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ORIGINAL RESEARCH

Clinical Characteristics, Prognosis, and Risk Factors for Mortality in Influenza-Associated Pulmonary Aspergillosis and COVID-19-Associated Pulmonary Aspergillosis: A Multicenter Retrospective Study

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Objective: Multiple studies have confirmed that viral pneumonia is a high-risk factor for invasive pulmonary aspergillosis (IPA), this retrospective study aims to analyze the differences in clinical characteristics, prognosis, and high-risk factors for mortality between patients with influenza virus-associated pulmonary aspergillosis (IAPA) and those with COVID-19-associated pulmonary aspergillosis (CAPA).

Methods: Clinical data from IAPA and CAPA patients diagnosed at four hospitals were collected. The clinical characteristics and prognostic differences between the two groups were analyzed and compared, with Cox regression used to identify the risk factors for mortality.

Results: A total of 106 patients were included in this study. Compared to CAPA patients, IAPA patients had a higher proportion of chronic obstructive pulmonary disease comorbidities, lower rates of history of solid organ transplantation, and a shorter time from viral infection to aspergillosis development. CAPA patients exhibited lower levels of white blood cells, and C-reactive protein. The CAPA group also received longer courses of antibiotic and corticosteroid therapy. Compared to IAPA, the CAPA group exhibited a higher incidence of complications, including bacterial infections, deep vein thrombosis in the lower limbs, gastrointestinal bleeding, and heart failure. The mortality rate was also higher in the CAPA group. The survival curve of IAPA was more favorable than that of CAPA. Cox regression analysis identified ICU admission at diagnosis as an independent risk factor for mortality in IAPA patients (OR= 9.578).

Conclusion: The IAPA group had a higher proportion of patients with COPD, a more acute disease onset, Admission to the ICU at diagnosis was identified as a risk factor for IAPA-related mortality. In comparison, the CAPA group had a higher proportion of immunodeficient patients, received more corticosteroid treatment, and was more susceptible to complications such as bacterial infections, thrombosis, and gastrointestinal bleeding, all of which contributed to an increased risk of death.

Keywords: influenza virus pneumonia, COVID-19 pneumonia, invasive pulmonary aspergillosis, clinical features, prognosis

Background

Invasive Pulmonary Aspergillosis (IPA) commonly occurs in immunocompromised individuals. Traditional risk factors include hematopoietic stem cell transplantation, solid organ transplantation, hematologic malignancies, previous

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exposure to corticosteroids, and neutropenia.[1] Severe viral pneumonias increase susceptibility to *Aspergillus fumigatus* due to disruption of the alveolar epithelial barrier, secretion of pro-inflammatory factors, and immune dysfunction.[2] IPA is now recognized as a significant complication of severe respiratory viral infections,[3] with influenza-associated pulmonary aspergillosis (IAPA) and COVID-19-associated pulmonary aspergillosis (CAPA) being particularly notable In 2021, the EORTC/MSGERC introduced definitions for invasive fungal diseases applicable to ICU, recognizing severe viral pneumonia as a high-risk host factor.[4] These conditions are characterized by a high prevalence, insidious onset, atypical clinical manifestations, elevated mortality, and a lack of classic host factors.[1,5] Previous studies have suggested that the incidence of IAPA ranges from 14% to 32%,[6,7] with a mortality rate of 45% to 51%.[6,8] The incidence of CAPA ranges from 1.7% to 26.8%,[9–12] with a mortality rate of 38% to 59%.[9,11,12] A retrospective study from China, found an IAPA incidence rate of 20% among influenza pneumonia patients and a CAPA incidence rate of 15% among COVID-19 patients in respiratory wards.[13] Significant heterogeneity in reported IPA incidence rates arises from variations in environmental *Aspergillus* spore loads across regions, host genetic factors among ethnic groups, vaccination coverage rates, and disparities in diagnostic capabilities—including bronchoscopy, galactomannan testing, and NGS (Next-generation sequencing).[3] Existing studies largely focus on risk factors for the onset of IAPA and CAPA, lacking analysis of factors associated with mortality, our study investigates these mortality-related risk factors.

This study collected the clinical data of 50 IAPA and 56 CAPA inpatients from four hospitals in Zhejiang Province between January 2018 and March 2024, and retrospectively analyzed their clinical characteristics, prognosis, and mortality risk factors.

Methods

Research Subjects

This study is a multicenter retrospective case-control study that included 50 patients with IAPA and 56 patients with CAPA who were hospitalized at four hospitals in Zhejiang Province, China, between January 2018 and March 2024. Clinical data were obtained from these patients. Imaging data were determined by consensus among two experienced respiratory physicians and one radiologist. This retrospective study was performed in compliance with the Declaration of Helsinki and was approved by the medical ethics committee of the First Affiliated Hospital Zhejiang University School of Medicine (Ethics approval No. IIT20230650A). The requirement for informed consent was waived by the Ethics Commission due to the retrospective and anonymous characteristics of the study.

Inclusion and Exclusion Criteria

Inclusion Criteria

① Age≥18 years; ② Positive nucleic acid test for influenza virus or SARS-CoV-2 from nasopharyngeal swabs or bronchoalveolar lavage fluid, accompanied by clinical and radiological evidence of pneumonia; ③ Diagnosis of invasive pulmonary aspergillosis, either confirmed or clinically suspected, based on the diagnostic criteria jointly proposed by the European Organization for Research and Treatment of Cancer (EORTC) and the Mycology Study Group (MSG) in 2020.

Exclusion Criteria

① Incomplete medical records; ② Patients with baseline chest CT images showing cavities, masses, and other features that may interfere with the diagnosis of pulmonary aspergillosis; ③ Patients with a confirmed diagnosis of pulmonary aspergillosis prior to viral infection.

Diagnostic Criteria

In this study, patients with confirmed or clinically diagnosed IPA were included, with the following specific diagnostic criteria: (1) confirmation: presence of *Aspergillus* hyphae observed in tissue examination accompanied by evidence of tissue destruction, or a positive tissue culture for *Aspergillus*. (2) clinical diagnosis: fulfillment of all three criteria of host factors, clinical features, and microbiological evidence. Host factors include hematopoietic stem cell transplantation or solid organ transplantation, hematological malignancies, previous exposure to corticosteroids, neutropenia, use of T-cell immunosuppressants, or other severe inherited immune deficiencies. However, given that multiple studies have

demonstrated that a significant portion of patients infected with the influenza virus or SARS-CoV-2 lack classic immunosuppressive factors when infected with *Aspergillus*, viral infection can increase susceptibility to *Aspergillus*.[5] Furthermore, severe viral infection itself is a high-risk factor for fungal infection in the host.[5,6,14,15] Therefore, host factors are not included in the diagnostic criteria of this study. Clinical features must include at least one of the following three signs on chest CT: ① solid, well-defined nodular shadows, with or without the halo sign, ② the air crescent sign, ③ a cavity. Microbiological evidence includes the detection of fungal components or positive *Aspergillus* culture in sputum, bronchoalveolar lavage fluid, or bronchoscopy brush specimens; positive galactomannan (GM) test in serum or bronchoalveolar lavage fluid; or a positive result using the *Aspergillus* polymerase chain reaction (PCR) / next-generation sequencing (NGS)[16] in bronchoalveolar lavage fluid or blood.

Collection of Clinical Data

Collect general patient information, including underlying diseases, and medication history (such as corticosteroids, immunosuppressants, and cytotoxic drugs). Document the interval between viral infection and the onset of IPA, ICU admission during the disease course, the use of advanced supportive therapies, including high-flow nasal cannula (HFNC), extracorporeal membrane oxygenation (ECMO), invasive mechanical ventilation, and continuous renal replacement therapy (CRRT). Record clinical manifestations, laboratory test results, chest CT imaging, and bronchoscopy findings when secondary aspergillosis occurs. Also collect data on the use of antiviral agents, antibiotics, and antifungal drugs before and during the treatment course, the administration of glucocorticoids, the occurrence of complications throughout the illness, and the final clinical outcome.

Statistical Methods

Statistical analysis was performed using SPSS version 27.0 software (IBM SPSS Inc., Chicago, Illinois, USA). Categorical data were described as frequency and proportion, and normally distributed quantitative variables were described as mean ± standard deviation. Non-normally distributed quantitative variables were presented as median (interquartile range). *T*-tests were used for comparisons between groups for normally distributed quantitative data, and Mann–Whitney *U*-tests were applied for non-normally distributed data. Chi-square tests, adjusted chi-square tests, or Fisher's exact tests were used for comparisons between groups for categorical data. In univariate analyses, variables with $p < 0.05$ were included in the Cox proportional hazards regression model for multivariate analysis. Survival status comparisons between groups were made using the Kaplan-Meier method, and survival rates were compared using the Log rank test. The significance level (α) for all statistical tests was set at 0.05, unless otherwise specified. The sample size was determined based on all eligible patients identified during the current study period. Missing data were identified and excluded from analysis prior to conducting relevant statistical analyses.

Results

General Clinical Characteristics at Admission

This study included a total of 106 patients, with 50 IAPA patients and 56 CAPA patients, with mean ages of 63.4±12.3 and 64.1±13.1 years, respectively. There were no statistically significant differences between the two groups in terms of age, BMI, and gender *(P*> 0.05). The proportion of patients with a history of solid organ transplantation was higher in the CAPA group than in the IAPA group (25.0% vs 4.0%, $p = 0.003$), whereas the proportion of COPD was lower (5.4% vs 34.0%, $p < 0.001$), as shown in Table 1. The IAPA group had higher level of white blood cells (11.7×10^9/L vs 7.4×10^9/L), neutrophils (10.2×10^9/L vs 6.0×10^9/L), T lymphocytes (519.0 cells/μL vs 180.0 cells/μL), B lymphocytes (70.0 cells/μL vs 23.0 cells/μL), absolute $CD4^+$ T lymphocytes (256.0 cells/μL vs 92.2 cells/μL), CD4/CD8 ratios (1.92 vs 1.26), and C-reactive protein (42.1mg vs.71.0mg) compared to the CAPA group (*P*< 0.05), as shown in Table 1. Additionally, the proportion of patients with concurrent bacterial infections during the disease course was higher in the CAPA group than in the IAPA group (50.0% vs 24.0%, $p < 0.05$), as shown in Figure 1. The most commonly combined infection bacterium in CAPA was *Klebsiella pneumoniae*, while *Pseudomonas aeruginosa* was the most common in the IAPA group.

Table 1 Clinical Characteristics at Admission

	Total (N=106)	IAPA (N=50)	CAPA (N=56)	*p*
Age(years)	63.8±12.7	63.4±12.3	64.1±13.1	0.765
BMI	22.2±3.6	20.8±3.1	22.8±3.6	0.060
Male (%)	79 (74.5%)	41 (82.0%)	38 (67.9%)	0.095
Comorbidity				
Diabetes	29 (27.3%)	14 (28.0%)	15 (26.8%)	0.889
Hypertension	48 (45.2%)	19 (38.0%)	29 (51.8%)	0.155
Chronic obstructive pulmonary diseases	20 (18.8%)	17 (34.0%)	3 (5.4%)	**<0.001**
Chronic renal diseases	28 (26.4%)	11 (22.0%)	17 (30.4%)	0.330
Liver cirrhosis / Liver failure	9 (8.4%)	5 (10.0%)	4 (7.1%)	0.859
Rheumatic autoimmune diseases	9 (8.4%)	3 (6.0%)	6 (10.7%)	0.603
Active solid malignancy	12 (11.3%)	4 (8.0%)	8 (14.3%)	0.308
Active hematologic malignancy	21 (19.8%)	10 (20.0%)	11 (19.6%)	0.963
History of solid organ transplantation	16 (15.0%)	2 (4.0%)	14 (25.0%)	**0.003**
History of hematopoietic stem cell transplantation	1 (0.9%)	0 (0.0%)	1 (1.8%)	1.000
Assisted examination				
White blood cells ($X10^9$/L)	9.0 (5.8, 14.1)	11.7 (7.2, 16.7)	7.4 (5.0, 11.2)	**0.005**
Neutrophils ($X\ 10^9$/L)	7.8 (4.5, 12.3)	10.2 (5.8, 15.4)	6.0 (3.9, 9.4)	**0.004**
Lymphocytes ($X\ 10^9$/L)	0.6 (0.4, 0.9)	0.6 (0.4, 0.9)	0.5 (0.3, 0.8)	0.134
CRP (mg/L)	53.4 (22.6, 97.4)	71.0 (27.1, 135.5)	42.1 (17.5, 85.0)	**0.036**
PCT (ng/mL)	0.2 (0.1, 0.7)	0.3 (0.1, 0.7)	0.2 (0.1, 0.6)	0.159
IL-6 (μg/L)	39.3 (8.5, 248.4)	94.8 (22.7, 332.1)	27.4 (7.8, 248.4)	0.189
IL-2 (μg/L)	2.19 (0.53, 3.23)	0.98 (0.10, 2.91)	2.19 (0.53, 3.23)	0.420
IL-4 (μg/L)	2.75 (0.73, 3.45)	2.91 (0.39, 3.90)	2.75 (0.73, 3.45)	0.834
IL-8 (μg/L)	30.39 (15.94, 108.68)	39.91 (15.13, 130.54)	30.39 (15.94, 108.68)	0.847
IL-10 (μg/L)	9.44 (4.28, 18.20)	10.10 (3.23, 13.71)	9.44 (4.28, 18.20)	0.637
IFNγ (μg/L)	2.23 (0.62, 3.08)	3.76 (0.17, 11.42)	2.23 (0.62, 3.08)	0.125
TNF (μg/L)	3.18 (1.00, 4.80)	2.77 (0.47, 5.26)	3.18 (1.00, 4.80)	0.806
CD4/CD8	1.4 (0.8, 2.1)	1.92 (1.32, 2.17)	1.26 (0.74, 1.82)	**0.036**
NK lymphocytes (cells /μL)	38.0 (18.0, 90.8)	52.0 (22.0, 157.0)	35.0 (16.0, 68.0)	0.176
T cells (cells /μL)	213.0 (128.3, 322.0)	519.0 (227.5, 735.0)	180.00 (92.00, 286.0)	**0.007**
B cells (cells /μL)	30.0 (6.3, 77.5)	70.0 (18.5, 122.5)	23.00 (5.0, 63.0)	**0.029**
$CD4^+$ T cells (cells/μL)	110.0 (42.3, 194.5)	256.0 (120.5, 441.5)	92.00 (37.0, 163.0)	**0.003**
$CD8^+$ T cells (cells/μL)	95.5 (37.0, 152.5)	142.0 (88.5, 229.0)	84.0 (32.0, 132.0)	0.052
Positive blood fungal G test	24/79 (30.4%)	11/34 (32.4%)	13/45 (28.9%)	0.740
Time points				
Time from symptom onset to hospital admission in virus-positive cases (days)	7.0 (3.0, 14.0)	3.5 (1.0, 7.0)	11.0 (5.5, 20.5)	**<0.001**
Time from symptom onset to initiation of antiviral therapy (days)	4.0 (1.0, 13.0)	4.0 (1.0, 5.0)	8.5 (2.8, 16.0)	**<0.001**
Viral shedding duration (days)	16.5 (8.0, 33.5)	8.00 (6.00, 14.00)	29.00 (18.00, 44.00)	**<0.001**

Note: The bold text indicates statistically significant results with $p < 0.05$.

Clinical Features of Confirmed Aspergillosis

Patients in the CAPA group had a longer interval from viral infection to the onset of aspergillosis compared to those in the IAPA group (mean duration: 23.0 days vs 4.0 days, $p < 0.001$). Before the confirmation of pulmonary aspergillosis, a higher proportion of patients in the CAPA group received glucocorticoid therapy (94.6% vs 47.9%, $P<0.001$) and at higher cumulative doses (all glucocorticoid doses converted to methylprednisolone equivalents: 786.7mg vs 177.3mg, $P <0.001$), as shown in Table 2.

When concurrent *Aspergillus* infection was confirmed, the CAPA group exhibited significantly higher rates of respiratory failure (67.9% vs 46.0%), invasive mechanical ventilation (35.7% vs 16.0%), ICU admission (42.9% vs

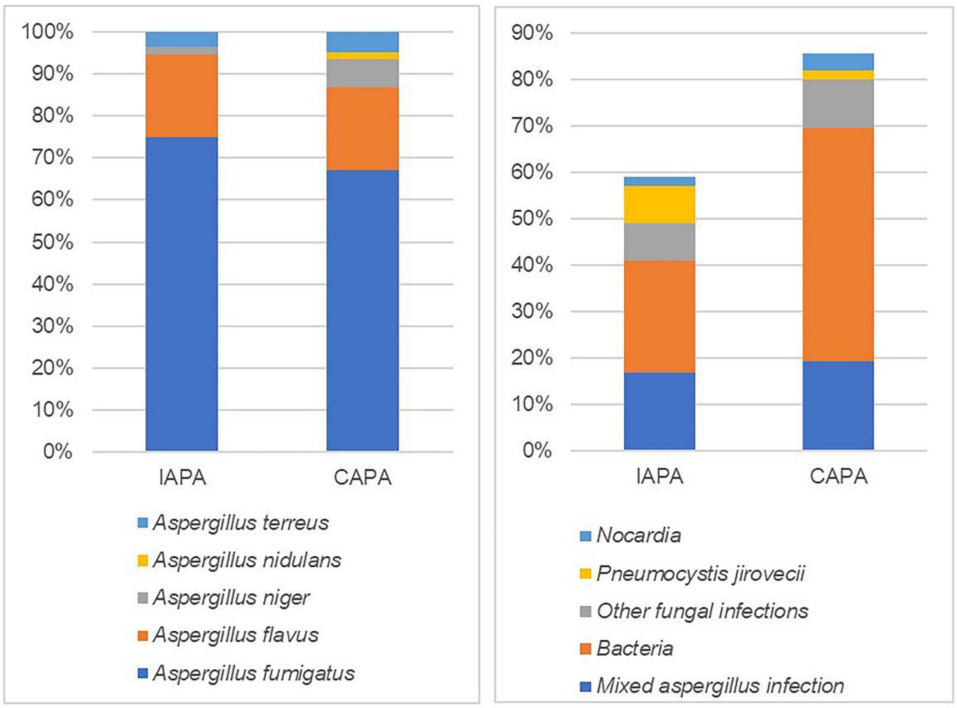

Figure 1 Comparative analysis of Aspergillus species distribution and coinfection with pathogens during the disease course in IAPA and CAPA.

24.0%), and baseline sepsis-related organ failure assessment (SOFA) scores (7.0 vs 3.0) than the IAPA group ($p < 0.05$), as presented in Table 2.

The most frequently identified species in both the CAPA and IAPA groups were *Aspergillus fumigatus*, followed by *Aspergillus flavus*, with no significant difference between the two groups, as shown in Figure 1. Regarding imaging findings, the CAPA group predominantly showed masses and areas of consolidation, whereas the IAPA group mainly showed masses and nodular opacities. Additionally, the CAPA group had a higher proportion of ground-glass opacities

Table 2 Clinical Features of Confirmed Aspergillosis

	Total (N=106)	IAPA (N=50)	CAPA (N=56)	*p*
Time from symptom onset to diagnosis in virus-positive cases (days)	8.0 (4.0, 22.5)	4.0 (0.5, 7.5)	23.0 (10.0, 29.0)	**<0.001**
Total length of stay (days)	25.0 (15.0, 44.5)	16.5 (12.0, 26.3)	38.0 (21.0, 66.0)	**<0.001**
Pre-diagnosis pharmacological management plan				
Antiviral drug utilization rate (%)	73 (68.8%)	29 (59.2%)	44 (78.6%)	**0.031**
Antibiotic utilization rate (%)	100 (94.3%)	46 (92.0%)	54 (96.4%)	0.573
Duration of antibiotic therapy (days)	10.0 (6.0, 17.25)	7.0 (4.0, 11.0)	14.5 (8.3, 23.8)	**<0.001**
Glucocorticoid utilization rate (%)	76 (71.6%)	23 (47.9%)	53 (94.6%)	**<0.001**
Duration of glucocorticoid therapy (days)	8.0 (0.0, 18.0)	0.0 (0.0, 7.0)	14.0 (8.0, 24.8)	**<0.001**
Total glucocorticoid dose administered (mg)	280.0 (0.0, 825.0)	0.0 (0.0, 250.0)	616.9 (270.0, 1063.1)	**<0.001**
Diagnostic findings				
Classic Host Risk Factors	45 (42.4%)	14 (28.0%)	31 (55.4%)	**0.004**
Respiratory failure	61 (57.5%)	23 (46.0%)	38 (67.9%)	**0.023**

(*Continued*)

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Table 2 (Continued).

	Total (N=106)	IAPA (N=50)	CAPA (N=56)	*p*
High-flow nasal cannula	33 (31.1%)	13 (26.0%)	20 (35.7%)	0.281
Invasive mechanical ventilation	28 (26.4%)	8 (16.0%)	20 (35.7%)	**0.022**
ICU	36 (33.9%)	12 (24.0%)	24 (42.9%)	**0.041**
CRRT	10 (9.4%)	3 (6.0%)	7 (12.5%)	0.418
Shock	5 (4.7%)	3 (6.0%)	2 (3.6%)	0.897
SOFA	4.0 (2.0, 6.0)	3.0 (1.5, 5.0)	7.0 (2.8, 7.0)	**0.009**
Post-diagnosis therapeutic regimen				
Glucocorticoid utilization rate (%)	93 (87.7%)	38 (76.0%)	55 (98.2%)	**<0.001**
Total duration of glucocorticoid therapy (days)	23.0 (6.0, 41.5)	9.0 (0.0, 20.0)	39.0 (23.3, 56.0)	**<0.001**
Total cumulative glucocorticoid dose (mg)	700.0 (222.0, 1796.2)	260.0 (0.0, 669.7)	1541.1 (655.8, 2663.0)	**<0.001**
Post-treatment evaluation at 2 weeks				
Respiratory failure	46 (43.3%)	11 (28.9%)	35 (62.5%)	**0.001**
High-flow nasal cannula	21 (19.8%)	3 (7.9%)	18 (32.1%)	**0.006**
Invasive mechanical ventilation	28 (26.4%)	6 (15.8%)	22 (39.3%)	**0.015**
ICU	34 (32.0%)	7 (18.4%)	27 (48.2%)	**0.003**
CRRT	17 (16.0%)	4(10.5%)	13 (23.2%)	0.117
ECMO	2 (1.8%)	0 (0.0%)	2 (3.6%)	0.513
Shock	12 (11.3%)	2 (5.3%)	10 (17.9%)	0.139
SOFA	4.5 (2.0, 8.0)	2.0 (0.0, 4.0)	5.0 (4.0, 9.3)	**<0.001**
Viral Shedding Status	50/80 (47.1%)	28/32 (87.5%)	22/48 (45.8%)	**<0.001**
Complications during disease course				
Deep vein thrombosis	24 (22.6%)	5 (10.0%)	19 (33.9%)	**0.003**
Heart failure	17 (16.0%)	4 (8.0%)	13 (23.2%)	**0.033**
Gastrointestinal bleeding	23 (21.6%)	3 (6.0%)	20 (35.7%)	**<0.001**

Note: The bold text indicates statistically significant results with $p < 0.05$.

(33.9% vs 12.0%), interstitial changes (17.9% vs 4.0%), and pleural effusion (44.6% vs 26.0%) compared to the IAPA group *(p* <0.05), as shown in Figure 2.

Clinical Status After Diagnosis of Aspergillus Infection

After a confirmed diagnosis of *Aspergillus* infection, the proportion of patients receiving glucocorticoids was higher in the CAPA group (98.2% vs 76.0%), the duration of treatment (39.0 days vs 9.0 days) and the total glucocorticoid dose (all glucocorticoids converted to methylprednisolone equivalents: 1541.1mg vs 260.0mg) were higher than in the IAPA group. Additionally, the CAPA group had a significantly longer total hospital stay was longer (average 38.0 days vs.16.5 days, p <0.001), as shown in Table 2.

Regarding complications involving other organ systems following diagnosis and during treatment, the CAPA group had a significantly higher incidence of lower extremity deep vein thrombosis (33.9% vs 10.0%), gastrointestinal bleeding (35.7% vs 6.0%), and heart failure (23.2% vs 8.0%) compared to the IAPA group ($p < 0.05$), as detailed in Table 2.

Survival and Prognosis

Based on the Log rank test, the IAPA group had significantly better survival compared to the CAPA group ($\chi2 = 4.718$, $p = 0.030$). The survival rates of the two groups were analyzed as follows: 30-day survival rate (74.0% vs 64.3%, p=0.281), 60-day survival rate (62.0% vs 51.8%, $p = 0.290$), and 120-day survival rate (40.0% vs 30.4%, p=0.298), as shown in Figure 3.

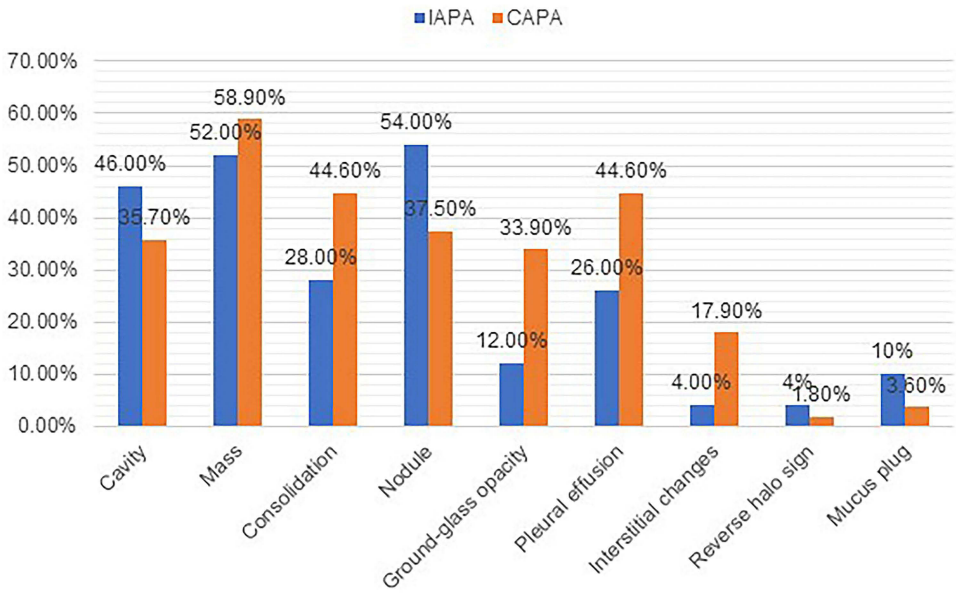

Figure 2 Radiographic findings on chest CT at the time of IPA diagnosis.

In patients with IAPA, those in the mortality group had a higher proportion of confirmed respiratory failure, invasive mechanical ventilation, ICU admission, and shock at diagnosis compared to the survival group. The SOFA score, white blood cell count, neutrophil count, and procalcitonin (PCT) level were also significantly higher in the mortality group (p <0.05), as shown in Supplementary 1. Variables with statistically significant differences in univariate analysis were included in the Cox regression analysis, which identified ICU admission at diagnosis as a risk factor for IAPA-related mortality (OR = 9.578; 95% CI: 1.778–51.603; p = 0.009), as shown in Table 3.

In patients with CAPA, the mortality group had a lower prevalence of baseline hypertension compared to the survival group at diagnosis. They also had higher rates of confirmed respiratory failure, ICU admissions, and invasive mechanical ventilation, along with higher levels of IL-6, increased incidences of new-onset gastrointestinal bleeding and deep vein thrombosis during the disease course (p <0.05), as shown in Supplementary 2. Based on a literature review, hypertension was not identified as a protective factor for CAPA mortality and was therefore excluded from further analysis. The remaining variables with statistically significant differences in univariate analysis were then subjected to a multivariate

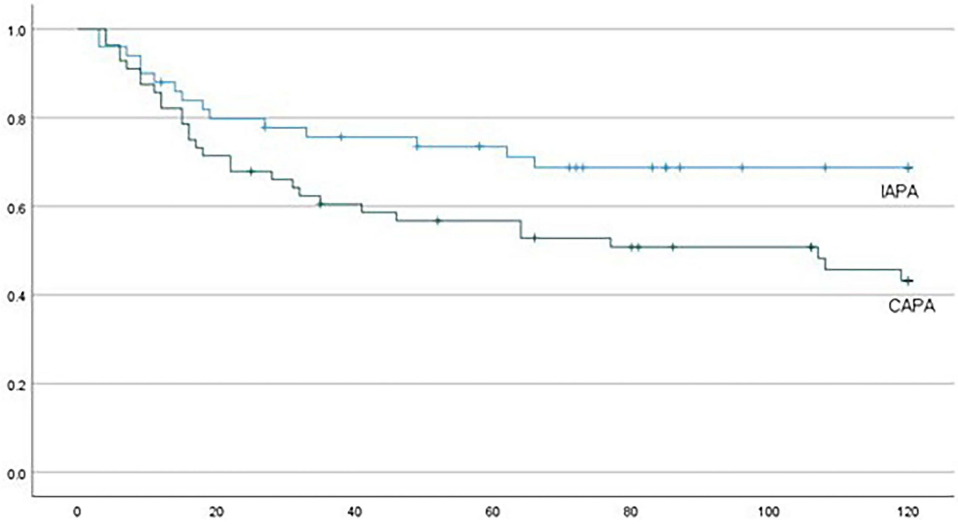

Figure 3 Kaplan-Meier survival curves.

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Table 3 Univariate and Cox Regression Analyses of High-Risk Factors for Mortality in IAPA

	Survival (N=35)	Deaths (N = 15)	*p*	Multiplicity	
				The 95% CI of OR	*p*
Assisted examination					
White blood cells (X 10^9/L)	9.0 (6.3, 13.7)	16.6 (12.4, 28.9)	**0.005**	0.416–1.497	0.468
Neutrophils (X10^9/L)	7.4 (4.8, 12.5)	15.0 (10.1, 26.1)	**0.006**	0.657–2.877	0.399
PCT (ng/mL)	0.2 (0.1, 0.5)	2.3 (0.3, 7.6)	**0.003**	0.960–1.040	0.981
Diagnostic findings					
Respiratory failure	11 (31.4%)	12 (80.0%)	**0.002**	0.429–12.288	0.332
Invasive mechanical ventilation	2 (5.7%)	6 (40.0%)	**0.009**	0.016–1.296	0.084
ICU	3 (8.6%)	9 (60.0%)	**<0.001**	1.778–51.603	**0.009**
Shock	0 (0.0%)	3 (20.0%)	**0.023**	0.052–15.242	0.936
SOFA	2.0 (1.0, 3.0)	6.0 (4.0, 12.8)	**<0.001**	0.958–1.410	0.128

Note: The bold text indicates statistically significant results with $p < 0.05$.

Table 4 Univariate and Cox Regression Analyses of High-Risk Factors for Mortality in CAPA

	Survival (N = 26)	Deaths (N = 30)	*p*	Multiplicity	
				The 95% CI of OR	*p*
Assisted examination after admission					
IL-6 (μg/L)	8.4 (4.9, 143.6)	52.5 (11.4, 438.0)	**0.023**	1.000–1.000	0.537
The severity of the condition was assessed at diagnosis					
Respiratory failure	13 (50.0%)	25 (83.3%)	**0.008**	0.763–7.349	0.135
Invasive mechanical ventilation	5 (19.2%)	15 (50.0%)	**0.017**	0.364–5.460	0.619
ICU	6 (23.1%)	18 (60.0%)	**0.005**	0.255–5.170	0.858
Complications during disease course					
Deep vein thrombosis	4 (15.4%)	15 (50.0%)	**0.006**	0.665–3.197	0.346
Gastrointestinal bleeding	5 (19.2%)	15 (50.0%)	**0.017**	0.725–4.281	0.211

Note: The bold text indicates statistically significant results with $p < 0.05$.

Cox proportional hazards regression model, but no risk factors for CAPA-related death were identified, as shown in Table 4 (26 survivors, 30 deaths).

Discussion

Viral infections can lead to a reduction in lymphocyte counts,[17] thereby impairing both T-cell- and B-cell-mediated immune responses. This results in diminished immune function and an increased risk of *Aspergillus* infection. In this study, both influenza and SARS-CoV-2 infections were associated with reduced absolute counts of T lymphocytes, B lymphocytes, and $CD4^+$ T lymphocytes. The CAPA group showed more significant immune suppression than the IAPA group, this alteration may be associated with the extensive use of cortisol during therapeutic management of COVID-19,[18] which is consistent with previous studies.[13] In this study, individuals in the CAPA group often had classic IPA risk factors before viral infection, whereas most patients in the IAPA group were individuals without immunodeficiency, consistent with previous reports indicating that about half of IAPA patients lack classic immunosuppressive factors.[7] Multiple previous studies have demonstrated that severe influenza virus infection is a significant risk factor for *Aspergillus* infection.[6,14,15] Regarding CAPA, research has shown that 36.8% of affected individuals have classic risk factors for *Aspergillus* infection.[12] In our study, 55.4% of CAPA patients had classic fungal infection host factors;

however, whether COVID-19 is a risk factor for *Aspergillus* infection remains to be confirmed and requires further research and validation.[10] IL-6 receptor antagonist use[19] and elevated IL-6 levels post-COVID-19 infection[20] have been reported as risk factors for CAPA. Our univariate analysis of IAPA mortality revealed significantly higher IL-6 levels in non-survivors compared to survivors, although this difference was not observed in the CAPA group. Overall, larger sample sizes may be required to robustly analyze associations between cytokine changes and the incidence and mortality of both IAPA and CAPA.

In our study, the median time from influenza virus infection to confirmed aspergillosis was 4 days, while for COVID-19 infection, it was 23 days. Previous literature has reported that patients with influenza virus infection can develop invasive aspergillosis within 2 to 5 days,[7,8,15] and the median time from COVID-19 symptom onset to CAPA diagnosis is 14 (11–22) days.[10,12] In severe COVID-19 patients, CAPA typically develops 8 (4–15) days after ICU admission.[9,10,12] The discrepancy in the timing of CAPA aspergillosis diagnosis in this study may be attributable to differences in calculation methods. We measured the interval from COVID-19 symptom onset to confirmed fungal infection, whereas most international studies use the interval from ICU admission or initiation of mechanical ventilation to confirmed fungal infection. COVID-19 typically progresses to viral pneumonia in 10 days (range 2–21).[12]

In our study, the incidence of deep vein thrombosis and gastrointestinal bleeding was higher in the CAPA group than in the IAPA group. Previous studies have indicated that the rate of thromboembolic complications in patients with COVID-19 ranges from 10.9% to 45%,[21–23] while the incidence of venous thromboembolism in hospitalized influenza patients is 5.3% to 11%. The risk of venous thromboembolism in COVID-19 pneumonia is higher than that in influenza pneumonia.[21,22] Multiple reports have shown that the incidence of gastrointestinal bleeding in patients infected with COVID-19 ranges from 1.8% to 3.1%,[24,25] whereas in this study, the proportion of gastrointestinal bleeding was 35.7%, which may be attributed to the more severe condition of the patients enrolled and the extensive use of medications such as corticosteroids and anticoagulants. Studies have confirmed that the use of corticosteroids and anticoagulants during COVID-19 treatment increases the risk of gastrointestinal bleeding.[25,26] The higher incidence of gastrointestinal bleeding in CAPA compared to IAPA may also be related to the binding of SARS-CoV-2 to angiotensin-converting enzyme 2 receptors in the gastrointestinal tract, leading to inflammation and hemorrhage.[27]

In this study, the primary causes of death in IAPA and CAPA were septic shock and multiple organ failure, consistent with the pathophysiology of sepsis. Therefore, the use of the SOFA score has been proposed to predict short-term mortality in patients. Previous studies have confirmed that for infected patients admitted to the ICU, an increase of two or more points in the SOFA score within a short period is predictive of in-hospital mortality.[28] Based on this, this study conducts a correlation analysis between changes in SOFA scores and patient outcomes. By comparing SOFA scores between the deceased and surviving groups in IAPA and CAPA in this study, we found that SOFA scores increased in both groups after one week and two weeks. These findings suggest that changes in SOFA scores after one week may be useful in predicting the prognosis of IAPA and CAPA. Future large-scale studies are warranted to validate the predictive value of this indicator.

However, this study still has some limitations. First, the retrospective nature of the study results in missing information, such as the inability to accurately assess the total amount and duration of corticosteroids and antibiotics used before hospitalization, which may introduce confounding bias. Second, since influenza and SARS-CoV-2 are highly contagious, many patients did not undergo invasive procedures, such as bronchoscopy, to improve diagnostic accuracy. Therefore, the cases included in this study are primarily confirmed or clinically diagnosed, which could result in the exclusion of some IAPA and CAPA patients. Third, the small sample size may affect the authenticity of the research results.

Conclusion

Patients in the IAPA group were more likely to have underlying lung disease and exhibited a more acute onset. The median time of infection was 4 days after viral infection. Admission to the ICU at diagnosis was identified as a risk factor for IAPA-related mortality. In contrast, CAPA patients exhibited greater immune dysfunction, a more insidious onset, and a longer treatment duration. The median time of infection was 23 days after viral infection, making these patients more susceptible to complications such as bacterial infections, thrombosis, and gastrointestinal bleeding. The overall prognosis

for CAPA is poor, with a high risk of death. In terms of therapeutic management, early diagnosis and identification, coupled with the timely initiation of antifungal therapy, are critical determinants of clinical outcomes, additionally, corticosteroid administration in CAPA patients requires particular caution to avoid immunosuppression that may trigger secondary infections.

Ethics Statement

This retrospective study has been approved by the Medical Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine, and informed consent had been waived. Ethics approval number: IIT20230650A.

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Disclosure

The authors declared no conflicts of interest in this work.

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