Annals of Clinical Microbiology and Antimicrobials

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SARS-CoV-2 coinfection in patients with invasive pulmonary aspergillosis: clinical characteristics and prognosis

Mengshu Xie[1,2†], Xiaofeng Zhu[1,2†], Ao Ma[1,2†], Jiaqi Fan[2], Guangru Fei[2], Qianqian Zhou[2], Yan Zhang[3*], Huimei Wu[4*] and Xuqin Jiang[1,2*]

Abstract

Background COVID-19 associated pulmonary aspergillosis (CAPA) has been globally reported to be a life-threatening complication of severe COVID-19. Previous studies primarily focused on an association between secondary *Aspergillus* infection and elevated mortality risk in COVID-19 patients, while potential confounding factors and alternative pathogenic mechanisms remain insufficiently investigated. The risk factors and outcomes of patients with secondary SARS-CoV-2 infection following invasive pulmonary aspergillosis (IPA) were not been well explored either.

Methods This retrospective monocentric study enrolled 152 hospitalized IPA patients with and without SARS-CoV-2 infection from 1 November 2022 to 31 October 2023. The characteristics of IPA patients and related risk factors were investigated, and the relationship between different SARS-CoV-2 infection status and the prognosis in IPA patients was further evaluated.

Results Our analysis demonstrated that IPA patients subsequently diagnosed with SARS-CoV-2 infection exhibited significantly elevated mortality risk compared to those without viral coinfection (53.6% vs. 22.9%, $P<0.001$). SARS-CoV-2 infection status (OR 3.708; $P=0.001$; 95%CI 1.674–8.212), albumin concentration (OR 0.885; $P=0.005$; 95%CI 0.813–0.964), and C-reactive protein level (OR 1.007; $P=0.012$; 95%CI 1.002–1.013) were statistically significant independent risk factors for prognosis of IPA patients. Subsequent analysis established a multivariate risk prediction model incorporating independent prognostic factors, which exhibited robust discriminative capacity for mortality risk stratification via ROC curve validation (AUC = 0.792, 95%CI 0.721–0.862, $P<0.0001$). A statistically significant difference in mortality rate existed between IPA patients with secondary SARS-CoV-2 infection and CAPA patients (63.2% and 33.3%, $P=0.037$). Notably, comparative analysis revealed no statistically significant differences in 28-day (22/96, 22.9% vs. 6/18, 33.3%) or 90-day mortality rates (22/96, 22.9% vs. 6/18, 33.3%) between patients with IPA without SARS-CoV-2 infection and IPA patients with secondary SARS-CoV-2 infection.

Conclusions IPA patients with secondary SARS-CoV-2 coinfection had a lower mortality compared to those with CAPA. Considering the high mortality rate, more medical cares are needed for these patients.

†Mengshu Xie, Xiaofeng Zhu, and Ao Ma contributed equally to this work.

*Correspondence:
Yan Zhang
zhangymail@ahmu.edu.cn
Huimei Wu
wuhm@ahmu.edu.cn
Xuqin Jiang
xqjiang@ustc.edu.cn
Full list of author information is available at the end of the article

Keywords COVID-19, COVID-19 associated pulmonary aspergillosis (CAPA), Invasive pulmonary aspergillosis (IPA), Secondary SARS-CoV-2 infection, Risk factor

Introduction

Since late 2019, COVID-19 has been a critical public health concern. By the end of 2023, more than 772 million confirmed cases and nearly seven million deaths have been reported globally [1]. COVID-19 carries a high mortality rate in severe cases [2, 3]. Co-infections and secondary infections with other micro-organism such as bacterial and fungus are partly responsible [4, 5]. *Aspergillus* infection is the most common type of secondary fungal infection in patients with COVID-19 infection [6, 7]. COVID-19 associated pulmonary aspergillosis (CAPA) has gained increasing attention since the COVID-19 pandemic, and the ECMM/ISHAM 2020 consensus criteria was widely used to diagnose and manage CAPA patients [8]. Several previous studies reported worse outcomes of CAPA patients, including earlier Intensive Care Unit (ICU) admission from illness onset, increased mechanical ventilation requirement, multi-organ dysfunction and higher all-cause in-hospital mortality [9–11].

Invasive pulmonary aspergillosis (IPA) mainly occurs in the immunocompromised hosts and imposes an extremely high mortality rate ranging from 30 to 90%[12]. The risk factors of IPA include severe or prolonged neutropenia, defects in cell-mediated immunity, receipt of immunosuppressive therapy, and viral pneumonias, etc. [13–16]. Besides, our clinical observations revealed that some patients diagnosed with invasive pulmonary aspergillosis (IPA) develop secondary COVID-19 infections during pandemic conditions. While both patient with IPA and secondary SARS-CoV-2 infection or the reverse manifest distinct clinical profiles depending on pathogen acquisition sequence Nevertheless, current evidence remains limited regarding the comparative clinical trajectories and prognostic outcomes between these distinct infection chronotypes.

In this study, we presented the clinical characteristics of IPA patients. Then we analysis the risk factors of outcomes in patients with *Aspergillus* and COVID-19 co-infection. At last, the differences between patients with CAPA, with IPA and those with secondary SARS-CoV-2 infection following IPA were analysed.

Materials and methods

Study design and settings

This is a single-centre retrospective study conducted at the First Affiliated Hospital of University of Science and Technology of China. During the pandemics, the hospital was appointed as the key hospital for COVID-19 management. The data of patients who had been hospitalized from 1 November 2022 to 31 October 2023 were collected in the present study. All consecutive patients admitted to the participating centers were eligible for inclusion if they met the diagnostic criteria for IPA as defined by the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) [17]. Patients were excluded if they met any of the following criteria: (1) age < 18 years; (2) pulmonary aspergillus colonization; (3) HIV infected; (4) incomplete clinical data.

Data collection

The data were collected retrospectively using electronic medical records (EMRs). Baseline characteristics including age, sex, weight, etc., hospital days, complications including hypertension, diabetes, coronary heart disease, cancer, etc., SARS-CoV-2 infection status, treatments including oxygen requirements, mechanical ventilation, ECMO, CRRT, etc., laboratory test results, admission to intensive care unit (ICU), and treatment outcomes (alive/dead, hospital death, 28- or 90-day mortality) were collected.

Microbiological methods

The diagnosis of COVID-19 was established by real-time RT-PCR of nasopharyngeal and throat swabs. Sputum samples were collected and subjected to direct microscopic examination and fungal culture. Bronchoalveolar lavage fluid (BALF) was performed by experienced bronchoscopists following standard procedures for detection according to the guidelines [18]. Serum or BALF galactomannan (GM) antigen tests were performed using ELISA (Dynamiker Biotechnology, Tianjin, Co., Ltd.).

Diagnostic criteria and definitions

In our study, the diagnosis of IPA was made according to the EORTC/MSG criteria [17]. For intensive care patients, the AspICU criteria [19] were used to diagnose IPA. For the diagnosis of CAPA, the modified ECMM/ISHAM 2020 consensus criteria were applied [8]. We defined"no COVID-19 infection at admission"as meeting the following criteria upon hospitalization: no epidemiological history, absence of COVID-19 symptoms, and two consecutive negative COVID-19 nucleic acid tests (with a 24-h interval between tests). A positive COVID-19 nucleic acid test 48 h after admission was

then classified as a new-onset infection. Moreover, we differentiated between CAPA and secondary SARS-CoV-2 infection following IPA based on the timing of diagnosis. Patients with secondary SARS-CoV-2 infection after IPA were defined as those diagnosed with IPA upon admission, in whom SARS-CoV-2 infection was subsequently confirmed ≥48 h after hospitalization. Aspergillus colonization was defined by either: 1)A positive Aspergillus culture or microscopic identification of septate filamentous fungi in sputum or bronchoalveolar lavage fluid (BALF) samples; 2) the absence of new infiltrates on high-resolution computed tomography (HRCT) or structural lung abnormalities suggestive of IPA; 3)The diagnosis was established through independent assessment by two board-certified pulmonologists. In cases of diagnostic discrepancy, consensus was achieved through adjudication by a third senior consultant with expertise in pulmonary infections. [20–22]. The clinical diagnosis was made by two experienced physicians; in cases where they disagreed, a third senior physician made the final judgment.

Statistical analysis

The data were analysed using SPSS Statistics version 27.0 (IBM, New York, NY, USA). Standard descriptive statistics were used to summarize the study population characteristics. Student's t tests or Mann–Whitney U tests were used for continuous variables. The associations between categorical variables were evaluated using the Chi-square test or Fisher's exact test. Univariate logistic regression was used to identify predictors of mortality, and significant variables ($P< 0.05$) were subsequently subjected to stepwise backwards multivariate logistic regression analysis. The area under the ROC curve was calculated using GraphPad Prism 8.0 (GraphPad Software, Inc.). $P< 0.05$ was considered significant.

Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki. The study had been approved by the First Affiliated Hospital of University of Science and Technology of China (Ethics approval 2023-RE-410). As this was a retrospective study, the ethics committee granted a waiver of written informed consent.

Results

Clinical and laboratory characteristics of IPA patients

Initially, 152 patients with IPA were included in this study. The patients were divided into two groups according to whether infected with SARS-CoV-2 or not. Among the 152 patients, 56 had SARS-CoV-2 infection, while 96 did not, and 38 patients classified according to AspICU criteria and 114 patients classified according to EORTC/MSG criteria. The host factors of EORTC/MSG criteria have showed in Supplement Table 1. The characteristics of the patients are compared in Table 1. IPA patients who were diagnosed with COVID-19 demonstrated significantly longer hospitalization duration ($P= 0.017$), higher rates of high-flow oxygen therapy utilization (25.0% vs 11.5%, $P= 0.030$), and increased need for mechanical ventilation (44.6% vs 14.6%, $P< 0.001$). Most strikingly, COVID-19 patients exhibited substantially elevated mortality rates, including overall mortality (53.6% vs 22.9%, $P< 0.001$), 28-day mortality ($P< 0.001$), and 90-day mortality ($P< 0.001$). Furthermore, these patients showed greater susceptibility to shock (25.0% vs 11.5%, $P= 0.030$) and higher ICU admission rates (53.6% vs 19.8%, $P< 0.001$).

The laboratory results, such as lymphocyte count ($P= 0.002$), AST ($P= 0.048$), BUN ($P= 0.021$), the BUN/CRE index ($P= 0.001$), and APTT ($P= 0.043$), were significantly greater in SARS-CoV-2-infected patients with IPA than in SARS-CoV-2-negative patients.

Additionally, we also conducted a subgroup analysis on patients with proven/probable IPA, as showed in Supplement Table S2. The results showed that patients with COVID-19 exhibited a prolonged hospitalization time ($P= 0.013$), higher demand for mechanical ventilation (48.4% vs. 15.6%, $P< 0.001$) and ECMO (9.7% vs. 0%, $P= 0.034$), as well as significantly elevated mortality rates (67.7% vs. 19.5%; $P< 0.001$), encompassing in-hospital (25.8% vs. 9.1%; $P= 0.049$), 28-day, and 90-day mortality (67.7% vs. 19.5%; $P< 0.001$), and were more prone to shock (32.2% vs. 7.8%; $P= 0.003$) and ICU admission (61.3% vs. 20.8%; $P< 0.001$). In terms of laboratory findings, patients with COVID-19 had a statistically significant elevation in BUN/CRE index ($P= 0.001$).

Risk factors for prognosis in IPA patients

Univariate analysis revealed that SARS-CoV-2 infection status, the neutrophil count, the lymphocyte count, the ALB level, the CRE concentration and the CRP concentration were associated with the prognosis ($P< 0.05$) in patients with *As*pergillus infection or colonization, as shown in Table 2. We next subjected to univariate variables whose P values were less than 0.05 to multivariate logistic regression. A backwards (*LR*) selection approach was adopted. The results showed that the SARS-CoV-2 infection status (OR 3.708; $P= 0.001$; 95%CI 1.674–8.212), ALB concentration (OR 0.885; $P= 0.005$; 95%CI 0.813–0.964), and CRP level (OR 1.007; $P= 0.012$; 95%CI 1.002–1.013) were independently associated with the increased mortality. The ROC curve analysis indicated that the model had a certain predictive capacity, as presented in Fig. 1. The ROC curve

Table 1 The clinical features of 152 patients with IPA

	Without COVID-19 (N = 96)	With COVID-19 (N = 56)	t/Z/χ2	*P*
Demographics				
Sex (male, n, %)	61(63.5)	35(62.5)	0.016	0.898
Age (years, mean ± SD)	61.25 ± 15.20	66.14 ± 16.35	− 1.862	0.065
Weight (kg, median, IQR)	59.75(52.41,66.80)	63.10(54.30,68.91)	− 1.194	0.232
Inpatient days (days, median, IQR)	13(9,19.75)	17.5(12.25,22)	− 2.391	0.017
BMI (kg/m^2, mean ± SD)	22.94 ± 3.31	22.89 ± 3.60	0.078	0.938
Comorbidities				
Hypertension (n, %)	24(25.0)	18(32.1)	0.902	0.342
Diabetes (n, %)	18(18.8)	14(25.0)	0.831	0.362
Coronary heart disease (n, %)	6(6.3)	3(5.4)	0.000	1.000#
Cancer (n, %)	19(19.8)	8(14.3)	0.734	0.392
COPD/pulmonary emphysema/pulmonary bulla (n, %)	18(18.8)	8(14.3)	0.497	0.481
Interstitial pneumonia (n, %)	3(3.1)	7(12.5)	3.647	0.056#
Renal transplantation (n, %)	2(2.1)	5(8.9)	2.375	0.123#
Chronic hepatic insufficiency (n, %)	8(8.3)	3(5.4)	0.129	0.720#
Autoimmune disease (n, %)	7(7.3)	9(16.1)	2.895	0.089
Chronic heart failure (n, %)	2(2.1)	2(3.6)	0.001	0.978#
Charlson Comorbidity Index (mean ± SD)	6.92 ± 2.02	6.63 ± 2.16	0.836	0.405
Oxygen supplementation therapy				
Oxygen any requirements (n, %)	57(59.4)	28(50.0)	1.261	0.261
Noninvasive positive pressure ventilation (n, %)	2(2.1)	3(5.4)	0.385	0.535#
Oxygen high requirements (n, %)	11(11.5)	14(25.0)	4.720	0.030
Mechanical ventilation (n, %)	14(14.6)	25(44.6)	16.754	< 0.001
ECMO (n, %)	1(1.0)	3(5.4)	1.162	0.281#
CRRT (n, %)	4(4.2)	1(1.8)	0.104	0.747#
IPA(Proven/probable) (n, %)	77(80.2)	31(55.4)	10.620	0.001
Laboratory findings				
WBC (10^9/L, median, IQR)	7.7(4.84,13.01)	8.98(6.58,12.30)	− 0.710	0.477
NEU (10^9/L, median, IQR)	6.02(2.61,11.52)	7.55(4.89,10.43)	− 1.234	0.217
LYM (10^9/L, median, IQR)	0.87(0.55,1.41)	0.6(0.31,0.9)	− 3.070	0.002
PLT (10^9/L, median, IQR)	190(117,277)	162(118,230.75)	− 0.974	0.330
HB (g/L, median, IQR)	112.5(95.5,124.75)	119(94.25,129.5)	− 0.905	0.365
ALT (U/L, median, IQR)	24.0(15.0,48.5)	26.5(17.25,48.0)	− 0.535	0.593
AST (U/L, median, IQR)	27.0(18.5,44.3)	32.7(24.4,57.6)	− 1.977	0.048
ALB (g/L, mean ± SD)	32.9 ± 5.68	31.3 ± 4.6	1.790	0.075
Cre (umol/L, median, IQR)	62.5(48.1,77.8)	68.4(47.3,101.6)	− 1.400	0.162
BUN (mmol/L, median, IQR)	6.1(4.13,9.13)	8.1(4.95,13.25)	− 2.315	0.021
BUN/Cre (median, IQR)	18.8(9.55,26.59)	25.21(15.87,30.73)	− 3.373	0.001
CRP (mg/L, median, IQR)	51.18(11.60,122.81)	74.40(39.00,112.60)	− 1.354	0.176
PT (s, median, IQR)	13.3(11.95,14.95)	13.1(12.03,14.18)	− 0.829	0.407
APTT (s, median, IQR)	35.65(29.3,41.95)	31.5(27.6,36.65)	− 2.028	0.043
D-dimer (mg/L, median, IQR)	1.35(0.47,2.64)	1.66(0.68,4.05)	− 1.451	0.147
Shock (n, %)	11(11.5)	14(25.0)	4.720	0.030
ICU (n, %)	19(19.8)	30(53.6)	18.475	< 0.001
Mortality				
Death (n, %)	22(22.9)	30(53.6)	14.767	< 0.001
Hospital deaths (n, %)	11(11.5)	10(17.9)	1.216	0.270
Death within 28-days (n, %)	22(22.9)	30(53.6)	14.767	< 0.001
Death within 90-days (n, %)	22(22.9)	30(53.6)	14.767	< 0.001

Table 1 (continued)

[#]: Chi-square test with continuity correction

COPD, chronic obstructive pulmonary disease; IPA, invasive pulmonary aspergillosis; ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; WBC, white blood cell; NEU, neutrophil count; LYM, lymphocyte count; PLT, platelet count; HB, hemoglobin; ALT, alanine transaminase; AST, aspartate transaminase; ALB, albumin; Cre, creatinine; BUN, blood urea nitrogen; CRP, C-reaction protein; PT, prothrombin time; APTT, activated partial thromboplastin time; ICU, intensive care unit

Table 2 Univariate analysis and multivariate analysis of variables related to the prognosis in IPA patients

	Univariate analysis			Multivariate analysis		
	OR	**95%CI**	***P***	**OR**	**95%CI**	***P***
Sex	0.864	0.429–1.739	0.682			
Age	1.004	0.983–1.026	0.726			
Weight	1.028	0.997–1.060	0.080			
Inpatient days	1.000	0.968–1.032	0.982			
SARS-CoV-2 infection	3.881	1.911–7.884	< 0.001	3.708	1.674–8.212	0.001
With basic chronic disease	1.498	0.692–3.240	0.305			
IPA(Proven/probable) (n, %)	1.143	0.549–2.379	0.721			
NEU	1.048	1.001–1.097	0.045			
LYM	0.518	0.290–0.923	0.026			
ALT	0.998	0.991–1.004	0.528			
AST	0.999	0.996–1.002	0.534			
ALB	0.861	0.798–0.929	< 0.001	0.885	0.813–0.964	0.005
Cre	1.005	1.000–1.010	0.040	1.004	0.999–1.008	0.100
CRP	1.009	1.004–1.014	< 0.001	1.007	1.002–1.013	0.012
D-dimer	1.069	0.998–1.146	0.056			

Input variables: SARS-CoV-2 infection, NEU, LYM, ALB, Cre, CRP

IPA, invasive pulmonary aspergillosis; NEU, neutrophil count; LYM, lymphocyte count; ALT, alanine transaminase; AST, aspartate transaminase; ALB, albumin; Cre, creatinine; CRP, C-reaction protein

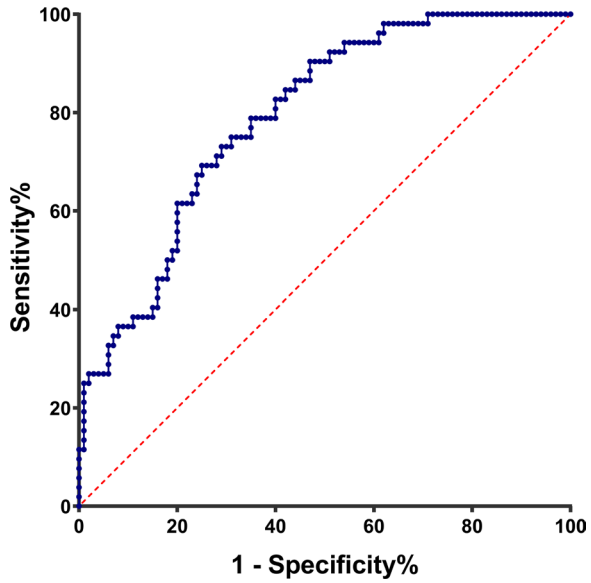

Fig.1 The ROC curves analysis for prognosis predication. AUC = 0.792 (95%CI: 0.721–0.862, *P* < 0.0001)

showed an area under the curve (AUC) of 0.792 (95%CI 0.721–0.862, *P* < 0.0001).

Clinical features between patients with CAPA and secondary SARS-CoV-2 infection following IPA

To further validate the difference between patients with CAPA and patients with secondary SARS-CoV-2 infection following IPA, we compared the clinical features of the two groups, as shown in Table 3. CAPA patients demonstrated significantly higher body weight (*P* = 0.026), elevated creatinine indices (*P* = 0.022), and increased D-dimer levels (*P* = 0.037) than did those with secondary SARS-CoV-2 infection following IPA. Furthermore, CAPA patients was associated with significantly higher rates of both ICU admission (63.2% and 33.3%, *P* = 0.037) and 28-day mortality (63.2% and 33.3%, *P* = 0.037).

Table 3 Clinical difference between patients in CAPA and secondary SARS-CoV-2 infection following IPA

	Secondary SARS-CoV-2 infection following IPA (N = 18)	CAPA (N = 38)	t/Z/χ2	*P*
Demographics				
Sex (male, n, %)	12(66.7)	23(60.5)	0.196	0.658
Age (years, mean ± SD)	69.5 ± 14.549	64.55 ± 17.091	1.059	0.294
Weight (kg, median, IQR)	55.0(45.5,63.5)	65.0(54.0,71.3)	2.221	0.026
Inpatient days (days, median, IQR)	18(14,23)	18(12,23)	0.544	0.586
BMI (kg/m^2, mean ± SD)	7.00 ± 2.54	6.45 ± 1.97	0.892	0.377
Comorbidities				
Hypertension (n, %)	7(38.9)	11(28.9)	0.553	0.457
Diabetes (n, %)	4(22.2)	10(26.3)	0.000	1.000#
Coronary heart disease (n, %)	1(5.6)	2(5.3)	0.000	1.000##
Cancer (n, %)	3(16.7)	5(13.2)	0.000	1.000#
COPD/pulmonary emphysema/pulmonary bulla (n, %)	3(16.7)	5(13.2)	0.000	1.000#
Interstitial pneumonia (n, %)	5(27.8)	2(5.3)	3.789	0.052#
Renal transplantation (n, %)	2(11.1)	3(7.9)	0.000	1.000#
Chronic hepatic insufficiency (n, %)	0(0)	3(7.9)	–	0.544##
Autoimmune disease (n, %)	4(22.2)	5(13.2)	0.224	0.636#
Chronic heart failure (n, %)	0(0)	2(5.3)	0.049	0.826##
Charlson Comorbidity Index (mean ± SD)	23.0 ± 3.43	22.8 ± 3.72	0.152	0.880
IPA(Proven/probable) (n, %)	11(61.1)	20(52.6)	0.355	0.551
Laboratory findings				
WBC (10^9/L, median, IQR)	7.83(5.63,10.32)	9.66(7.04,12.54)	1.640	0.101
NEU (10^9/L, median, IQR)	6.60(3.98,8.25)	8.52(5.58,11.02)	1.912	0.056
LYM (10^9/L, median, IQR)	0.77(0.53,1.04)	0.50(0.30,0.86)	1.625	0.104
PLT (10^9/L, median, IQR)	172(146,263)	153(111,208)	1.412	0.158
HB (g/L, median, IQR)	118(89.25,125)	120(98,135)	0.921	0.357
ALT (U/L, median, IQR)	24.0(13.0,36.5)	27.0(20.3,54.0)	1.466	0.143
AST (U/L, median, IQR)	30.8(23.4,44.4)	34.1(24.9,63.0)	1.140	0.254
ALB (g/L, mean ± SD)	31.1 ± 4.3	31.4 ± 4.8	0.246	0.807
Cre (umol/L, median, IQR)	63(43.5,72.5)	78.35(51.15,136.7)	2.298	0.022
CRP (mg/L, median, IQR)	60.6(22.7,92.1)	82.6(46.5,122.1)	1.794	0.073
PT (s, median, IQR)	13.0(11.5,14.0)	13.1(12.1,14.1)	0.547	0.585
APTT (s, median, IQR)	30.4(28.0,34.4)	31.3(27.3,36.5)	0.117	0.907
D-dimer (mg/L, median, IQR)	1.10(0.48,1.90)	2.22(0.74,5.54)	2.086	0.037
Shock (n, %)	3(16.7)	11(28.9)	0.437	0.509#
ICU (n, %)	6(33.3)	24(63.2)	4.368	0.037
Mortality				
Death (n, %)	6(33.3)	24(63.2)	4.368	0.037
Hospital deaths (n, %)	3(16.7)	7(18.4)	0.000	1.000#
Death within 28-days (n, %)	6(33.3)	24(63.2)	4.368	0.037
Death within 90-days (n, %)	6(33.3)	24(63.2)	4.368	0.037

: Chi-square test with continuity correction; ##: Fisher's exact test

COPD, chronic obstructive pulmonary disease; IPA, invasive pulmonary aspergillosis; WBC, white blood cell; NEU, neutrophil count; LYM, lymphocyte count; PLT, platelet count; HB, hemoglobin; ALT, alanine transaminase; AST, aspartate transaminase; ALB, albumin; Cre, creatinine; CRP, C-reaction protein; PT, prothrombin time; APTT, activated partial thromboplastin time; ICU, intensive care unit

Clinical differences between patients of IPA with and without secondary SARS-CoV-2 infection

In our study, a total of 96 patients with IPA were enrolled. We proceeded to compare these patients with those who developed secondary SARS-CoV-2 infection following IPA, as elaborated in Table 4. Patients with secondary

Table 4 Clinical difference between IPA patients without COVID-19 and secondary SARS-CoV-2 infection following IPA

	IPA without COVID-19 (N = 96)	Secondary SARS-CoV-2 infection following IPA (N = 18)	t/Z/χ2	*P*
Demographics				
Sex (male, n, %)	61(63.5)	12(66.7)	0.064	0.800
Age (years, mean ± SD)	61.25 ± 15.196	69.5 ± 14.549	− 2.127	0.036
Weight (kg, median, IQR)	59.75(52.41,66.80)	56.88(47.50,64.35)	− 1.026	0.305
Inpatient days (days, median, IQR)	13(9,19.75)	17.5(13.5,22.75)	− 2.093	0.036
BMI (kg/m^2, mean ± SD)	6.68 ± 2.21	7.00 ± 2.54	0.101	0.601
Comorbidities				
Hypertension (n, %)	24(25.0)	7(38.9)	0.859	0.354#
Diabetes (n, %)	18(18.8)	4(22.2)	0.000	0.986#
Coronary heart disease (n, %)	6(6.3)	1(5.6)	0.000	1.000#
Cancer (n, %)	19(19.8)	3(16.7)	0.000	1.000#
COPD/pulmonary emphysema/pulmonary bulla (n, %)	18(18.8)	3(16.7)	0.000	1.000#
interstitial pneumonia (n, %)	3(3.1)	5(27.8)	10.593	0.001#
Renal transplantation (n, %)	2(2.1)	2(11.1)	–	0.117##
Chronic hepatic insufficiency (n, %)	8(8.3)	0(0)	0.589	0.443#
Autoimmune disease (n, %)	7(7.3)	4(22.2)	2.352	0.125#
Chronic heart failure (n, %)	2(2.1)	0(0)	–	1.000##
Charlson Comorbidity Index (mean ± SD)	22.94 ± 3.31	23.0 ± 3.43	− 0.073	0.942
IPA(Proven/probable) (n, %)	77(80.2)	11(61.1)	2.149	0.143#
Laboratory findings				
WBC (10^9/L, median, IQR)	7.70(4.84,13.01)	7.83(5.63,10.32)	− 0.412	0.680
NEU (10^9/L, median, IQR)	6.02(2.61,11.52)	6.60(3.98,8.25)	− 0.093	0.926
LYM (10^9/L, median, IQR)	0.87(0.55,1.41)	0.77(0.53,1.04)	− 1.053	0.292
PLT (10^9/L, median, IQR)	190(117,277)	172(144.75,262.50)	− 0.066	0.947
HB (g/L, median, IQR)	112.50(95.50,124.75)	118(89.25,125.00)	− 0.027	0.978
ALT (U/L, median, IQR)	24.0(15.0,48.5)	24.0(13.0,36.5)	− 0.579	0.562
AST (U/L, median, IQR)	27.0(18.5,44.3)	30.8(23.4,44.4)	− 0.766	0.444
ALB (g/L, mean ± SD)	33.0 ± 5.7	31.1 ± 4.3	1.293	0.199
Cre (umol/L, median, IQR)	62.5(48.1,77.8)	63.0(43.5,72.5)	− 0.758	0.449
CRP (mg/L, median, IQR)	51.18(11.60,122.81)	54.84(23.2,86.7)	− 0.221	0.825
PT (s, median, IQR)	13.3(12.0,15.0)	13.2(11.7,14.1)	− 0.676	0.499
APTT (s, median, IQR)	35.7(29.3,42.0)	30.7(28.1,37.1)	− 1.360	0.174
D-dimer (mg/L, median, IQR)	1.35(0.47,2.64)	1.11(0.51,2.02)	− 0.548	0.584
Shock (n, %)	11(11.5)	3(16.7)	0.051	0.821#
ICU (n, %)	19(19.8)	6(33.3)	0.929	0.335#
Mortality				
Death (n, %)	22(22.9)	6(33.3)	0.414	0.520#
Hospital deaths (n, %)	11(11.5)	3(16.7)	0.051	0.821#
Death within 28-days (n, %)	22(22.9)	6(33.3)	0.414	0.520#
Death within 90-days (n, %)	22(22.9)	6(33.3)	0.414	0.520#

: Chi-square test with continuity correction; ##: Fisher's exact test

COPD, chronic obstructive pulmonary disease; IPA, invasive pulmonary aspergillosis; WBC, white blood cell; NEU, neutrophil count; LYM, lymphocyte count; PLT, platelet count; HB, hemoglobin; SII, Systemic Immune-Inflammation Index; ALT, alanine transaminase; AST, aspartate transaminase; ALB, albumin; Cre, creatinine; CRP, C-reaction protein; PT, prothrombin time; APTT, activated partial thromboplastin time; ICU, intensive care unit

SARS-CoV-2 infection following IPA were older (P= 0.036), had a longer duration of hospitalization (P =0.036) and were more prone to developing interstitial pneumonia (P= 0.001). However, no statistically significant difference between IPA patients with and without secondary SARS-CoV-2 infection in the 28-day and

90-day mortality rate (both 22/96, 22.9% vs. 6/18, 33.3%) was found.

Discussion

Since the onset of the COVID-19 pandemic, accumulating clinical evidence has demonstrated that SARS-CoV-2-infected patients exhibit heightened susceptibility to secondary fungal infections, particularly *Aspergillus* infections [23–25]. COVID-19 patients who developed fungal infection were prone to poor prognosis and high mortality. However, few studies explored the characteristics of patients with IPA who subsequently infected with SARS-CoV-2 [26, 27], especially the difference between CAPA and secondary SARS-CoV-2 infection following IPA. In this study, we showed that patients with IPA who had SARS-CoV-2 infection had a poor prognosis, although not worse than that of CAPA patients.

Previous studies claimed that CAPA patients had a significantly higher overall mortality. A previous study by Jesús Fortún et al. [27] reported that the isolation of *Aspergillus* spp. in respiratory samples, whether diagnosed as IPA (proven/probable) or colonization, was linked to a high mortality. In this study, we assessed the clinical significance of COVID-19 infection in IPA patients. Our data indicated that IPA patients with following SARS-CoV-2 infection had significantly higher mortality rate than non-infected patients (53.6% vs. 22.9%), which concurred with previous findings [27]. Furthermore, these patients had a prolonged hospitalization time ($P= 0.017$), greater rates of high oxygen requirements (25.0% vs. 11.5%, $P= 0.030$), mechanical ventilation (44.6% vs. 14.6%, $P< 0.001$), shock (25.0% and 11.5%, $P= 0.030$) and ICU admission (53.6% and 19.8%, $P< 0.001$). These findings indicate more extensive pulmonary compromise and greater requirement for intensive respiratory support. Given the significantly increased morbidity and mortality, early identification, diagnosis, and prompt treatment initiation are paramount to reducing mortality among these IPA patients [28–31].

To determine the independent predictors of clinical outcomes in patients with combined IPA and COVID-19 infection, we initially performed univariate analysis of potential prognostic factors, followed by multivariate regression modelling to adjust for confounding variables. Our analysis revealed significant intergroup differences in SARS-CoV-2 infection status, albumin concentration, and CRP levels. As a well-established inflammatory biomarker, CRP demonstrates particular clinical utility for infection monitoring. Current evidence consistently associates elevated CRP levels with poorer clinical outcomes in aspergillosis patients, corroborating our findings [32, 33]. Albumin, a critical protein that influences the body's nutritional and immune status, is frequently employed as an indicator of nutritional and inflammatory responses. Prior research indicated that hypoalbuminemia was not the etiological factor for the heightened incidence or mortality rate of certain conditions; rather, it could serves as a prognostic marker for outcomes [34]. Additionally, Jesús Fortún et al. [27] demonstrated that SARS-CoV-2 infection was an independent predictor of mortality in patients with the isolation of Aspergillus spp. in their respiratory samples. In our cohort analysis, the composite model incorporating CRP, SARS-CoV-2 infection status, and albumin concentration demonstrated significant predictive value for adverse outcomes in IPA patients, with an area under the ROC curve of 0.792 (95% CI 0.721–0.862; $P< 0.0001$). These findings suggest that these three parameters may serve as clinically useful prognostic biomarkers for risk stratification in this patient population.

What intrigued us mostly is the difference between IPA followed by COVID-19 and CAPA. Since these patients have both SARS-CoV-2 and aspergillus infections but differ in sequential order, will their outcomes differ? Our data, as presented in Table 3, showed that patients with IPA followed by COVID-19 had a poorer prognosis, a higher mortality, but not worse than that of the CAPA patients.

CAPA, representing invasive pulmonary aspergillosis complicating COVID-19, carries significant prognostic implications. Current evidence from multiple studies [35–37]reveals disturbingly high mortality rates in this population. For instance, a comprehensive analysis of 192 CAPA patients demonstrated an overall mortality rate approaching 50% (48.4%, 93/192), with reported mortality rates across studies ranging from 22.2% to a striking 100% [37].Anna Beltrame et al. [35] reported that CAPA patients admitted to intensive care units had a median mortality of 56.8%, ranging from 30% to 91.8%. Shreya Singh et al. [36] summarized 20 peer-reviewed studies and reported that the pooled mortality in CAPA patients was 51.2% (95%CI: 43.1–61.1, $I^2= 38\%$). But little is known about the clinical features of IPA patients with secondary SARS-CoV-2 infection. In our study, the mortality of these patients was markedly increased but still lower than that of CAPA patients (33.3% vs. 63.2%, $P= 0.037$). The 28-day and 90-day mortality rates were rather high but not higher than those of CAPA patients (both 6/18, 33.3% vs. 24/38, 63.2%). Current evidence indicates that hematopoietic stem cell transplantation, solid organ transplantation, corticosteroid therapy combined with other immunosuppressants, prolonged neutropenia, and concurrent viral pneumonias (especially COVID-19 or influenza infections) are all significant risk factors for the high mortality in IPA patients [12, 38, 39]. Regarding COVID-19 patients, male gender, ethnicity,

and pre-existing comorbidities (including cardiovascular diseases, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, and malignancies) have been identified as critical determinants of disease progression and severity. Routine hospital laboratory markers—including eosinopenia, lymphocytopenia, elevated leukocyte/neutrophil counts, elevated acute-phase reactants (CRP and procalcitonin), and heightened pro-inflammatory cytokine levels-along with clinical manifestations of immune dysregulation, multi-organ dysfunction, and hypoalbuminemia, have demonstrated significant prognostic value for predicting COVID-19 disease severity and mortality risk. [40–42]. These findings suggest that immunocompromised populations and long-term corticosteroid users exhibit heightened susceptibility to both IPA and COVID-19, which substantially contributes to their elevated mortality rates. Notably, while most CAPA cases represent secondary IPA infections in critically ill COVID-19 patients with alarmingly high mortality [43], the clinical severity of COVID-19 following primary IPA infection demonstrates considerable heterogeneity. Some patients achieve rapid viral clearance post-treatment, leading us to hypothesize that the differential COVID-19 severity profiles may constitute a key determinant underlying the mortality disparity between these two patient cohorts. Considering the high mortality of both groups of patients, regardless of whether they experienced CAPA or secondary SARS-CoV-2 infection following IPA, we should pay more attention to essential surveillance and management.

Currently, there remains a critical knowledge gap regarding the differential clinical manifestations between patients developing secondary SARS-CoV-2 infection following IPA and those with IPA alone. No published studies have systematically compared these distinct patient populations. Therefore, we further investigated the differences between the two groups. We found that these patients although had a high rate of 28-day and 90-day mortality (both 22/96, 22.9% vs. 6/18, 33.3%), but there was no statistical significance. We think that partly because the small sample size of patients with secondary SARS-CoV-2 infection following IPA. Although SARS-CoV-2 variant typing was not performed in our study, it is noteworthy that the Omicron variant was predominant during the study period (November 2022 to October 2023), a factor known to be associated with reduced COVID-19 mortality rates compared to previous variants. The predominance of Omicron variants during the study period likely modified the clinical trajectory of IPA patients acquiring secondary SARS-CoV-2 infection, with potentially important implications for: (1) viral-fungal immune interactions, (2) cytokine response patterns, and (3) therapeutic outcomes. Several distinctive features of Omicron variants—including enhanced transmissibility, altered tissue tropism, and immune escape capabilities mediated by spike protein mutations—likely played a role in reducing clinical severity, thereby potentially modifying population-level mortality trends [44]. Future studies should focus on clarifying the specific effects of viral variants on clinical outcomes in patients with secondary infections.

This study has several limitations. Firstly, this was a retrospective study and single-centre data review. Secondly, this study retrieved data from a not enough large sample size and lacks some clinical details due to the urgent situations in the epidemic period of the COVID-19 outbreak. Thirdly, temporal variations in circulating SARS-CoV-2 variants could potentially influence mortality outcomes. These constraints highlight the need for larger, multicentre prospective studies to validate our findings.

In summary, SARS-CoV-2 infection significantly increases mortality risk in patients with IPA. SARS-CoV-2 coinfection, hypoalbuminemia, and elevated CRP levels are considerable risk factors for the prognosis of IPA patients. Notwithstanding the mortality rate being comparatively lower than in CAPA cases, the persistently high fatality observed in this patient cohort necessitates heightened clinical vigilance and optimized diagnostic-therapeutic approaches.

Abbreviations

IPA	Invasive pulmonary aspergillosis
CAPA	COVID-19 associated pulmonary aspergillosis
BALF	Bronchoalveolar Lavage Fluid
ICU	Intensive Care Unit
GM	Galactomannan
AUC	Area under the curve

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12941-025-00805-8.

Additional file1

Author contributions

Conceptualization: M. X., H. W., Y. Z. & X. J.; Data curation: M. X., X. Z., A. M., J. F., G. F. and Q. Z.; Formal analysis: M. X., X. Z., A. M., Q. Z., H. W., Y. Z. & X. J.; Funding acquisition: X. J.; Methodology: H. W., Y. Z. & X. J.; Validation: M. X., X. Z., J. F., G. F., Q. Z., H. W., Y. Z. and X. J.; Supervision: H. W. and Y. Z.; Visualization: M. X.; Writing—original draft: M. X.; Writing—review and editing: H. W., Y. Z. & X. J.. All authors read and approved the final manuscript.

Funding

This work was supported by Research Funds of Center for Big Data and Population Health of IHM (JKS2023007), Joint Fund for Medical Artificial Intelligence (MAI2023C013) and Anhui Provincial Research Project for the Inheritance and Innovation of Traditional Chinese Medicine(2024CCCX012).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study had been approved by the First Affiliated Hospital of University of Science and Technology of China (Ethics approval 2023-RE-410). The data utilized in this study were from retrospective research, the requirement for written informed consent was waived.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Pulmonary Medicine, School of Clinical Medicine, Bengbu Medical University, Bengbu, China. [2]Department of Pulmonary and Critical Care Medicine, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Lujiang Road 17, Hefei 230001, China. [3]School of Health Service Management, Anhui Medical University, 81-Meishan Road, Hefei 230032, China. [4]Anhui Geriatric Institute, Department of Geriatric Respiratory and Critical Care Medicine, The First Affiliated Hospital of Anhui Medical University, Jixi Road 218, Hefei 230022, China.

Received: 24 December 2024 Accepted: 5 June 2025
Published online: 18 June 2025

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