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ORIGINAL RESEARCH

# Follow-up of Surgical and Nonsurgical Patients With Pulmonary Aspergillosis: A Real-World Study

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**Objective:** In the real clinical world, both surgery and medication are used to treat pulmonary aspergillosis (PA), but the prognosis of different treatments is unclear. The purpose of this study was to investigate the diagnosis and treatment, follow-up results and prognostic factors of PA patients in the real world, so as to deepen our understanding of PA and improve the prognosis of PA patients.

**Materials and Methods:** Eligible patients with pathologically diagnosed PA (n = 125) were retrospectively enrolled and followed up. Further comparisons and subgroup analyses were performed between patients receiving surgical and nonsurgical treatments. Univariate and multivariate logistic regression analyses were used to investigate the factors associated with treatment failure.

**Results:** A total of 125 patients with PA were included in the study. Of these, 49 (39.2%) received surgical treatment (25 of whom also received postoperative antifungal therapy), while 76 (60.8%) received antifungal therapy alone. The median age was 59 years (46.5–67 years). Compared with the nonsurgical group, the surgical group had lower inflammatory cell counts and less inflammatory response, and higher hemoglobin and albumin levels. Multivariate logistic regression analysis showed that white blood cell (WBC) levels $>9.5\times10^9$/L and C-reactive protein (CRP) levels >8 mg/L were independent predictors linked to treatment failure.

**Conclusion:** PA patients with severe inflammation and poor general health are usually treated with antifungal drugs only. Risk factors including elevated WBC levels and high CRP levels can help identify PA patients who may have a less favorable response to treatment at an early stage. It should be noted that increasing the dose and duration of antifungal therapy may improve patient prognosis.

**Keywords:** pulmonary aspergillosis, antifungal treatment, surgery, treatment failure, prognosis

## Introduction

Aspergillosis is primarily caused by *Aspergillus fumigatus* and is a common fungal infection of the lungs.[1] Pulmonary aspergillosis (PA) is a fungal disease that can be life-threatening and typically occurs in patients with severely impaired or defective immune responses, critically ill patients, and those with chronic lung disease.[2,3] PA is primarily divided into invasive PA (IPA), chronic PA (CPA) and allergic bronchopulmonary Aspergillosis (ABPA), and the specific phenotype depends on the immune status of the host and the interaction between Aspergillosis and the host.[4] The severity and duration of neutropenia are significant risk factors for the development of IPA, which often manifests as vascular infiltration.[5] However, CPA and ABPA often occur in patients with normal or mild immunosuppression and underlying lung diseases, and are less commonly associated

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with neutropenia.[6] With the widespread use of chemotherapy and immunosuppressive drugs, as well as the presence of non-neutropenic critically ill patients, there has been a growing recognition of overlap among these three types of PA.[4] The non-specific nature of PA symptoms complicates its diagnosis, leading to increased rates of misdiagnosis and delayed treatment.

The treatment of PA is difficult, and there are currently three classes of antifungal drugs used for its treatment: polyenes, triazoles and echinocandins.[7] Antifungal drugs are often preferred in clinical treatment, and voriconazole is the main treatment for many PA patients. Compared to amphotericin B, patients treated with voriconazole have higher survival rates.[8] However, voriconazole's adverse effects include visual impairment and interactions with a large number of drugs.[9] There are no prospective randomized studies that demonstrating that antifungal combination therapy is more effective in treating PA.

Surgical treatment complements to PA therapy. Although its therapeutic role is limited, surgery can be beneficial for PA patients who present with life-threatening hemoptysis or are refractory to other treatments. Antifungal therapy is necessary if there is a risk of fungal spillage after surgery, but there is no clear consensus on the optimal duration and dosage of antifungal therapy.[10] This study recruited patients undergoing surgical and antifungal therapy for PA, reviewed their clinical and imaging data, and followed up with these patients for six months to explore the effectiveness of different treatments and assess prognostic factors.

# Materials and Methods

## Study Participants and Definitions

The study protocol was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University (Ethics Code: 2021–039), all participants provided informed consent, and all experiments were performed in accordance with the Declaration of Helsinki. We included 125 patients with a pathological diagnosis of PA who were hospitalized at the Second Xiangya Hospital of Central South University between January 2010 and June 2022. The inclusion criteria included: a) PA confirmed by pathological biopsy (transbronchial lung biopsy); b) Complete clinical and chest CT imaging data available. The exclusion criteria were as follows: a) AIDS-infected patients; b) Extrapulmonary involvement; c) Concomitant pulmonary infiltrative diseases; d) Loss to follow-up. Subjects were divided into two groups: surgical and nonsurgical (antifungal only). The surgical group was further divided into those who underwent surgery alone and those who received postoperative antifungal therapy. Immunocompromised patients were defined as having at least one of the following conditions: malignancy, diabetes, use of immunosuppressive drugs, respiratory diseases, cirrhosis, chronic hepatitis, and other immunosuppressive conditions. The therapeutic doses of antifungal drugs were categorized into three groups: <200 mg/d, 200–400 mg/d, and >400 mg/d. The duration of treatment was classified as >2 months, 2–6 months, and >6 months, based on the clinical guidelines for PA.[7,10] Demographic data, clinical information, treatment details, and follow-up information were collected and recorded without any intervention. Follow-up commenced 1 week post-surgery in the surgical treatment group and 1 month post-antifungal treatment in the non-surgical treatment group. Follow-up data were obtained through periodic clinical assessments and telephone interviews. All subjects were followed up until February 2023, with a minimum follow-up period of 6 months. Clinical efficacy was assessed based on symptom response and radiological findings.[10,11] Recovery was defined as the complete resolution of both clinical symptoms and imaging findings. Improvement was characterized by partial alleviation of clinical symptoms and enhancement of imaging responses. Persistence was noted when there was minimal improvement or no change in clinical symptoms and imaging findings despite at least 2 months of antifungal treatment. Progression was indicated by worsening or recurrence of clinical symptoms and imaging findings following surgical treatment. Furthermore, the recovery and improvement groups were categorized as the effective treatment group, while the remaining two groups were classified as the treatment failure group. A detailed flow diagram for recruiting PA patients is provided in Figure 1.

## Statistical Analysis

Statistical analysis was performed using SPSS 27.0 software (IBM Corp). Continuous variables were described as the mean and standard deviation (SD) or median (interquartile range, IQR), while categorical variables were presented as the

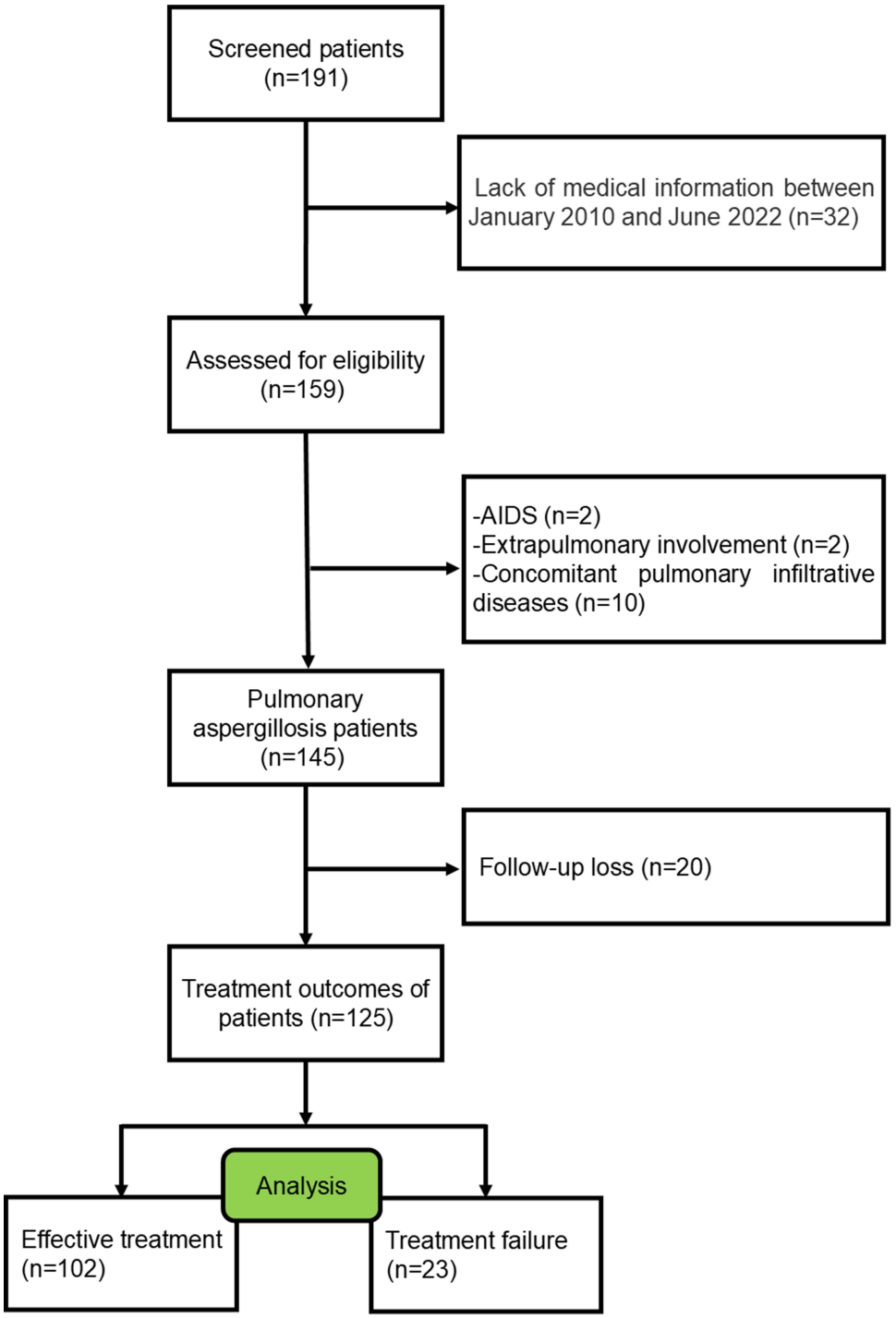


**Figure 1** Flow diagram of the study.

number (percentage). Differences between two groups were assessed using the Student's *t*-test, Mann–Whitney *U*-test, and chi-square or Fisher's exact test. Univariate and multivariate logistic regression analyses were conducted to calculate the odds ratio (OR) of each adjustment. A $P$-value<0.05 indicated a statistically significant difference.


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# Results

## Demographic Characteristics of Surgical and Nonsurgical Groups

Table 1 presents the demographic and sociological characteristics of 125 patients with PA, including 49 who underwent surgical treatment and 76 who received nonsurgical treatment. The median age of participants was 59 years (46.5–67 years). Among them, 42.4% were aged 45–64 years, 76% were married, and 55.2% lived in rural areas. Seventeen patients had a history of environmental exposure, including poultry (8 cases), paint (2 cases), dust (3 cases), mold (2 cases), and coal (2 cases). Additionally, 47 individuals had comorbidities, with diabetes being the most common (15 cases).

## Clinical Manifestations and Laboratory Indicators of Surgical and Nonsurgical Groups

Table 2 shows the clinical manifestations and laboratory indicators of the two groups of PA patients. The main symptoms of PA patients were cough and expectoration, followed by hemoptysis and wheezing. Chest CT imaging revealed that the lesions were mainly unilateral, with 92% presenting as single or multiple nodules/masses, often accompanied by patchy shadows, ground-glass opacities, cavities, and mediastinal lymphadenopathy. Compared to the surgical group, the nonsurgical group had higher levels of inflammation markers [including white blood cell (WBC), neutrophils (NEU),

**Table 1** Demographic Characteristics of Surgical and Nonsurgical Groups

| Items | Total (n=125) | Surgical Group (n=49) | Nonsurgical Group (n=76) | *P* value |
|---|---|---|---|---|
| Subjects, n (%) | | 49 (39.20) | 76 (60.80) | |
| Age (y), median (IQR) | 59 (46.5–67) | 50 (45–67) | 60 (48–67.8) | 0.120 |
| <45, n (%) | 25 (20.0) | 11 (22.4) | 14 (18.4) | 0.427 |
| 45–64 | 53 (42.4) | 23 (46.9) | 30 (39.5) | |
| ≥65 | 47 (37.6) | 15 (30.6) | 32 (42.1) | |
| Sex M/F, n/n (%/%) | 64/61 (51.2)/(48.8) | 21/28 (42.9)/(57.1) | 43/33 (56.6)/(43.4) | 0.147 |
| Disease duration (y), median (IQR) | 3 (2–5) | 4 (2–6) | 3 (1–4.7) | 0.193 |
| Marriage, n (%) | | | | 0.725 |
| Married | 95 (76.0) | 36 (73.5) | 59 (77.6) | |
| Unmarried | 12 (9.6) | 6 (12.2) | 6 (7.9) | |
| Widow | 18 (14.4) | 7 (14.3) | 11 (14.5) | |
| Education, n (%) | | | | 0.218 |
| Primary school | 52 (41.6) | 20 (40.8) | 32 (42.1) | |
| High school | 62 (49.6) | 22 (44.9) | 40 (52.6) | |
| University | 11 (8.8) | 7 (14.3) | 4 (5.3) | |
| Smoking history, n (%) | | | | 0.278 |
| Never-smoker | 109 (87.2) | 45 (91.8) | 64 (84.2) | |
| Smoker | 16 (12.8) | 4 (8.2) | 12 (15.8) | |
| Village | 69 (55.2) | 30 (61.2) | 39 (51.3) | 0.357 |
| History of environmental exposure, n (%) | 17 (13.6) | 3 (6.1) | 14 (18.4) | 0.063 |
| BMI ($kg/m^2$), M ± SD | 20.51 ± 3.42 | 20.41 ± 2.80 | 20.53 ± 3.78 | 0.088 |
| Immunocompromised, n (%) | 47 (37.6) | 14 (28.6) | 33 (43.4) | 0.130 |
| Diabetes mellitus | 15 (12.0) | 6 (12.2) | 9 (11.8) | 1.0 |
| Immunosuppressive drug therapy | 9 (7.2) | 3 (6.1) | 6 (7.9) | 1.0 |
| Malignancy | 7 (5.6) | 1 (2.0) | 6 (7.9) | 0.244 |
| Respiratory system disorders | 11 (8.8) | 4 (8.2) | 7 (9.2) | 1.0 |
| Cushing syndrome | 1 (0.8) | 0 | 1 (1.3) | 1.0 |
| Cirrhosis | 5 (4.0) | 1 (2.0) | 4 (5.3) | 0.647 |
| Chronic hepatitis | 12 (9.6) | 3 (6.1) | 9 (11.8) | 0.363 |

**Notes**: Comparisons were determined using Student's *t*-test, Mann–Whitney *U*-test, and chi-square or Fisher's exact test between the two groups. $P<0.05$ was considered statistically significant.

**Abbreviations**: BMI, body mass index; IQR, interquartile range; M±SD, mean ± standard deviation.

**Table 2** Clinical Manifestations and Laboratory Indicators of Surgical and Nonsurgical Groups

| Items | Total (n=125) | Surgical Group (n=49) | Nonsurgical Group (n=76) | *P* value |
|---|---|---|---|---|
| Clinical manifestations, n (%) | | | | |
| Cough | 98 (78.4) | 37 (75.5) | 61 (80.3) | 0.657 |
| Expectoration | 85 (68.0) | 32 (65.3) | 53 (69.7) | 0.695 |
| Hemoptysis | 38 (30.4) | 14 (28.6) | 24 (31.6) | 0.843 |
| Bloody sputum | 18 (14.4) | 11 (22.4) | 7 (9.2) | 0.065 |
| Dyspnea | 6 (4.8) | 3 (6.1) | 3 (3.9) | 0.678 |
| Fever | 29 (23.2) | 7 (14.3) | 22 (28.9) | 0.082 |
| Polypnea | 37 (29.6) | 12 (24.5) | 25 (32.9) | 0.422 |
| Chest discomfort | 14 (11.2) | 3 (6.1) | 11 (14.5) | 0.245 |
| Chest pain | 7 (5.6) | 2 (4.1) | 5 (6.6) | 0.704 |
| Laboratory indicators, median (IQR) | | | | |
| WBC ($\times 10^9$/L) | 8.0 (6.0–12.8) | 6.4 (5.0–10.7) | 8.7 (7.2–13.4) | 0.004 |
| Hemoglobin (g/L) | 122.0 (110.0–131.0) | 127 (117.5–133.0) | 117.5 (100.0–127.7) | 0.004 |
| NEU ($\times 10^9$/L) | 5.7 (3.7–7.9) | 4.4 (2.6–7.4) | 6.0 (4.9–8.1) | 0.009 |
| Albumin (g/L) | 35.4 (32.3–39.4) | 38.1 (36.5–41.2) | 33.6 (31.1–37.9) | <0.001 |
| ESR, %(Positive/Total) | 60.8 (76/125) | 42.9 (21/49) | 68.4 (52/76) | 0.006 |
| CRP, % (Positive/Total) | 48.0 (60/125) | 36.7 (18/49) | 55.3 (42/76) | 0.046 |
| PCT, % (Positive/Total) | 60.0 (75/125) | 49.0 (24/49) | 67.1 (51/76) | 0.061 |
| Image findings, n (%) | | | | |
| Unilateral lesions | 44 (35.2) | 18 (36.7) | 26 (34.2) | 0.849 |
| Single lobe | 19 (15.2) | 11 (22.4) | 8 (10.5) | 0.080 |
| Lesions patterns | | | | 0.578 |
| Nodules/masses | 115 (92.0) | 45 (91.8) | 70 (92.1) | 0.213 |
| Single | 33 (26.4) | 18 (36.7) | 16 (21.1) | |
| Multi | 80 (64.0) | 27 (55.1) | 54 (71.1) | |
| Pneumonic | 9 (7.2) | 4 (8.2) | 5 (6.6) | |
| Mixed | 1 (0.8) | 0 | 1 (1.3) | |
| Largest diameter of lesions (mm), median (IQR) | 21 (15–28) | 20 (17–28.5) | 21 (15–26.7) | 0.857 |
| Accompanying signs, median (IQR) | | | | |
| Patchy shadow | 43 (34.4) | 16 (32.7) | 27 (35.5) | 0.848 |
| Ground glass opacities | 41 (32.8) | 14 (28.6) | 27 (35.5) | 0.443 |
| Spiculation | 5 (4.0) | 2 (4.1) | 3 (3.9) | 1.0 |
| Lobulation | 2 (1.6) | 0 | 2 (2.6) | 0.519 |
| Cavity | 40 (32.0) | 10 (20.4) | 30 (39.5) | 0.031 |
| Air bronchogram | 17 (13.6) | 6 (12.2) | 11 (14.5) | 0.795 |
| Pleural involvement | 33 (26.4) | 11 (22.4) | 22 (28.9) | 0.534 |
| Pleural effusion | 23 (18.4) | 8 (16.3) | 15 (19.7) | 0.814 |
| Hilar lymphadenopathy | 21 (16.8) | 9 (18.4) | 12 (15.8) | 0.808 |
| Mediastinal lymphadenopathy | 42 (33.6) | 18 (36.7) | 24 (31.6) | 0.566 |

**Notes**: Comparisons were determined using the Mann–Whitney *U*-test and chi-square test between the two groups. $P<0.05$ was considered statistically significant.
**Abbreviations**: BMI, body mass index; IQR, interquartile range; WBC, white blood cell; NEU, neutrophil; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; PCT, procalcitonin.

erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)] and a great number of lung cavities, but lower levels of hemoglobin and albumin.

## Diagnosis and Treatment Outcomes of Surgical and Nonsurgical Groups

As shown in Table 3, the main consideration at the time of initial diagnosis was pneumonia (29.6%), followed by tuberculosis (19.2%) and uncertainty (17.2%). Regarding treatment, 76 PA patients were treated solely with antifungal


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**Table 3** Diagnosis and Treatment Outcomes of Surgical and Nonsurgical Groups

| Items | Total (n=125) | Surgical Group (n=49) | Nonsurgical Group (n=76) | *P* value |
|---|---|---|---|---|
| Primary Diagnosis, n (%) | | | | 0.812 |
| Uncertainty | 22 (17.6) | 8 (16.3) | 14 (18.4) | |
| Cancer | 14 (11.2) | 7 (14.3) | 7 (9.2) | |
| Connective tissue diseases | 13 (10.4) | 5 (10.2) | 8 (10.5) | |
| Lymphomatoid granulomatosis | 8 (6.4) | 3 (6.1) | 5 (6.6) | |
| Tuberculosis | 24 (19.2) | 12 (24.5) | 12 (15.8) | |
| Pneumonia | 37 (29.6) | 12 (24.5) | 25 (32.9) | |
| Pulmonary aspergillosis | 7 (5.6) | 2 (4.1) | 5 (6.6) | |
| Therapy, n (%) | | | | <0.001 |
| Antifungal drugs only | 76 (60.8) | — | 76 (100.0) | |
| Simple surgery | 24 (19.2) | 24 (49.0) | — | |
| Surgery + antifungal drugs | 25 (20.0) | 25 (51.0) | — | |
| Fluconazole | 15 (14.9) | 9 (18.4) | 6 (7.9) | |
| Itraconazole | 28 (27.7) | 6 (12.2) | 22 (28.9) | |
| Voriconazole | 58 (57.4) | 10 (20.4) | 48 (63.2) | |
| Antifungal dosage (mg/d), median (IQR) | 300 (200–400) | 300 (200–400) | 400 (300–500) | <0.001 |
| Antifungal course (M), | 4 (2–7) | 4 (3–5) | 6 (4–7) | <0.001 |
| Treatment effects, n (%) | | | | 0.003 |
| Effective treatment | 102 (81.6) | 35 (71.4) | 67 (88.2) | |
| Recovery | 67 (53.6) | 21 (42.9) | 46 (60.5) | |
| Improvement | 35 (28.0) | 14 (28.6) | 21 (27.6) | |
| Treatment failure | 23 (18.4) | 14 (28.6) | 9 (11.8) | |
| Persistence | 3 (2.4) | 0 | 3 (3.9) | |
| Progression | 20 (16.0) | 14 (28.6) | 6 (7.9) | |

**Notes**: Comparisons were determined using the Mann–Whitney *U*-test and chi-square test between the two groups. *P*<0.05 was considered statistically significant.
**Abbreviation**: IQR, interquartile range.

drugs, primarily voriconazole (63.2%), with a median dose of 400 mg/day (300–500 mg/day) and a median duration of 6 months (4–7 months).

Of the 49 PA patients who received surgical treatment, 25 underwent postoperative antifungal therapy with a median drug dose of 300 mg/day (200–400 mg/day) and a median duration of 4 months (3–5 months). The number of patients with immunocompromised function in the surgery-only group was higher than that in the postoperative antifungal treatment group, and the number of patients with ESR >15mm/h was higher in the postoperative antifungal treatment group compared to the surgery-only group (see Supplement Table 1). In terms of efficacy, 81.6% of PA patients either recovered or improved, while 18.4% of patients either persisted or progressed. Although the dose and duration of postoperative antifungal therapy were lower than those in the nonsurgical group, the progression rate was higher in the surgical group than in the nonsurgical group (Table 3).

## Univariate and Multivariate Logistic Regression Analysis of Factors Associated With Treatment Failure in 125 Patients With PA

Univariate and multivariate logistic regression analyses were performed for the surgical and nonsurgical groups to determine prognostic factors in PA patients undergoing different treatment modalities (Table 4). Univariate analysis indicated that WBC >$9.5\times10^9$/L (P<0.001), NEU >$6.3\times10^9$/L (P=0.027), and CRP >8 mg/L (P=0.026) were related to treatment failure. Multivariate analysis identified WBC >$9.5\times10^9$/L (P=0.032) and CRP >8 mg/L (P=0.013) as independent predictors of treatment failure.

**Table 4** Univariate and Multivariate Logistic Regression Analysis of Factors Associated With Treatment Failure in 125 Patients With PA

| Variable | Effective Treatment (n=102) | Treatment Failure (n=23) | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|---|---|
| | | | *P* value | *OR* (95% CI) | *P* value | *OR* (95% CI) |
| Age (y), median (IQR) | 59.5 (45–68.2) | 52 (47–62) | 0.736 | 0.99 (0.96–1.02) | | |
| Sex | | | | | | |
| Male | 52 (51.0) | 12 (52.2) | Reference | | | |
| Female | 50 (49.0) | 11 (47.8) | 0.918 | 0.95 (0.38–2.35) | | |
| Village | 57 (55.9) | 12 (52.2) | 0.747 | 0.86 (0.34–2.13) | | |
| Smoking history, n (%) | 11 (10.8) | 5 (21.7) | 0.144 | 0.45 (0.15–1.30) | | |
| Disease duration (y) | 3 (2–5) | 2 (1–5) | 0.965 | 1.00 (0.86–1.16) | | |
| History of environmental exposure, n (%) | 13 (12.7) | 4 (17.4) | 0.559 | 1.44 (0.42–4.90) | | |
| Immunocompromised, n (%) | 42 (41.2) | 5 (21.7) | 0.564 | 0.53 (0.06–4.49) | | |
| WBC>9.5 ($\times10^9$/L) | 26 (25.5) | 15 (65.2) | <0.001 | 5.48 (2.08–14.41) | 0.003 | 4.73 (1.68–13.33) |
| Hemoglobin<130 (g/L) | 76 (74.5) | 14 (60.9) | 0.192 | 0.53 (0.20–1.37) | | |
| NEU>6.3 ($\times10^9$/L) | 32 (31.4) | 13 (56.5) | 0.027 | 2.84 (1.12–7.16) | 0.823 | 1.175 (0.284–4.857) |
| Albumin<40 (g/L) | 77 (75.5) | 18 (78.3) | 0.779 | 1.16 (0.39–3.47) | | |
| ESR>15 (mm/h) | 61 (59.8) | 12 (52.2) | 0.503 | 0.73 (0.29–1.82) | | |
| CRP>8 (mg/L) | 44 (43.1) | 16 (69.6) | 0.026 | 3.01 (1.14–7.95) | 0.013 | 6.82 (1.51–30.83) |
| Procalcitonin>0.05 (ng/mL) | 60 (58.8) | 15 (65.2) | 0.572 | 1.31 (0.51–3.37) | | |
| Bilateral lesions | 48 (47.1) | 15 (65.2) | 0.120 | 2.10 (0.82–5.41) | | |
| Multiple lobes | 86 (84.3) | 20 (87.0) | 0.750 | 1.24 (0.32–4.66) | | |
| Lesions patterns | | | | | | |
| Single nodules/masses | 28 (27.5) | 6 (26.1) | Reference | | | |
| Multi nodules/masses | 68 (66.7) | 13 (56.5) | 0.328 | 0.48 (0.11–2.08) | | |
| Pneumonic | 5 (4.9) | 4 (17.4) | 0.462 | 1.90 (0.34–10.49) | | |
| Mixed | 1 (1.0) | 0 | 0.489 | 2.37 (0.20–27.47) | | |
| Largest diameter of lesions (mm), median (IQR) | 21 (15.7–28.2) | 18 (14–22) | 0.114 | 0.95 (0.90–1.01) | | |
| Antifungal drugs only | 67 (65.7) | 9 (39.1) | 0.526 | 0.35 (0.01–8.94) | | |
| Simple surgery | 19 (18.6) | 5 (21.7) | 0.835 | 0.71 (0.03–16.93) | | |
| Surgery + antifungal drugs | 16 (15.7) | 9 (39.1) | 0.552 | 1.40 (0.05–33.19) | | |
| Antifungal dosage (mg/d) | | | | | | |
| <200 | 1 (1.0) | 2 (8.7) | Reference | | | |
| 200–400 | 62 (60.8) | 14 (60.9) | 0.793 | 0.85 (0.27–2.69) | | |
| >400 | 20 (19.6) | 2 (8.7) | 0.280 | 0.38 (0.06–2.20) | | |
| Antifungal course (M) | | | | | | |
| <2 | 1 (1.0) | 1 (4.3) | Reference | | | |
| 2–6 | 52 (51.0) | 15 (65.2) | 0.974 | 1.01 (0.32–3.20) | | |
| >6 | 30 (29.4) | 2 (8.7) | 0.108 | 0.24 (0.04–1.36) | | |

**Notes**: Values were expressed as odds ratio (OR) and 95% confidence interval (CI). Factors associated with treatment failure were determined by univariate and multivariate logistic regression analysis. Multivariate analysis was adjusted for age, sex, disease duration, smoking history.
**Abbreviations**: IQR, interquartile range; WBC, white blood cell; NEU, neutrophil; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

To determine prognostic factors in PA patients undergoing different treatment modalities, univariate and multivariate logistic regression analyses were performed for the surgical or nonsurgical groups. In the nonsurgical group (Table 5), univariate analysis showed that antifungal dose and duration (P<0.05) were negatively associated with treatment failure. Multivariate analysis revealed that WBC >$9.5\times10^9$/L (P<0.001) and CRP >8 mg/L (P =0.017) were independent predictors of treatment failure. In the surgical group (Table 6), univariate analysis indicated that WBC >$9.5\times10^9$/L (P<0.001), NEU >$6.3\times10^9$/L (P<0.001), and bilateral pulmonary lesions (P=0.015) were associated with treatment failure, while antifungal duration was negatively correlated with treatment failure. Multivariate analysis showed that WBC >$9.5\times10^9$/L (P<0.001) and bilateral pulmonary lesions (P=0.025) were independent predictors of treatment failure.


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**Table 5** Univariate and Multivariate Logistic Regression Analysis of Factors Associated With Treatment Failure in 76 Nonsurgical Patients With PA

| Variable | Effective Treatment (n=67) | Treatment Failure (n=9) | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|---|---|
| | | | *P* value | *OR* (95% CI) | *P* value | *OR* (95% CI) |
| Age (y), median (IQR) | 62 (47–69) | 58 (50.5–61) | 0.751 | 0.99 (0.94–1.04) | | |
| Sex | | | | | | |
| Male | 37 (55.2) | 6 (66.7) | Reference | | | |
| Female | 30 (44.8) | 3 (33.3) | 0.518 | 0.61 (0.14–2.67) | | |
| Village | 35 (52.2) | 4 (44.4) | 0.661 | 1.36 (0.33–5.54) | | |
| Smoking history, n (%) | 9 (13.4) | 3 (33.3) | 0.140 | 3.22 (0.68–15.23) | | |
| Disease duration (y) | 3 (1–5) | 2 (1.5–5.5) | 0.847 | 1.02 (0.81–1.28) | | |
| History of environmental exposure, n (%) | 11 (16.4) | 3 (33.3) | 0.231 | 2.54 (0.55–11.74) | | |
| Immunocompromised, n (%) | 30 (44.8) | 3 (33.3) | 0.581 | 0.617 (0.14–2.67) | | |
| WBC>9.5 ($\times 10^9$/L) | 22 (32.8) | 4 (44.4) | 0.494 | 1.63 (0.39–6.70) | <0.001 | 5.481 (2.084–14.411) |
| Hemoglobin<130 (g/L) | 54 (80.6) | 6 (66.7) | 0.344 | 0.48 (0.10–2.18) | | |
| NEU>6.3 ($\times 10^9$/L) | 27 (40.3) | 4 (44.4) | 0.812 | 1.18 (0.29–4.81) | | |
| Albumin<40 (g/L) | 54 (80.6) | 6 (66.7) | 0.344 | 0.48 (0.10–2.18) | | |
| ESR>15 (mm/h) | 47 (70.1) | 5 (55.6) | 0.382 | 0.53 (0.12–2.19) | | |
| CRP>8 (mg/L) | 34 (50.7) | 8 (88.9) | 0.060 | 7.76 (0.92–65.55) | 0.017 | 6.50 (1.391–30.387) |
| Procalcitonin>0.05 (ng/mL) | 46 (68.7) | 5 (55.6) | 0.436 | 0.57 (0.13–2.34) | | |
| Bilateral lesions | 37 (55.2) | 5 (55.6) | 0.985 | 1.01 (0.25–4.11) | | |
| Multiple lobes | 60 (89.6) | 8 (88.9) | 0.951 | 0.93 (0.10–8.60) | | |
| Lesions patterns | | | | | | |
| Single nodules/masses | 13 (19.4) | 3 (33.3) | Reference | | | |
| Multi nodules/masses | 49 (73.1) | 5 (55.6) | 0.142 | 0.20 (0.02–1.71) | | |
| Pneumonic | 4 (6.0) | 1 (11.1) | 0.215 | 0.25 (0.02–2.23) | | |
| Mixed | 1 (1.5) | 0 | 0.112 | 0.12 (0.06–1.96) | | |
| Largest diameter of lesions (mm), median (IQR) | 21 (15–28) | 18 (13.5–26.5) | 0.312 | 0.95 (0.87–1.04) | | |
| Antifungal dosage (mg/d) | | | | | | |
| <200 | 1 (1.5) | 0 | Reference | | | |
| 200–400 | 46 (68.7) | 7 (77.8) | <0.001 | 0.15 (0.06–0.37) | | |
| >400 | 20 (29.9) | 2 (22.2) | 0.002 | 0.10 (0.02–0.42) | | |
| Antifungal course (M) | | | | | | |
| <2 | 1 (1.5) | 1 (11.1) | Reference | | | |
| 2–6 | 39 (58.2) | 6 (66.7) | <0.001 | 0.15 (0.06–0.36) | | |
| >6 | 27 (40.3) | 2 (22.2) | <0.001 | 0.07 (0.01–0.31) | | |

**Notes**: Values were expressed as odds ratio (OR) and 95% confidence interval (CI). Factors associated with treatment failure were determined by univariate and multivariate logistic regression analysis. Multivariate analysis was adjusted for age, sex, disease duration, smoking history.
**Abbreviations**: IQR, interquartile range; WBC, white blood cell; NEU, neutrophil; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

**Table 6** Univariate and Multivariate Logistic Regression Analysis of Factors Associated With Treatment Failure in 49 Surgical Patients With PA

| Variable | Effective Treatment (n=35) | Treatment Failure (n=14) | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|---|---|
| | | | *P* value | *OR* (95% CI) | *P* value | *OR* (95% CI) |
| Age (y), median (IQR) | 54 (43–67) | 50 (46–66.5) | 0.798 | 1.0 (0.96–1.04) | | |
| Sex | | | | | | |
| Male | 15 (42.9) | 6 (42.9) | Reference | | | |
| Female | 20 (57.1) | 8 (57.1) | 1.0 | 1.0 (0.28–3.49) | | |
| Village | 22 (62.9) | 8 (57.1) | 0.711 | 1.26 (0.36–4.48) | | |
| Smoking history, n (%) | 2 (5.7) | 2 (14.3) | 0.338 | 2.75 (0.34–21.75) | | |
| Disease duration (y) | 4 (2–6) | 3 (1–5.5) | 0.686 | 0.95 (0.78–1.17) | | |
| History of environmental exposure, n (%) | 2 (5.7) | 1 (7.1) | 0.851 | 1.26 (0.10–15.22) | | |
| Immunocompromised, n (%) | 12 (34.3) | 2 (14.3) | 0.176 | 0.31 (0.06–1.66) | | |

(*Continued*)

**Table 6** (Continued).

| Variable | Effective Treatment (n=35) | Treatment Failure (n=14) | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|---|---|
| | | | *P* value | *OR* (95% CI) | *P* value | *OR* (95% CI) |
| WBC>9.5 (×$10^9$/L) | 4 (11.4) | 11 (78.6) | <0.001 | 28.41 (5.47–147.58) | <0.001 | 33.18 (5.31–207.06) |
| Hemoglobin<130 (g/L) | 22 (62.9) | 8 (57.1) | 0.711 | 0.78 (0.22–2.78) | | |
| NEU>6.3 (×$10^9$/L) | 5 (14.3) | 9 (64.3) | <0.001 | 10.80 (2.54–45.86) | | |
| Albumin<40 (g/L) | 23 (65.7) | 12 (85.7) | 0.176 | 3.13 (0.60–16.32) | | |
| ESR>15 (mm/h) | 14 (40.0) | 7 (50.0) | 0.524 | 1.50 (0.43–5.22) | | |
| CRP>8 (mg/L) | 10 (28.6) | 8 (57.1) | 0.067 | 3.33 (0.92–12.08) | | |
| Procalcitonin>0.05 (ng/mL) | 14 (40.0) | 10 (71.4) | 0.054 | 3.75 (0.98–14.35) | | |
| Bilateral lesions | 11 (31.4) | 10 (71.4) | 0.015 | 5.45 (1.39–21.28) | 0.025 | 8.02 (1.29–49.63) |
| Multiple lobes | 26 (74.3) | 12 (85.7) | 0.393 | 2.07 (0.38–11.12) | | |
| Lesions patterns | | | | | | |
| Single nodules/masses | 15 (42.9) | 3 (21.4) | Reference | | | |
| Multi nodules/masses | 19 (54.3) | 8 (57.1) | 0.327 | 0.47 (0.10–2.10) | | |
| Pneumonic | 1 (2.9) | 3 (21.4) | 0.110 | 7.12 (0.64–79.26) | | |
| Largest diameter of lesions (mm) | 23 (16–29) | 18 (16.5–21.2) | 0.187 | 0.95 (0.88–1.02) | | |
| Antifungal dosage (mg/d) | | | | | | |
| <200 | 0 | 2 (14.3) | Reference | | | |
| 200–400 | 16 (45.7) | 7 (50.0) | 0.453 | 1.66 (0.44–6.26) | | |
| Antifungal course (M) | | | | | | |
| <6 | 13 (37.1) | 9 (64.3) | Reference | | | |
| ≥6 | 3 (8.6) | 0 | 0.008 | 0.26 (0.09–0.70) | | |

**Notes**: Values were expressed as odds ratio (OR) and 95% confidence interval (CI). Factors associated with treatment failure were determined by univariate and multivariate logistic regression analysis. Multivariate analysis was adjusted for age, sex, disease duration, smoking history.
**Abbreviations**: IQR, interquartile range; WBC, white blood cell; NEU, neutrophil; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

## Discussion

In this study, the PA patients were mainly middle-aged and elderly. 39.2% of the patients underwent surgery, which carries a risk of recurrence or progression without adequate antifungal therapy. We found that higher levels of WBC and CRP, inadequate antifungal therapy, and other factors increase the risk of treatment failure.

PA, a pulmonary fungal infection caused by Aspergillus, commonly occurs in hosts with severely compromised immune function.[12] Aspergillus molds, ubiquitous in the environment, are commonly found in soil and decaying matter and derive their energy by secreting proteases to digest organic material.[13] PA is the most common fungal infection among patients undergoing hematopoietic stem cell transplantation.[14] The number of PA infections has increased in recent years, likely due to the increased use of chemotherapy and immunosuppressants, as well as advancements in diagnostic testing techniques.[15] In this study, it was found that 37.6% of PA patients had comorbid conditions, primarily including diabetes mellitus, use of immunosuppressive drugs, and chronic hepatitis, all of which can reduce immune function in patients. Studies have shown that patients who receive solid organ transplants, especially lung transplant recipients, as well as those with kidney disease, diabetes, and chronic respiratory diseases associated with corticosteroid use, are at an increased risk for PA.[16–19]

Surgical treatment of PA is uncommon, except in cases where the lesion spreads to adjacent structures, involves extrapulmonary lesions, causes severe hemoptysis, or when control of the infection source is necessary due to inadequate antifungal treatment.[20] Our early diagnosis method involves surgery, particularly for patients with obvious symptoms and radiological findings, which may lead to a higher incidence of surgical interventions. In this study, 39.2% of PA patients underwent surgical treatment, which could be significantly beneficial for managing persistent lesions. For refractory PA patients with normal lung function, surgical removal of aspergilloma is often necessary.[21] In addition, patients with severe hemoptysis should also consider surgery.[22] In this study, 28.6% of patients with hemoptysis underwent surgery. There were more immunocompromised patients in the surgery-only group compared to the postoperative antifungal treatment group. The surgery-only group did not receive antifungal treatment, which may be attributed to the reluctance

of patients in this group alone to take antifungal drugs. Although the surgery group had better baseline conditions compared to the nonsurgery group (eg, less severe symptoms, reduced inflammatory responses, and better immune status), they experienced a higher rate of disease progression. This may be due to the limited effectiveness of surgery alone and potential fungal spillage during the procedure. When the lesion needs to be excised, postoperative antifungal therapy should be administered if there is a risk of fungal spillover or evidence of fungal invasion into adjacent structures.[10]

When PA is suspected, it is necessary to initiate antifungal therapy for PA as early as possible. Triazole drugs serve as the mainstay of PA treatment, with voriconazole being the preferred choice.[23] Clinical practice guidelines recommend administering voriconazole (200–300 mg/day, twice daily) to PA patients for a duration of 4–6 months.[7] Continuous antifungal therapy inevitably has side effects, which may affect patient compliance. Therefore, monitoring drug concentrations during therapy is essential, as blood levels can vary between individuals.[24,25] In our study, more than half of the patients received an antifungal dose of less than 400 mg/d, which is a risk factor for treatment failure in PA, particularly among those receiving antifungal therapy alone. This suggests that an adequate antifungal dose is crucial for preventing PA treatment failure. The optimal duration of treatment remains uncertain; however, it is generally recommended to be at least 2–3 months. For chronic PA, the treatment duration can be extended to 4–6 months. Some studies, such as those by Sehgal, have even suggested that treatment durations exceeding 12 months may be beneficial for chronic PA.[26] The duration may depend on the recovery of immunocompromised patients and the progress observed in CT radiological responses.[7,27] Additionally, the duration of postoperative antifungal therapy is not clearly defined and should be determined based on the patient's immunosuppressive recovery and disease progression. This study found that less than 6 months of postoperative antifungal therapy was a risk factor for treatment failure, suggesting that extending the duration of postoperative antifungal therapy may improve patient outcomes.

Antifungal therapy is essential, and improving the patient's overall condition is a crucial measure to prevent the failure of PA treatment.[10] Elevated levels of WBC and CRP were identified as independent risk factors for treatment failure in PA. Although a history of environmental exposure could not be identified as a risk factor for treatment failure in this study, the widespread distribution of Aspergillus in the environment and the patients' own immune deficiency are significant factors contributing to the poor prognosis of PA.[10,28] Studies have reported that respiratory infections, including avian influenza, respiratory syncytial virus, and coronavirus, contribute to the colonization of the lung epithelium by Aspergillus.[29,30] Therefore, PA patients should take additional precautions during treatment to prevent other infections, address malnutrition, and actively manage underlying conditions to avoid the aggravation or recurrence of PA due to poor overall health.

This study has several limitations: (a) As it is retrospective, it only provides data related to treatment failure and cannot draw conclusions about causality. Additionally, the historical data only diagnosed PA without specific classification (IPA, CPA, and ABPA), which may limit the findings. (b) There are few reports on the prognostic factors of PA treatment, and further investigation into the mechanisms of action is need. (c) Although postoperative antifungal therapy is recommended, specific implementation strategies still require exploration in prospective studies and clinical practice.

## Conclusions

It is essential for PA patients to commence antifungal medication promptly. Surgical intervention is a viable option for treating severe hemoptysis and refractory PA, and postoperative antifungal therapy plays a crucial role in preventing the spread or recurrence of PA. Additionally, it is worth noting that increasing the dosage and duration of antifungal drugs can positively impact the prognosis of patients with underlying health conditions.

## Data Sharing Statement

The data used and analyzed in this study are available from the corresponding author on reasonable request; Ruoyun Ouyang, E-mail: ouyangruoyun@csu.edu.cn.

## Statement of Ethics

The study protocol was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University (Ethics Code: 2021-039), and all participants signed informed consent.

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## Disclosure

The authors declare that they have no competing interests for this work.

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