JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Coronavirus Pandemic

Observational study on *Aspergillus* infections in critically ill patients with coronavirus disease 2019 at a single medical center using sputum samples

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Abstract

Objective: To explore *Aspergillus* infection's risks, treatment, and prognostic factors in critically ill COVID-19 patients.
Methodology: Retrospective analysis of 50 critically ill COVID-19 patients' data. Patients were divided into *Aspergillus* infection group (10 cases) and non-*Aspergillus* infection group (40 cases) to examine risk factors and compare hospitalization length, expenses, and survival outcomes.
Results: Logistic regression showed a significant correlation between *Aspergillus* infection and diabetes history, and steroid use duration in COVID-19 patients. Diabetes increased *Aspergillus* infection risk 9.708 times (not statistically significant). Each extra steroid use day raised infection risk by 25.6%. The *Aspergillus* infection group had longer hospital stays, and higher costs ($p < 0.05$) but surprisingly higher survival rate than the non-infection group ($p < 0.05$).
Conclusions: The main risk factor for *Aspergillus* infection in critically ill COVID-19 patients is steroid use duration. The infection group had longer hospital stays and higher costs, and *Aspergillus* infection affected the survival duration of critically ill COVID-19 patients.

Key words: *Aspergillus* infection; COVID-19; diabetes mellitus; steroid; survival time; total hospitalization cost.

J Infect Dev Ctries 2025; 19(5):677-682. doi:10.3855/jidc.20072

(Received 04 March 2024 – Accepted 23 September 2024)

Introduction

The global outbreak of the coronavirus disease 2019 (COVID-19), resulting from infection by the new coronavirus, has profoundly disrupted the normal course of human life. Literature reports indicate that a substantial proportion, ranging from 5% to 30%, of patients diagnosed with COVID-19 necessitate admission to intensive care units (ICUs) [1,2]. Furthermore, certain patients, particularly those requiring invasive mechanical ventilation, are susceptible to secondary invasive fungal infections, such as pulmonary aspergillosis [3,4]. In the present study, we aimed to explore the risk factors associated with *Aspergillus* infection, explore parameters such as the length of hospital stay and hospitalization costs, and assess the impact of *Aspergillus* infection on survival duration.

Methodology

Research participants

A total of 50 patients were admitted to the Emergency Intensive Care Unit of our hospital due to COVID-19 between December 1, 2022, and July 31, 2023.

Inclusion criteria

Patients who met any of the following criteria were qualified for screening: (1) All patients included in the study met the diagnostic criteria outlined in the 10th edition of the diagnostic criteria for severe or critical cases of COVID-19: This involved presenting clinical manifestations indicative of COVID-19 infection, having positive COVID-19 nucleic acid results, and exhibiting any of the following conditions: shortness of breath, a respiratory rate > 30 times/min; PaO2/FiO2 ≤ 300 mmHg; shock; or other organ failure. (2) Definition of *Aspergillus* infection: In accordance with the clinical guidance and expert consensus on COVID-19-associated *Aspergillus* infection established by ECMM/ISHAM (European Confederation of Medical Mycology/International Society for Human and Animal Mycology) in 2020 [5], the diagnosis of *Aspergillus* infection is confirmed upon the detection of *Aspergillus* in sputum using microscopic examination. Grain stain was used to confirm the presence of *Aspergillosis*. In our patients, no *Aspergillus* was detected in sputum samples during the initial stage of COVID-19. The distinction between *Aspergillus* infection and *Aspergillus* colonization is determined based on relevant clinical manifestations. Considering the

persistence of lung infection despite the use of antibiotics, a clinical diagnosis of *Aspergillus* colonization was made. Patients were treated with voriconazole 200 mg every 12 hours.

Exclusion criteria

Patients who met any of the following criteria were excluded, as they often have compromised immune systems, which increases their susceptibility to *Aspergillus* infections: (1) Patients who tested positive for nucleic acids and were admitted to the hospital with concurrent diseases lacking any signs of pneumonia. (2) Mild to moderate COVID-19. (3) History of neutropenia prior to coronavirus infection. (4) History of organ transplantation prior to coronavirus infection. (5) History of hematologic malignancy. (6) Patients with tumors who are undergoing chemoradiotherapy.

Sputum sampling

Tracheal suctioning through bronchoscopy was performed for intubated ventilator patients, while deep cough sputum was collected after mouth rinsing for non-intubated patients.

Statistical methods

Statistical analysis was conducted using SPSS 27.0 software. Measurement data are presented as mean ± standard deviation. The normality of data was examined before statistical analysis and all data complied with normal distribution. The t-test was used for analysis. Count data are expressed as [case (%)], and the chi-squared test was used. A significance level of $p < 0.05$ was considered as significant difference. Logistic regression analysis was used to assess the risk factors associated with *Aspergillus* infection, with a significance threshold set at $p < 0.05$. The Kaplan–Meier survival curve was used to compare the survival time between the two groups.

Results

Clinical data

This group comprised of 33 males and 17 females, with an average age of (74.16 ± 11.28) years. Among

Table 1. Comparison of fundamental clinical data between the two groups.

	***Aspergillus* infection group (n = 10)**	**Non-*Aspergillus* infection group (n = 40)**	**t/χ^2**	***p***
General condition				
Sex			0.089	0.765
Male	7(70%)	26(65%)		
Female	3(30%)	14(35%)		
Age	74.70 ± 14.14	74.03 ± 10.66	0.168	0.868
Previous history				
Smoking	4(40%)	7(17.5%)	2.36	0.124
Tumor	3 (30%)	9(22.5%)	0.247	0.619
Diabetes mellitus	9(90%)	21(52.5%)	4.688	0.03
Hypertension	8(80%)	23(57.5%)	1.179	0.190
CKD	4(40%)	11(27.5%)	0.595	0.440
Autoimmune diseases	2(20%)	0(0%)	8.333	0.004
Condition on admission				
HR	85.40 ± 20.09	83.45 ± 18.29	0.296	0.769
MAP	95.03 ± 11.99	95.11 ± 12.23	-0.017	0.986
APACHEII scores	14.25 ± 7.059	17.60 ± 8.435	-1.159	0.203
SOFA scores	4.08 ± 2.759	6.10 ± 5.363	-1.156	0.099
Oxygenation index	119.0 ± 72.75	207.9 ± 120.90	-2.217	0.031
Total white blood cell count	8.36 ± 4.14	9.27 ± 4.66	-0.565	0.574
Total lymphocyte count	0.548 ± 0.346	0.872 ± 0.477	-2.01	0.05
CRP	85.35 ± 78.63	66.10 ± 50.07	0.963	0.34
Cr	123.4 ± 124.39	97.68 ± 99.14	0.697	0.489
Mechanical ventilation				
Invasive ventilations person-time	4(40%)	9(22.5%)	1.273	0.259
Duration of mechanical ventilation (days)	15.25 ± 9.95	10.44 ± 5.73	1.122	0.286
Occurrence of complications				
EF%	60.9 ± 9.83	61.10 ± 11.43	-0.051	0.96
Thrombosis of lower limbs person-time	4(40%)	11(27.5%)	0.595	0.44
AKI person-time	2(20%)	7(17.5%)	0.034	0.854
Multidrug-resistant infections person-time	6(60%)	13(32.5%)	2.568	0.109
Treatment				
Duration of steroid use (days)	13.8 ± 5.35	6.13 ± 5.81	3.789	0.001
Vasoactive drug uses person-time	5(50%)	12(30%)	1.426	0.232
Vasoactive drugs (days)	8.8 ± 10.55	6.58 ± 6.10	0.552	0.589

CKD: chronic kidney disease; HR: heart rate; MAP: mean arterial pressure; APACHEII: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; CRP: C-reactive protein; Cr: creatinine; EF: ejection fraction; AKI: acute kidney injury.

these patients, 13 patients underwent invasive mechanical ventilation, and vasoactive drugs were administered to 17 patients. A total of 50 patients diagnosed with COVID-19, with an average age of (74.16 ± 11.28) years were enrolled in this study. Among them, 11 (22%) had a history of smoking, 12 (24%) had a history of malignancy, 30 (60%) had a history of diabetes mellitus, 31 (62%) had a history of hypertension, 15 (30%) had a history of chronic kidney diseases, and 2 (4%) had a history of autoimmune diseases. Of the enrolled patients, 13 (26%) required mechanical ventilation, and 17 (34%) received vasoactive drugs. The *Aspergillus* infection group comprised of 10 (20%) patients. All 10 cases in this study exhibited *Aspergillus* in sputum, including 8 cases of *A. fumigatus*, 1 case of *A. niger*, and 1 case of *A. terreus*. The non-*Aspergillus* infection group comprised of 40 (80%) patients. Detailed clinical data for both groups are presented in Table 1.

Univariate analysis revealed that diabetes mellitus, autoimmune diseases, oxygenation index on the day of admission to the ICU, total lymphocyte count, and duration of steroid use were associated with *Aspergillus* infection. Patients with a history of diabetes mellitus had a higher risk of *Aspergillus* infection compared to those without (90% vs. 52.5%; $\chi^2 = 4.688$, $p < 0.05$). Similarly, patients with a history of autoimmune diseases had an increased risk of *Aspergillus* infection compared to those without (20% vs. 0%; $\chi^2 = 8.333$, $p < 0.05$). A lower oxygenation index on the day of admission to the ICU correlated with a higher risk of *Aspergillus* infection (119.0 ± 72.75 vs. 207.9 ± 120.90; t = -2.217, $p < 0.05$). Additionally, a lower lymphocyte count on the day of admission to the ICU was associated with a higher risk of *Aspergillus* infection (0.548 ± 0.346 vs. 0.872 ± 0.477; t = -2.01, $p < 0.05$). Furthermore, an extended duration of steroid use was linked to a higher risk of *Aspergillus* infection (13.8 ± 5.35 vs. 6.13 ± 5.81; t = 3.789, $p < 0.05$).

Analysis of risk factors for Aspergillus infection

Multivariate analysis, using logistic regression for variable selection, indicated a correlation between *Aspergillus* infection and a history of diabetes mellitus, as well as the duration of steroid use (Table 2). For patients diagnosed with COVID-19, the risk of *Aspergillus* infection escalated by 25.6% for each additional day of steroid use. Patients with a history of diabetes mellitus demonstrated a 9.708-fold increased likelihood of developing *Aspergillus* infection compared to those without such a medical history, although this difference did not achieve statistical significance.

Comparison of the number of days of ICU stay and hospitalization cost

In the comparison of the duration of ICU stay and hospitalization costs between the *Aspergillus* infection group and the non-*Aspergillus* infection group, the *Aspergillus* infection group exhibited a longer ICU stay, of 21.5 ± 10.82 days, in contrast to the non-*Aspergillus* infection group, which had a mean ICU stay of 14.03 ± 6.75 days. This difference was statistically significant ($p < 0.05$) (Table 3).

Kaplan–Meier survival curves of the Aspergillus infection group and non-Aspergillus infection group

Within the *Aspergillus* infection group, 5 (50%) patients died within 28 days, while in the non-*Aspergillus* infection group, 7 (17.5%) patients experienced mortality within the same timeframe. Significantly, *Aspergillus* infection exerted an impact on the survival duration of patients diagnosed with COVID-19 who were critically ill, with a notable difference between the two groups ($p < 0.05$). The survival curves for both groups are depicted in Figure 1.

Discussion

Invasive *Aspergillus* infection is well-established in populations characterized by prolonged neutropenia, hematologic malignancies, allogeneic stem cell or solid

Table 2. Risk factors for *Aspergillus* infection.

Item	Correlation coefficient	Standard deviation	OR	*p*
Diabetes mellitus	2.273	1.234	9.708	0.065
Duration of steroid use (days)	0.228	0.084	1.256	0.006

Table 3. Comparative analysis of the ICU stay duration and hospitalization expenses between the two groups.

	Aspergillus infection group (n = 10)	Non-Aspergillus infection group (n = 40)	t/χ^2	*p*
Duration of hospital stay (days)	21.5 ± 10.82	14.03 ± 6.75	2.752	0.008
Total hospitalization cost (in RMB)	102851 ± 68069	57542 ± 44747	2.565	0.013

organ transplantation, long-term use of steroids, and patients with hereditary or congenital severe immunodeficiencies, including those with immune factor deficiencies [6-9].

Recent literature highlights that viral pneumonia, including COVID-19, increases susceptibility to bacterial and fungal infections, such as invasive pulmonary aspergillosis (IPA) [8-11]. Studies, including one by Schauwvlieghe *et al.*, indicate that influenza independently poses a risk for IPA, with a 90-day mortality rate twice that of non-influenza-associated aspergillosis.

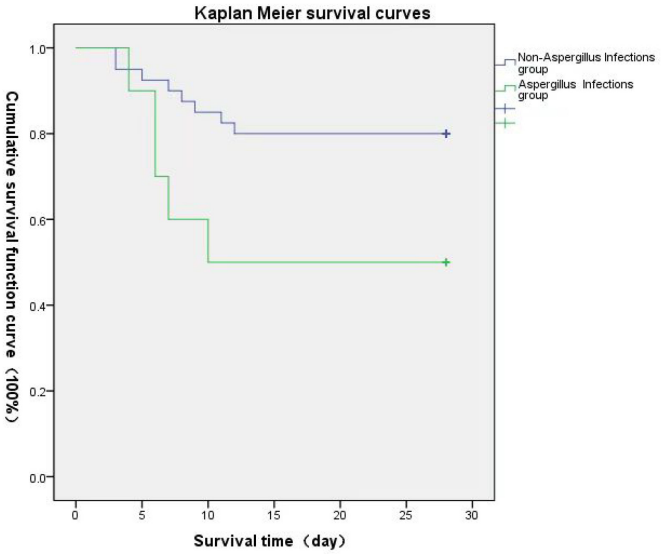
Given the clinical similarities between COVID-19 and influenza, both characterized by acute respiratory distress syndrome (ARDS), lymphopenia, bilateral pulmonary infiltrates, sepsis, and multiple organ failure, there is a rationale to suspect susceptibility to *Aspergillus* in patients with COVID-19 who are critically ill [12]. Mechanistically, viral-induced damage to respiratory epithelium and impairment of ciliary movement, along with local or systemic immune dysfunction, may contribute to *Aspergillus* invasion [13-15].

In this study, we identified *Aspergillus* infection in 20% of patients with COVID-19 who were critically ill and admitted to the ICU, a finding consistent with a multicenter study by the US Centers for Disease Control and Prevention, which reported a 15% incidence in patients with COVID-19 hospitalized in the ICU [4]. Univariate analysis indicated a higher prevalence of comorbid diabetes mellitus and autoimmune diseases in patients with COVID-19 with *Aspergillus* infection, potentially linked to exacerbated immune dysregulation post-COVID infection, a hypothesis supported by existing literature.

The findings suggest a reduction in the T-cell population among patients with COVID-19, concomitant with decreased lymphocyte counts and functional deficits, especially in critically ill individuals [15-17]. Severe lymphopenia is a recognized risk factor for predicting invasive fungal infections in patients with hematologic malignancies. The results of our study corroborate these findings, revealing a significantly lower lymphocyte count in the *Aspergillus* infection group compared to the non-*Aspergillus* infection group, which is consistent with the results in the literature.

Systemic steroids have become a standard therapeutic approach for patients with severe COVID-19, with reports indicating that 46% of such patients who are critically ill have been subjected to steroid treatment [13-15,18]. Steroids, while essential in managing severe COVID-19, are concurrently

Figure 1. Kaplan–Meier survival curves of the non-*Aspergillus* infection group and the *Aspergillus* infection group.



associated with immunosuppression, heightening the risk of *Aspergillus* infection. Raeseok highlighted that the daily administration of high-dose steroids serves as a predictor for COVID-19-related pulmonary aspergillosis, significantly correlating with elevated mortality rates [19]. This observation aligns with our study results, wherein the *Aspergillus* infection group exhibited a significantly prolonged duration of steroid use compared to the non-*Aspergillus* infection group.

Furthermore, the oxygenation index in patients with COVID-19 with *Aspergillus* infection was notably lower compared to those without *Aspergillus* infection. This lower oxygenation index may contribute to a heightened likelihood of resorting to invasive ventilators and vasoactive drugs in these patients, albeit there was no statistical significance between the two groups. Importantly, these interventions are directly linked to prognosis. Our findings suggest that the mortality and hospitalization costs of patients with COVID-19 with *Aspergillus* infection were significantly higher than those in the non-*Aspergillus* infection group. The findings suggest that pulmonary *Aspergillus* infection is a prevalent co-infection in patients with COVID-19 who are critically ill and requiring ICU admission. This co-infection is associated with an increased risk of mortality, which aligns with the results of our study [16].

Conclusions

In conclusion, our study showed that patients with COVID-19 with a history of diabetes mellitus face a high risk of concurrent *Aspergillus* infection. Prolonged

steroid use is associated with an increased likelihood of concurrent *Aspergillus* infection. Moreover, patients with *Aspergillus* infection exhibit more severe diseases, higher hospitalization costs, and a greater mortality rate compared to those without *Aspergillus* infection. These findings suggest that *Aspergillus* presence in sputum is a valuable clinical warning sign, particularly in COVID-19 cases, associated with higher mortality and poorer prognosis. Additional diagnostic measures, such as the serum galactomannan test and alveolar lavage fluid galactomannan, alongside sputum findings, may enhance sensitivity and specificity.

Limitations

The relatively small sample size limits the generalizability of our findings and may result in underpowered analyses. The results may be subject to bias, necessitating further investigations with larger sample sizes in the future. Additionally, the diagnostic criteria for *Aspergillus* infection were dependent on sputum culture, which may not effectively differentiate between colonization and true infection. Thirdly, the clinical diagnosis alone may not distinguish between invasive pulmonary aspergillosis and other conditions. Further investigations accounting for potential confounders are necessary.

Acknowledgements

We would like to acknowledge the hard and dedicated work of all the staff that implemented the intervention and evaluation components of the study.

Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon request.

Authors' contributions

Qiu-mei Cao and Rui-ming Xu conceived the idea and conceptualized the study. Rui-ming Xu, Qing-qing Ge, and Yan-yun He collected the data. Xiao-li Yuan and Qing-qing Ge analyzed the data. Rui-ming Xu, Xiao-li Yuan and Yan-yun He made a statistical analysis of the data. Xiao-li Yuan drafted the manuscript, then Qiu-mei Cao and Xiao-li Yuan reviewed the manuscript. All authors read and approved the final draft.

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Conflict of interests

No conflict of interests is declared.

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