	2–3	2–3	2–3	0.053
Charlson score	3.21	3.26	3.20	0.036
Residual lesions, *n* (%)	26 (49)	81 (43.5)	107 (44.7)	0.532
Diabetes mellitus, *n* (%)	12 (22.6)	34 (18.2)	46 (19.2)	0.554
Chronic renal insufficiency, *n* (%)[c]	6 (11.3)	10 (5.3)	16 (6.6)	0.130
Chronic heart insufficiency, *n* (%)	28 (52.8)	49 (26.3)	77 (32.2)	0.001
Corticosteroid consumption before admission, *n* (%)[d]	49 (92.4)	105 (56.4)	154 (64.4)	<0.001
<20 mg/day	26 (49.0)	94 (50.5)	120 (50.2)	
≥20 mg/day	23 (43.4)	11 (5.9)	34 (14.2)	
Accumulated corticosteroid dose before admission, *n* (%)[d]				
<100 mg	1 (2.0)	5 (2.7)	6 (2.5)	0.003
100–700 mg	26 (49.0)	80 (43.0)	106 (44.3)	
>700 mg	22 (41.5)	20 (10.7)	42 (17.6)	
Broad-spectrum antibiotics before admission, *n* (%)[d]	33 (62.2)	54 (29.1)	87 (36.4)	<0.001
Accumulated corticosteroid dose during admission, *n* (%)[e]	52 (98.1)	155 (83.3)	207 (86.6)	
<100	1 (1.9)	4 (2.1)	5 (2.1)	<0.001
100–700	10 (18.8)	105 (56.5)	115 (48.1)	
>700	41 (77.3)	46 (24.7)	87 (36.4)	
Fever (>38°C) at admission, *n* (%)	18 (33.9)	58 (31.2)	76 (31.8)	0.868
Exacerbation of dyspnoea during admission, *n* (%)	50 (94.3)	130 (69.9)	180 (75.3)	<0.001
Mechanical ventilation, *n* (%)[f]	29 (54.7)	41 (22.1)	70 (29.3)	<0.001
Central venous catheter, *n* (%)[f]	25 (47.1)	37 (19.8)	62 (25.9)	<0.001
Chest radiograph, *n* (%)[f]				
Specific images				
Consolidation	12 (22.6)	19 (10.21)	31 (12.9)	0.034
Nodules	11 (20.7)	13 (6.9)	24 (10.4)	0.007
Cavitations	9 (16.9)	2 (1.0)	11 (4.6)	<0.001
Bilateral infiltrates	29 (54.7)	36 (19.3)	65 (27.2)	<0.001
Unilateral infiltrates	10 (18.8)	25 (13.4)	35 (14.6)	0.378
Worsening radiological findings[g]	35 (66)	12 (6.4)	47 (19.7)	<0001
CT Scan, *n* (%)[f]	13 (24.5)	38 (20.4)	51 (21.3)	
Halo sign	3 (5.7)	0	3 (1.3)	0.013
Nodules	10 (18.8)	14 (7.5)	24 (10.0)	0.030
Infiltrates	10 (18.8)	9 (4.8)	19 (7.9)	0.003
Other	7 (13.2)	29 (15.6)	36 (15.0)	0.302

CT, computed tomography; ICU, intensive-care unit.
[a]Arithmetic mean.
[b]Patients who required admission to the ICU.
[c]Creatinine >1.5 mg/dL.
[d]Within the 3 months before the current admission.
[e]From admission to the first clinical isolation of *Aspergillus*.
[f]At the time of the first clinical isolation of *Aspergillus*.
[g]Worsening radiological findings during admission. Specific images of infection may appear or even worsen in comparison with previous chest radiographs.

(<6 g/L) were frequently observed in the later stages of IPA (Table 2).

In 23 (43.3%) of the 53 patients with probable IPA, another pathogen (such as *Nocardia*, methicillin-resistant *Staphylococcus aureus*, *Pseudomonas*, *Stenotrophomonas maltophilia*, *Enterobacteriaceae*) was isolated in at least one LRT sample. All patients were receiving correct broad-spectrum antibiotic therapy, but with a poor clinical response.

At admission, 49 (92.4%) patients with IPA and 105 (56.4%) without IPA were taking corticosteroids. During admission, corticosteroids were given to 98.1% of patients with IPA and to 83.3%% of patients without IPA. An accumulated corticosteroid dose >700 mg of prednisone or equivalent during admission was achieved in 41 (77.3%) of the patients with IPA and in 46 (24.7%) of those without (p <0.001) (Table 1). Before admission, 97 of the 239 patients received inhaled corticosteroids, and 27 (27.8%) of them developed IPA. During admission, 119 patients received inhaled corticosteroids, and 43 (36.1%) developed IPA. The exact doses received were not available in the medical his-

TABLE 2. Summary of analytical findings of patients with chronic obstructive pulmonary disease and clinical isolation of *Aspergillus* included in the study; both groups of patients (with and without invasive pulmonary aspergillosis (IPA)) were compared at the time of the first isolation of *Aspergillus*

Analytical parameter	Patients with IPA *n* (%)		Patients without IPA *n* (%)		p
	At admission	At time of the first isolation of *Aspergillus*	At admission	At time of the first isolation of *Aspergillus*	
P_aO_2 <60 mmHg	34 (64.1)	34 (64.1)	74 (39.7)	65 (34.9)	<0.001
P_aCO_2 >45 mmHg	32 (60.3)	35 (66.0)	65 (34.9)	52 (27.9)	<0.001
pH <7.35 or >7.45	31 (58.4)	32 (60.3)	34 (18.2)	26 (13.9)	<0.001
HCO_3 <23 or >29 mmol/L	28 (52.8)	29 (54.7)	35 (18.8)	34 (18.2)	<0.001
S_aO_2 <90 mmHg	37 (69.8)	35 (66.0)	58 (31.1)	43 (23.1)	<0.001
Haemoglobin <12 mg/dL	18 (33.9)	39 (73.5)	35 (18.1)	66 (35.4)	<0.001
Haematocrit <35%	18 (33.9)	38 (71.6)	33 (17.7)	61 (32.7)	<0.001
Leukocytes >12 000/mL	31 (58.4)	41 (77.3)	84 (45.1)	93 (50.0)	<0.001
Platelets <120 000/mm^3	5 (9.4)	15 (28.3)	9 (4.8)	10 (5.3)	<0.001
Lactate dehydrogenase >460 U/L	12 (22.6)	26 (49.0)	24 (12.9)	25 (13.4)	<0.001
Total protein <6 g/dL	14 (26.4)	44 (83.0)	9 (4.8)	49 (26.3)	<0.001
Creatinine >1.5 mg/dL	6 (11.3)	8 (15.0)	8 (4.3)	10 (5.3)	0.034

tory. Most cases of IPA had only pulmonary involvement, but two patients also had probable brain invasion, as demonstrated by suggestive radiological findings.

Probability of infection and risk factors for IPA in patients with COPD and clinical isolation of *Aspergillus*

The overall probability of having IPA in a patient with COPD and clinical isolation of *Aspergillus* from the LRT was 22.1%. However, this probability may be influenced by the number of samples studied in patients with higher clinical suspicion of IPA.

Variables with a p-value <0.1 in the univariate analysis are shown in Table 1. Of these, five were included in the multivariate model: admission to the ICU, chronic heart failure, antibiotic treatment received in the 3 months prior to admission, accumulated doses of corticosteroids (>700 mg) received in the 3 months prior to admission, and accumulated doses of corticosteroids (>700 mg) received from admission to the first clinical isolation of *Aspergillus*. The multivariate analysis selected the five variables with independent statistical significance (Table 3). The model gave an area under the curve of 0.925 (95% CI 0.888–0.962; chi-square test, p <0.001).

TABLE 3. Variables selected for prediction of invasive pulmonary aspergillosis by multivariate logistic regression analysis in patients with chronic obstructive pulmonary disease and clinical isolation of *Aspergillus* from lower respiratory tract (LRT) samples

	Wald	p	OR	95% CI Inferior	Superior
ICU admission	4.758	0.029	2.406	1.093	5.294
Chronic heart failure	3.649	0.056	2.102	0.981	4.504
Accumulated dose of corticosteroids prior to admission[a]	6.213	0.013	2.987	1.263	7.060
Accumulated dose of corticosteroids during admission[b]	13.338	0.000	4.568	2.022	10.324
Antibiotic treatment[a]	5.924	0.015	2.570	1.202	5.497
Constant	66.327	0.000	0.034		

ICU, intensive-care unit.
[a]In the 3 months prior to admission.
[b]From admission to the first clinical isolation of *Aspergillus* from LRT samples.

Antifungal treatment and outcome

Overall, 49 patients survived long enough to receive antifungal therapy (26 monotherapy, and 23 combination therapy with two or more antifungals). The drugs used were voriconazole (38; 68.4%), itraconazole (nine; 15.7%), amphotericin B (21; 40.3%), and caspofungin (17; 31.5%). The global mortality rate was 71.6% (38 patients) (Table 4).

TABLE 4. Outcome of the 239 patients included; survival was analysed 120 days after admission; differences in survival are shown for patients with and without invasive pulmonary aspergillosis (IPA) (p <0.001)

Outcome	Probable IPA *n* (%)	Patients without IPA *n* (%)	Overall *n* (%)
Survival	15 (28.3)	128 (68.8)	143 (59.8)
Death attributable to *Aspergillus*	11 (20.7)	0	11 (4.6)
Death attributable to *Aspergillus* and to other causes	26 (49.0)	3 (1.6)	29 (12.1)
Death not attributable to *Aspergillus*	1 (1.9)	44 (23.6)	45 (18.8)
Not evaluable[a]	0	11 (5.9)	11 (4.6)

[a]These patients could not be evaluated because they were outpatients or the clinical chart was not available.

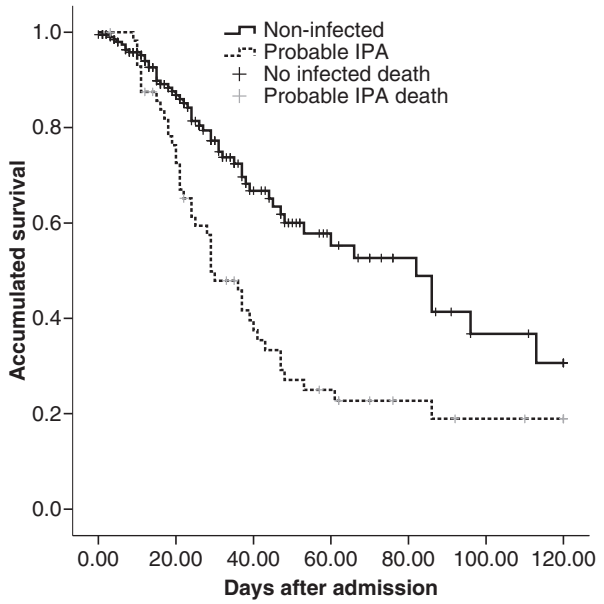

FIG. 2. Outcome of patients at day 120 from admission. Survival curves for the overall population and for both infected and non-infected patients were plotted using the Kaplan–Meier method. IPA, invasive pulmonary aspergillosis.

We followed up patients from admission to day +120, if survival allowed this. The overall mean survival rate of the cohort was 64.1% (28.3% for IPA patients and 75.2% for non-IPA patients). The median number of days of survival was 48 (95% CI 33.07–62.92). However, we found statistically significant differences between patients with IPA (29 days; 95% CI 20.59–37.40) and patients without IPA (86 days; 95% CI 61.13–110.86) (log rank, $p < 0.001$) (Fig. 2).

Discussion

The most common underlying condition in IPA in our institution is COPD, and almost one in every four patients with COPD and isolation of *Aspergillus* from the LRT had IPA. IPA is more frequent in patients receiving high cumulative doses of corticosteroids and in those with imaging evidence of progressive lung disease after admission. Mortality in patients with COPD and IPA is higher than in those without IPA, and remains very high despite administration of effective antifungal therapy.

Although prolonged neutropenia and immunosuppression associated with solid organ transplantation have been recognized as the most common underlying conditions in patients with IPA [3,24–28], patients with other underlying conditions (e.g. COPD) are receiving more and more attention [11,19,29–31].

Several reports have described COPD as an important underlying condition for IPA [7,9,10,20,32,33]. COPD as an underlying condition for IPA may be underdetected or under-reported, because clinical manifestations of the condition are non-specific and because the severity of the underlying condition can mask lung invasion by *Aspergillus*. Alternatively, better care of COPD patients may prolong life-expectancy in cases where corticosteroids and broad-spectrum antibiotics are administered more liberally [34]. The use of these drugs may play a role in the later colonization of the lungs by *Aspergillus*.

An overview of the cases in our institution (not only of a single service or unit) shows that COPD was the main predisposing condition for IPA, representing 53% of all cases occurring during the study period.

An important shortcoming in this population is to be found in the criteria used for diagnosis. The European Organization for Research and Treatment of Cancer criteria for IPA were developed for patients with cancer, but, in the absence of better data, they have also been widely used for non-cancer populations [35]. In 2007, Bulpa *et al.* relied on several case reports to draw up their definitions of IPA, specifically for patients with COPD and isolation of *Aspergillus* [9]. According to these criteria, proven cases require histological evidence of invasion, and the procedure needed to obtain this is rarely performed in late-stage COPD patients. In our series, we were not able to perform lung biopsies or autopsies; therefore, all cases were classified as probable IPA, and this prevented us from ruling out false positives and false negatives. Nevertheless, it is clear that the clinical outcomes of the populations classified as IPA and non-IPA are different. Although the clinical manifestations and imaging findings of patients with COPD and with IPA are non-specific, the two conditions share common features and predisposing factors.

Our study is biased, because we selected only those patients with isolation of *Aspergillus* from LRT samples, and not infected patients without isolation. In the absence of histopathological data, we decided to exclude patients without *Aspergillus* in the LRT.

Serum galactomannan determinations and CT scans are not routinely performed in this population. Galactomannan was detected in only 33 patients with IPA (62.2%) (≥0.5 ng/mL). These findings are consistent with other reports [8,15,36,37]. The value of imaging is high for neutropenic patients [38], although the use of the CT scan in COPD patients has not been prospectively evaluated. Of the 14 patients with a CT scan in our series, only three (5.7% of all patients with IPA) presented halo signs.

In order to minimize the limitations of diagnostic procedures and the overestimation of isolation of *Aspergillus* in

patients with COPD, we studied the predictive variables for IPA in patients with COPD and isolation of *Aspergillus* in LRT samples. The analysis showed that, in patients with COPD and in poor clinical condition (ICU admission and chronic heart failure) who have received antibiotics and high accumulated dose of corticosteroids, the isolation of *Aspergillus* in LRT samples should suggest to physicians the performance of a CT scan and the initiation of antifungal therapy.

Further prospective studies evaluating the outcome of COPD patients with *Aspergillus* isolated from the LRT are required. The impact of early and adequate antifungal therapy in this population has to be assessed, and high-risk patients should be selected for preventive or early therapy.

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Transparency Declaration

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