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ORIGINAL RESEARCH

New insights into the clinical characteristics and prognostic factors of pulmonary fungal infections from a retrospective study in Southwestern China

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Background: Despite increasing incidence of pulmonary fungal infections (PFIs) worldwide, the clinical characteristics and prognostic factors remain poorly understood. The goal of this study was to investigate the clinical features, laboratory findings, and outcomes of hospitalized patients diagnosed with PFIs.

Methods: We retrospectively enrolled 123 patients at a university hospital in Southwestern China between February 2014 and May 2016, who were diagnosed with PFIs based on clinical presentations and laboratory tests including fungal culture and pathological examination. Medical records were reviewed and analyzed. Prognostic factor associated with mortality was evaluated by multivariate regression analysis.

Results: Of the 123 PFI patients enrolled, the mean age was 67 years with 72% of them being males. In addition to common clinical features reported previously, these patients exhibited distinct characteristics, with the elderly accounting for 79% of all cases, and with prolonged hospitalization being the most prevalent risk factor (74%) and chronic obstructive pulmonary disease (COPD) being the most common underlying disease (45%). Invasive operation was significantly more frequently involved in patients with unfavorable treatment responses than in patients with favorable responses (45.6 vs 7.4%, P=0.000). By multivariate regression analysis, invasive operation (odds ratio [OR]: 5.736, 95% confidence interval [CI]: 2.008–16.389, P=0.001) and hypoalbuminemia (OR: 3.936, 95% CI: 1.325–11.696, P=0.014) were independent prognostic factors of mortality in PFIs.

Conclusion: This study provides new insights into the clinical characteristics and prognostic factors of PFIs and highlights the necessity to be aware of PFIs in patients with COPD and patients receiving invasive operation in order to improve clinical management of these patients.

Keywords: pulmonary fungal infection, risk factors, prognostic factors, chronic obstructive pulmonary disease, invasive operation

Introduction

With the advent of human immunodeficiency virus (HIV) epidemic and the ever-increasing use of broad-spectrum antibiotics, glucocorticoids, immunosuppressive agents, and various types of invasive procedures, there has been a dramatic increase in the incidence of systemic or deep mycoses.[1] Susceptible individuals are usually infected by the inhalation of fungal spores into the respiratory tract, initiating a pulmonary fungal infection (PFI) and subsequently spreading to other organs.[2] In most cases, the initial pulmonary infection is mild or subclinical. The clinical manifestations and imaging characteristics of PFIs are often not typical or specific and thus can be easily overlooked or misdiagnosed by clinician. In fact, currently, laboratory diagnosis

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of PFIs is also challenging. Although antigen and antibody tests are available for clinical use, the definitive diagnosis of PFIs relies primarily on in vitro fungal culture and/or microscopic examination of respiratory specimens, which are usually time-consuming or lack sensitivity, thereby leading to a delayed or missed diagnosis.[1,3]

As a result of the challenges earlier, many aspects of PFIs, including clinical characteristics and prognostic factor, remain poorly understood. Most of the reported studies on PFIs have focused on special population with a selected condition or infected with a particular fungal species, particularly *Aspergillus* spp. There are only sparse reports on PFIs in patients with a wide range of risk factors and clinical background.[4–6] In the present study, we retrospectively investigated a case series of PFI patients with diverse demographic factors and medical conditions and demonstrated their clinical characteristics as well as treatment outcomes.

Methods

PFI case definition

We reviewed the medical records of all hospitalized patients diagnosed with PFIs from February 2014 to May 2016 in the Department of Respiratory and Critical Care Medicine, a 3000-bed teaching hospital in southwestern China. PFI diagnosis and classification were established according to the revised definitions of invasive fungal disease.[7] Diagnostic criteria included 1) at least one of the 22 previously identified risk factors (Table 1);[1,8–12] 2) at least one of the symptoms including cough, expectoration, fever, hemoptysis, chest pain, and dyspnea; 3) positive chest radiological findings including halo sign, air crescent sign, macronodule (≥1 cm in diameter), nodule, consolidation, cavity lesion, air bronchograms or bronchiectasis;[13] 4) elevated serum 1,3-β-D-glucan level (>60 pg/mL) or identification of fungal species in the culture of blood sample (positive once) or respiratory samples (positive twice in culture of sputum or once in culture of pleural fluid, transtracheal aspirate, percutaneous needle aspiration biopsy, or bronchoalveolar lavage fluid); and 5) positive microscopic examination of computed tomography (CT)-guided percutaneous needle aspiration biopsy of the lung. PFI cases were classified into "possible", "probable", and "proven". Possible PFI was defined if the patient fulfilled criteria 1, 2, and 3; probable PFI was defined if the patient fulfilled criteria 1, 2, 3, and 4; and proven PFI was defined if the patient fulfilled all the five criteria. Excluded were cases with incomplete clinical data, no radiological data, or prophylactic use of antifungal drugs.

Table 1 Prevalence of risk factors in 123 patients with PFIs

Risk factors	Number of patients	%
Prolonged hospitalization (>10 days)	91	73.9
Smoking	66	53.6
Prolonged use of broad-spectrum antibiotics (>2 weeks)	60	48.7
Chronic obstructive pulmonary disease	55	44.7
Invasive operation	30[a]	24.3
Hypoalbuminemia (<30 g/L)	30	24.3
Hematological or solid organ malignancy	20	16.2
Prolonged high-dose corticosteroid treatment in previous 60 days (>3 weeks)	18	13.5
Other pulmonary structural disorders	18	13.5
Diabetes mellitus	14	11.3
Chronic renal disorder	10	7.5
Systemic inflammatory diseases	8	6.5
Invasive fungal infection in previous 2 years	7	5.6
Use of immunosuppression agents in previous 30 days	5	3.7
Advanced HIV/AIDS	3	2.4
Significant neutropenia for >10 days in previous 60 days	2	1.6
Bone marrow transplantation or solid organ transplantation	2	1.6
Primary immune deficiency affecting neutrophil function	0	0
History of sinus disease	0	0
Prolonged granulocytopenia (>3 weeks)	0	0
Chronic granulomatous disease	0	0
Liver cirrhosis	0	0

Note: [a]All received urinary catheterization for 2–30 days, with five of them also receiving invasive mechanical ventilation for 4–12 days.
Abbreviations: AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus; PFIs, pulmonary fungal infections.

Clinical data collection

For all patients, we retrieved medical data, including potential risk factors (Table 1), clinical presentations and laboratory findings (Tables 2 and 3), and treatment and outcomes (Table 4). All patients were treated with voriconazole, itraconazole, fluconazole, caspofungin, or amphotericin B (Table 4). The changes of symptoms, signs, and laboratory tests during and after treatment were recorded. None of these patients received surgical resection, growth factors, granulocyte transfusions, or other adjuvant therapies. Treatment outcomes included favorable and unfavorable responses during hospitalization. Favorable response was defined as a reduction of more than half of the symptoms and rale signs with or without a partial or complete resolution of pulmonary lesions observed before treatment. Unfavorable response was defined as worsening, or no symptomatic or radiological improvement, or death during hospitalization regardless of the cause.[14]

Table 2 Clinical characteristics of 123 patients with PFIs

Characteristics	Number of patients	%
Age[a]		
Children (0–9 years)	0	0
Adolescent and adults (10–59 years)	26	21.1
Elderly (≥60 years)	97	78.9
Gender (male)	89	72.4
Current or exsmoker	66	53.6
Current or former alcohol drinker	43	34.9
Pulmonary or systemic symptoms and signs		
Cough and expectoration	113	91.8
Fever	47	38.2
Dyspnea	25	20.3
Chest pain	14	11.3
Hemoptysis	8	6.5
Abnormal chest signs	103	83.7
Oral or skin fungal infection signs	42	34.1
Chest imaging findings		
Cavity lesions	11	8.9
Nodules	30	24.4
Pleural effusion	26	21.1
Underlying or accompanying diseases		
Chronic obstructive pulmonary disease	55	44.7
Hypertension	31	25.2
Heart disease	27	22.0
Malignant tumor	20	16.3
Diabetes mellitus	14	11.3
Chronic renal disorder	10	8.1
Bronchiectasis	9	7.3
Interstitial lung disease	6	4.9
Tuberculosis	6	4.9
Asthma	4	3.3
Pneumonia	4	3.3
Dermatomyositis	3	2.4
HIV infection	3	2.4
Renal transplantation	2	1.6
Systemic lupus erythematosus	2	1.6

Notes: [a]Classified according to the latest criteria of the World Health Organization.[36] The adolescent and adult groups were combined due to the small number of adolescents (only one).
Abbreviations: HIV, human immunodeficiency virus; PFI, pulmonary fungal infection.

Statistical analysis

Categorical variables were presented as numbers (percentages) and analyzed by Chi-square test or Fisher's exact test, while continuous variables were presented as medians and analyzed by Mann–Whitney test or *t* test. Multivariate logistic regression analysis was used to analyze the association between risk factors and mortality with IBM SPSS Statistics 22. Other statistical analyses were performed using GraphPad Prism 5.01 (GraphPad Software, Inc., La Jolla, CA, USA). A two side $P<0.05$ was considered statistically significant.

Table 3 Fungus culture and 1,3-β-D-glucan test in 60 patients with probable/proven PFIs

Fungus examination	Number of patients	%
1,3-β-D-Glucan test		
Positive (≥60 pg/mL)	44	73.3
Negative (<60 pg/mL)	16	26.7
Positive fungal culture	39[a]	65.0
Candida albicans	20[b]	51.3[d]
Candida tropicalis	3	7.6[d]
Candida glabrata	2	5.1[d]
Candida klebsiella	1	2.6[d]
Aspergillus fumigatus	10[c]	25.6[d]
Aspergillus niger	1	2.6[d]
Cryptococcus	2	5.1[d]
Negative fungal culture	21	35.0

Notes: [a]Confirmed by fungal culture and/or pathological examination. [b]Including eight from bronchoalveolar lavage fluids, two from pleural fluids, and 10 from lower respiratory tract secretions. [c]Including two from percutaneous needle aspiration biopsies, four from bronchoalveolar lavage fluids, and four from lower respiratory tract secretions. [d]Relative to the total number (39) of patients positive in fungal culture.
Abbreviation: PFI, pulmonary fungal infection.

Institutional review board statement

This study was approved by Institutional Review Board of the First Affiliated Hospital of Chongqing Medical University (no 20171801). Written informed consent was deemed unnecessary by the Institutional Review Boards for human studies due to the retrospective nature of the data. All patient data were de-identified and treated with the utmost confidentiality in accordance with Institutional Review Board requirements.

Results

Risk factors for PFIs

We identified a total of 123 patients with PFIs and evaluated the prevalence of risk factors known to be associated with PFIs (Table 1).[1,9–12] The most common risk factor was prolonged hospitalization (>10 days), which was noted in 74% of patients. Other common risk factors included smoking (54%), prolonged use of broad-spectrum antibiotics (48%), and chronic obstructive pulmonary disease (COPD; 45%). Relatively uncommon risk factors included invasive operation (24%), hypoalbuminemia (24%), hematological or solid organ malignancy (16%), high-dose corticosteroid treatment (14%), pulmonary structural disorder (14%), and diabetes mellitus (11%). All the remaining risk factors are rare (each <10%).

Clinical characteristics of PFIs

Of the 123 PFI patients enrolled, all were native Chinese from the Southwest of China and had a mean age of 67 years (ranging 16–91 years), with 79% of them being elderly (≥60 years),

Table 4 Comparison of characteristics between patients with favorable responses and those with unfavorable responses

Characteristics	Favorable response[a] (n=68)	Unfavorable response[a] (n=55)	*P*-value[b]
Age (years)	66.5±13.5	67.8±17.1	0.638
Gender (male)	49 (72.0)	40 (72.7)	0.933
Current or exsmoker	33 (48.5)	33 (60.0)	0.204
Co-morbidity			
Chronic obstructive pulmonary disease	28 (41.2)	25 (56.4)	0.633
Tumor	13 (33.8)	6 (10.9)	0.210
Chronic heart failure	10 (14.7)	15 (27.3)	0.085
Diabetes mellitus	4 (5.9)	10 (18.2)	0.032
Laboratory tests			
(1,3)-β-D-Glucan (normal: 60 pg/mL)	116.8±250.9	146.9±274.3	0.481
CRP (normal: <10 mg/L)	54.4±62.5	61.3±42.0	0.484
PCT (normal: <0.05 μg/L)	2.5±5.3	2.8±7.3	0.818
ESR (M: 2–21, F: 2–25 mm/h)	26.8±32.3	27.9±33.0	0.852
WBC (normal: 3.5–9.5×10^9/L)	10.7±5.6	10.3±5.2	0.339
Albumin (normal: 35–50 g/L)	34.7±7.2	29.8±5.3	<0.001
Fungal culture			
Positive fungal culture	17 (10.3)	22 (40.0)	0.075
Aspergillus infection	4 (5.9)	7 (12.7)	0.186
Candida infection	13 (19.1)	14 (25.5)	0.398
Chest imaging findings			
Cavity lesions	8 (11.8)	3 (5.5)	0.222
Nodules	22 (32.4)	8 (16.4)	0.022
Number with possible PFI	39 (57.4)	24 (43.6)	0.130
Treatment and medical cost			
Sequential antifungal therapy[c]	56 (82.4)	39 (70.9)	0.132
Voriconazole treatment	24 (35.3)	28 (50.9)	0.081
Duration of antifungal therapy (days)	12.2±19.9	8.7±6.3	0.159
Glucocorticoids	30 (44.1)	29 (52.7)	0.341
Invasive operations	5 (7.4)	25 (45.6)	0.000
Side effects of antifungal therapy	5 (7.4)	7 (12.7)	0.317
Hospitalization cost (RMB)	52,678±39,474	81,745±71,418	0.003
Hospitalization time (days)	17.0±9.9	16.0±12.2	0.418

Notes: [a]Values are shown as mean ± SD or n (%). [b]Underlined are values with statistical significance. [c]Including fluconazole plus itraconzole, fluconazole plus voriconazole, fluconazole plus caspofungin or fluconazole plus amphotericin B. The dose and duration used: voriconazole (200 mg twice a day for 2–165 days), itraconazole (200 mg daily for 7–14 days), fluconazole (300 mg twice a day for 1–30 days), caspofungin (50 mg daily for 4–14 days), or amphotericin B (10 mg daily for 4–10 days).
Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; F, female; M, male; PCT, procalcitonin; PFI, pulmonary fungal infection; WBC, white blood cell.

72% males, 54% smokers, and 35% alcohol drinkers. All presented pulmonary symptoms, with the cough and expectoration being the most common (92%), followed by dyspnea (20%), chest pain (11%), and hemoptysis (7%). Fever was recorded in 38% of patients. Abnormal breath sounds were noted in 84% of patients, and oral or skin fungal infection was noted in 34% of patients. The majority (93%) of the patients suffered at least one underlying disease, with COPD being the most common (45%), followed by hypertension (25%), heart disease (22%), and various immune dysfunctions (37%).

Comparing possible and probable/proven PFIs

Among the 123 patients with PFIs, there were 63, 57, and three patients classified as possible, probable, and proven PFIs, respectively. Due to the small sample size of the proven PFI group, it was combined into the probable PFI group forming the probable/proven PFI group. When comparing the clinical characteristics between these two groups (Table 5), a statistically significant difference was observed for the following characteristics, including a higher prevalence of hemoptysis (12 vs 2%, P=0.023) and lung cavity lesions (15 vs 3%, P=0.021), a higher level of 1,3-β-D-glucan (254.0 vs 12.3 pg/mL, P<0.0001), and a more frequent use of sequential antifungal therapy (30 vs 14%, P=0.035) in the probable/proven PFI group than in the possible PFI group. No statistically significant difference was observed for the remaining characteristics.

Of the 60 patients with probable/proven PFI, 44 (73%) patients were positive in 1,3-β-D-glucan test and 39 (65%)

Table 5 Comparison of clinical characteristics between possible PFI and probable/proven PFI

Characteristics	Possible PFI[a] (n=63)	Probable/proven PFI[a] (n=60)	*P*-value[b]
Age (years)	67.5±12.5	57.5±17.7	0.725
Gender (male)	46 (73.0)	44 (73.3)	0.964
Current or exsmoker	37 (58.7)	29 (48.3)	0.247
Current or former alcohol drinker	25 (39.7)	18 (30.0)	0.260
Underlying conditions			
Chronic obstructive pulmonary disease	32 (50.8)	23 (38.3)	0.164
Diabetes mellitus	8 (12.7)	6 (10.0)	0.637
Heart failure	14 (23.8)	11 (18.3)	0.592
Chronic renal disorder	5 (7.9)	5 (8.3)	0.956
Malignancy	12 (19.0)	8 (13.3)	0.257
Clinical manifestations			
Hemoptysis	1 (1.6)	7 (11.7)	0.023
Chest pain	5 (7.9)	9 (15.0)	0.217
Cavity lesions	2 (3.2)	9 (15.0)	0.021
Laboratory tests			
CRP (normal: <10 mg/L)	58.6±61.7	57.0±45.5	0.876
WBC (normal: 3.5–9.5×10^9/L)	10.8±6.6	10.2±4.1	0.561
ESR (M: 2–21, F: 2–25 mm/h)	25.9±25.9	28.4±34.3	0.678
PCT (normal: <0.05 μg/L)	3.2±8.5	1.0±1.9	0.0481
1,3-β-D-Glucan (normal: <60 pg/mL)	12.3±14.9	254.0±331.8	<0.0001
Albumin (normal: 35–50 g/L)	31.7±6.2	32.1±7.2	0.776
Treatment outcome and cost			
Duration of antifungal treatment (days)	8.7±5.7	13.1±21.7	0.125
Sequential antifungal therapy	9 (14.3)	18 (30.0)	0.035
Favorable response	40 (63.5)	29 (48.3)	0.090
Death	12 (19.0)	17 (28.3)	0.225
Hospitalization costs (RMB)	58,465±52,292	73,247±62,736	0.156
Hospitalization duration (days)	15.8±10.3	17.4±11.7	0.414

Notes: [a]Values are shown as mean ± SD or n (%). [b]Underlined are values with statistical significance.
Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; F, female; PCT, procalcitonin; M, male; PFI, pulmonary fungal infection; WBC, white blood cell.

patients were positive in fungal culture and/or microscopic examination (Table 3). A total of seven different fungal species were identified, with *Candida albicans* being the most prevalent species (20/39 or 51%), followed by *Aspergillus fumigatus* (10/39 or 26%). Other fungal species were rare (<8% each). Based on in vitro drug sensitivity test, no apparent drug resistance was noted for any of these fungal species. There was no significant difference in any demographic and clinical characteristics between *Candida*- and *Aspergillus*-infected patients except that the latter group had a younger age, a higher prevalence of lung cavity lesions, and a higher white blood cell (WBC) count ($P<0.05$ each) (Table S1).

Comparisons of treatment responses

All of the 123 patients with PFIs were treated with antifungal agents during hospitalization, with 68 (55%) of them showing favorable responses and the remaining 55 (45%) showing unfavorable responses (Table 4). Compared with patients with favorable responses, patients with unfavorable responses had a higher prevalence of diabetes mellitus ($P=0.032$), a lower albumin level ($P<0.001$), a lower prevalence of lung nodules in radiography ($P=0.022$), a higher rate of receiving invasive operation ($P=0.000$), and a higher medical cost during hospitalization ($P=0.003$). No statistically significant difference was observed for other categories compared.

Prognostic factors associated with mortality

Twenty-nine (24%) of the 123 PFI patients died during the hospital stay. As per multivariate logistic regression analysis (Table 6), hypoalbuminemia (odds ratio [OR]: 3.936, 95% confidence interval [CI]: 1.325–11.696, $P=0.014$), invasive operation (OR: 5.736, 95% CI: 2.008–16.389, $P=0.001$), and older ages (≥60 years, OR: 5.739, 95% CI: 1.049–31.401, $P=0.044$) were independent prognostic factors associated with mortality. Other risk factors surveyed were not associated with mortality ($P>0.05$ each).

Table 6 Regression analysis of prognostic factors associated with mortality for 29 PFI patients

Risk factors	OR (95% CI)	*P*-value[a]
Age ≥60 years	5.739 (1.049–31.401)	0.044
Gender (male)	0.440 (0.137–1.411)	0.167
Leukopenia (<4×10⁹/L)	0.000 (0.000)	0.999
Hypoalbuminemia (<30 g/L)	3.936 (1.325–11.696)	0.014
Invasive operations	5.736 (2.008–16.389)	0.001
Use of immunosuppressive agents	2.040 (0.222–18.750)	0.529
Use of broad-spectrum antibiotics >2 weeks	0.873 (0.385–1.980)	0.745
Use of glucocorticoids >2 weeks	1.403 (0.308–6.399)	0.662
Prolonged hospitalization (>10 days)	0.908 (0.210–3.924)	0.897
Diabetes mellitus	3.348 (0.741–15.125)	0.116
Hematological or solid organ malignancy	0.673 (0.131–3.452)	0.635

Note: [a]Underlined are values with statistical significance.
Abbreviations: CI, confidence interval; OR, odds ratio; PFI, pulmonary fungal infection.

Discussion

To better understand the clinical characteristics and prognostic factors of PFIs, we retrospectively investigated a panel of 123 PFI patients with diverse demographic and risk factors and clinical and laboratory profiles.

We evaluated the prevalence of known potential risk factors for PFIs (Table 1) and found that the most prevalent risk factor is prolonged hospitalization (74%). This observation is consistent with previous studies of fungal infection in the lungs[15] and other organs.[16] It is conceivable that prolonged hospitalization is likely to increase the chances of exposure to fungal pathogens, which are rich in the hospital environment.[17] Nevertheless, prolonged hospitalization is often not an independent risk factors and it is usually associated with chronic or severe disorders as presented in Table 1. Other common risk factors that we observed in this study are similar to previous reports.[10,18–21] Of note, neutrophil dysfunction was not noted in any of the PFI patients involved in this study, though it has been considered as one of the most significant traditional risk factors for PFI.[1,8,22]

The main clinical characteristics of the 123 PFI patients in this study include a high prevalence in elderly patients (79%) and males (72%), along with symptoms dominated by cough and expectoration (92%), fever (38%), dyspnea (20%), and chest pain (11%). The high prevalence in males is in line with previous studies (52–71%) from China[5,6] and other countries.[21,23,24] However, the mean age of the patients in our study (67 years) appears to be older than that reported in China (45 or 53 years).[5,6] In addition, we observed a much higher prevalence of PFI in the elderly (≥60 years) than in adults (<60 years). It is likely that the elders have weaker immune functions and/or are accompanied with other disorders, thus leading to a greater chance to be infected by fungal pathogens.

While the prevalence of most of the symptoms we observed appears to be similar to that reported previously, we observed a lower prevalence of hemoptysis (7%) and a higher prevalence of abnormal breath sounds (84%) compared to previous reports from China, in which hemoptysis and abnormal breath sounds were observed in 32–37% and 18–63% PFI patients, respectively.[4,6] Despite the low prevalence of hemoptysis in our study, we observed a significantly higher prevalence of hemoptysis in probable/proven PFI patients than in possible PFI patients (12 vs 2%, P=0.023), which is consistent with the higher prevalence of lung cavity lesions in probable/proven PFI patients than in possible PFI patients (15 vs 3%, P=0.021, Table 5). Of note, oral or skin fungal infection was observed in 34% of patients in this study, which has been rarely reported previously, with one study showing a lower incidence of 16% in PFI patients with hematological malignancies.[15] Further studies are needed to verify whether this observation is causal or coincidental. The most common underlying disease for the PFI patients in this study is COPD, with a prevalence of 45% (Table 2), which appears to be much higher than the previously reported rate of 0–19% from China[5,6,15] and 1.3–17% from other countries.[18,19,24–26] While it remains unclear why PFIs are highly prevalent in COPD, it has been hypothesized that COPD can increase susceptibility to fungal infection due to lung structure changes resulting from frequent bacterial infections or other underlying diseases, frequent hospitalization, and repeated use of systemic corticosteroids and broad-spectrum antibiotics.[25]

Clinical manifestations and radiological findings of PFI are nonspecific and highly variable; definite diagnosis relies on positive microscopic or culture findings.[27] In the present study, 39 (65%) of the 60 patients with probable/proven PFI were positive in fungal culture and microscopic examination (Table 3). Strikingly, most (67%) of the 39 fungal-positive patients were infected with *Candida* spp; only 28% of them were infected with *Aspergillus* spp (28%); and 5% of them were infected with

Cryptococcus spp. These findings are consistent with the report of Hu et al[15] from China but contradict the observation of the dominance of *A. fumigatus* infection among PFI patients in many other studies in China[5,6] and around the world.[8–10] Further comparison showed that *Candida*-infected patients had an older age, a lower rate of lung cavity lesions, and a lower WBC count compared to *Aspergillus*-infected patients. Nonetheless, these observations await further confirmation using a larger number of patients with diverse geographic origins.

In the present study, all PFI patients were treated with antifungal agents; 68 (55%) of them showed favorable responses (Table 4). Favorable responses were significantly associated with a higher level of serum albumin, a higher prevalence of lung nodules, a lower rate of invasive operations, a lower prevalence of diabetes mellitus, and a lower medical cost during hospitalization (Table 4). The treatment response rate in our study appears to be higher than the favorable response rate of 29% reported in China[6] but similar to the rate of 38–68% reported in other countries.[28–30] The relatively high rate of favorable responses in our study could be explained partially by the absence of apparent drug resistance in in vitro susceptibility test. Although previous studies have suggested that sequential treatment with different antifungal agents can improve responses,[6] we did not observe a positive correlation of sequential treatment with favorable responses (Table 4). Nevertheless, treatment response rates may vary based on the patient population, treatment regimens, and the definition of responses. Clearly, further well-controlled studies are needed to draw a reliable conclusion.

The mortality rate observed in this study is 24% (29/123). Multivariate regression analysis showed that hypoalbuminemia and invasive operations were independent prognostic factors associated with mortality (Table 6), which is consistent with the positive associations of these two factors with unfavorable treatment responses (Table 4). This mortality rate is similar to the rate of 21–39% reported previously in China and around the world.[30–34] The observation of hypoalbuminemia as an independent prognostic factor for mortality is in agreement with previous studies.[15,33] The association of hypoalbuminemia with poor treatment outcomes could be explained by its impact on pharmacokinetics of antifungal drugs shown in a recent study suggesting that hypoalbuminemia can increase unbound voriconazole concentrations in plasma, thereby increasing drug elimination and attenuating its therapeutic effects.[35] These findings suggest a need to correct or seek and treat the causes of hypoalbuminemia in patients with PFIs.

The observation of invasive operation as an independent risk factor for the mortality of PFIs in this study is intriguing as this has not been reported previously. In our case series, 30 (24%) of the 123 PFI patients received invasive operation (primarily urinary catheterization, Table 1) and it was significantly more frequently involved in patients with unfavorable treatment responses than in patients with favorable responses (45.6 vs 7.4%, P=0.000, Table 4). The strong association of invasive operation with both poor treatment responses and mortality supports it to be an important risk factor in the development of PFIs. Certainly, further investigation is warranted to validate this association by studying more patients from different regions and to determine its underlying mechanisms.

There are some limitations in this study. First, it was done in only one hospital without a large number of patients and, therefore, whether the clinical findings can be extrapolated to PFI cases in other regions is unclear. It is certainly desirable to extend this study to other geographical regions of our country. Second, none of the fungal species identified were confirmed by molecular methods such as polymerase chain reaction and sequence analysis and, thus, the possibility of misidentification cannot be completely ruled out. Third, treatment outcomes were evaluated based on the responses of patients after a variable duration of treatment and follow-up. In addition, the severity of patients prior to treatment was not scored, which may introduce bias in analysis of treatment outcomes.

Conclusion

We retrospectively investigated a case series of PFI patients with diverse demographic factors and medical conditions and demonstrated their clinical characteristics and treatment outcomes. The main novelty of this study is the demonstration, for the first time, that COPD is the most common underlying disease (45%) in PFI patients and that invasive operation is significantly associated with poor treatment responses and mortality in PFI patients. High index of suspicion of PFIs in patients with COPD and patients receiving invasive operation is necessary for timely, appropriate clinical management of these patients.

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Author contributions

LP is the guarantor of this article. LP and ZX contributed to the conception and design and to the acquisition, analysis, and interpretations of data. RL, ZH, and LM participated

in the analysis and interpretations of data. LP, ZX, and LM drafted and edited the submitted article. All authors provided final approval of the version to be published. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 Comparison of clinical characteristics between *Candida* and *Aspergillus* infection

Characteristics	*Candida* spp[a] (n=26)	*Aspergillus* spp[a] (n=11)	*P*-value[b]
Age (years)	72.6±12.7	57.9±22.9	0.022
Gender (male)	22 (84.6)	8 (72.7)	0.399
Current or exsmoker	15 (57.7)	5 (41.7)	0.495
Alcohol drinker	10 (38.5)	4 (36.7)	0.904
Underlying diseases/risk factors			
Chronic obstructive pulmonary disease	12 (46.2)	6 (54.5)	0641
HIV infection	2 (7.7)	0 (0)	0.344
Invasive operation	5 (19.2)	3 (27.3)	0.557
Diabetes mellitus	4 (15.4)	0 (0)	0.168
Skin/oral fungal infection	8 (30.8)	3 (27.3)	0.833
Clinical manifestations			
Hemoptysis	3 (11.5)	0 (0)	0.240
Fever	12 (46.2)	8 (72.7)	0.138
Nodules	9 (34.6)	5 (45.5)	0.534
Cavity lesions	1 (3.9)	4 (36.7)	0.008
Laboratory tests			
1,3-β-D-Glucan (normal: <60 pg/mL)	167.1±282.1	150.1±288.3	0.674
CRP (normal: <10 mg/L)	77.1±49.5	66.8±35.2	0.726
PCT (normal: <0.05 μg/L)	1.1±2.1	0.7±0.9	1.000
ESR (M: 2–21, F: 2–25 mm/h)	27.7±31.8	34.5±38.3	0.503
WBC (normal: 3.5–9.5×109/L)	9.6±3.8	13.6±3.5	0.013
Albumin (normal: 35–50 g/L)	32.3±8.5	30.2±6.7	0.368
Treatment outcome and cost			
Death	11 (42.3)	4 (36.7)	0.736
Favorable response	10 (38.5)	5 (45.5)	0.692
Hospitalization costs (RMB)	79,170±62,240	92,940±95,940	0.907
Hospitalization duration (days)	16.9±11.2	23.9±17.6	0.117

Notes: [a]Values are shown as mean ± SD or n (%). [b]Underlined are values with statistical significance.

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; F, female; HIV, human immunodeficiency virus; M, male; PCT, procalcitonin; WBC, white blood cell.