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ORIGINAL ARTICLE

Fungal coinfections among patients with COVID-19: demographics, risk factors and outcomes

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Abstract

Introduction: The COVID-19 pandemic has caused a rise in secondary infections, including invasive fungal diseases (IFDs), which have greatly increased morbidity and mortality. This study aimed to explore the demographics, risk factors and outcomes of IFDs in COVID-19 patients admitted to our centre. *Materials and Methods:* We retrospectively reviewed data from PCR-confirmed category 4 or 5 COVID-19 patients between 2020 and 2023 who also had positive mycology cultures or serology. Patients with positive fungal tests more than 90 days after their initial COVID-19 diagnosis were excluded. *Results:* Among 5,075 PCR-positive COVID-19 patients, 23 (0.45%) met the criteria. Of these, 15 (65.2%) had candidiasis, seven (30.4%) aspergillosis, and one (4.3%) *Exophiala* fungaemia. No mucormycosis cases were identified. The male-to-female ratio of IFDs was 2.8:1, with ages ranging from 26 to 77 years (mean 59.6). The interval between COVID-19 diagnosis and positive fungal test ranged from 3 to 38 days, averaging 12.6 days for candidiasis and 16 days for aspergillosis (difference not statistically significant). Only acute kidney injury was significantly linked to candidiasis. Common factors across all cases included indwelling vascular catheters (95.7%), ICU admission (91.3%), mechanical ventilation (87%), lung diseases (65.2%), kidney impairment (60.9%), poorly controlled diabetes (34.8%), and liver impairment (26.1%). Overall mortality was 91.3% (100% for aspergillosis and *Exophiala* fungaemia, 86.7% for candidiasis). *Conclusion:* Although IFD prevalence in COVID-19 patients is low, its high morbidity and mortality make it a critical concern. Early identification of risk factors may help reduce its occurrence and improve outcomes.

Keywords: COVID-19, invasive fungal diseases, *Aspergillus, Candida, Exophiala,* fungaemia

INTRODUCTION

The COVID-19 pandemic has led to a significant increase in secondary infections, especially invasive fungal diseases (IFDs), which substantially raise morbidity and mortality among critically ill and immunocompromised patients. The main fungal complications noted in COVID-19 patients are COVID-19-associated pulmonary aspergillosis (CAPA), mucormycosis (CAM), and candidiasis (CAC).[1] The incidence of these infections varies widely according to geographical location, patient demographics, and diagnostic capacities.[2] Early CAPA cases emerged in China in the early 2000s[3], with studies reporting CAPA rates ranging between 3.8% and 34% in ICU patients, particularly those requiring mechanical ventilation.[4] CAM became especially prominent during the pandemic's second wave in India, where its prevalence reached 0.27% among hospitalised COVID-19 patients.[5] CAC incidence is elevated in critically ill COVID-19 patients with factors such as mechanical ventilation, indwelling central venous catheters, and immunosuppressive therapies, compared to non-COVID patients.[6] Notably, infections with non-albicans *Candida* species like *Candida auris* and *Candida glabrata* are increasingly reported, with outbreaks of *C. auris* in some hospitals.[7]

Several risk factors contribute to IFD susceptibility in COVID-19 patients. The SARS-CoV-2 virus impairs immune function,

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weakens antifungal defenses, while prolonged corticosteroid use (e.g., dexamethasone) further suppresses immunity and increases infection risk.[8] Diabetes mellitus, often present in severe COVID-19, is a key risk factor for mucormycosis.[9] Extended ICU stays, mechanical ventilation, broad-spectrum antibiotic use, and disruptions of normal microbial flora create additional opportunities for fungal overgrowth and infection.[10] Diagnosing these fungal infections proves difficult. CAPA diagnosis relies on bronchoalveolar lavage galactomannan testing, fungal cultures, and PCR; however, sampling is challenging in intubated patients.[11] CAM diagnosis is based on clinical evaluation, biopsy, and histopathology[12], while candidemia is detected via blood cultures, a method with only about 50% sensitivity despite being the gold standard.[13]

Effective management and prevention of IFDs in COVID-19 require a comprehensive approach. Antifungal stewardship programs are essential to optimise drug use and prevent resistance. Routine screening of high-risk ICU patients facilitates prompt identification. Corticosteroid therapy should be carefully managed, favouring short-term, low-dose regimens—particularly dexamethasone—to reduce fungal risk. Strict glycaemic control in diabetic patients and stringent infection control protocols in critical care settings is also critical in preventing fungal infections.[1] Mortality rates associated with IFDs in COVID-19 patients are alarmingly high. CAPA has a pooled mortality rate of around 51.2%, unaffected by host factors, test results, COVID-19 treatments, or antifungal use.[14] CAM shows a pooled mortality near 29.6%[15], while candidemia carries even higher risks, with ICU mortality rates up to 66.8%.[16]

The escalating IFD incidence during the pandemic has placed considerable strain on healthcare systems worldwide. Timely recognition, effective antifungal therapy, and comprehensive patient management are vital to improving outcomes. As SARS-CoV-2 continues to evolve and treatment strategies advance, ongoing epidemiological surveillance and research on fungal co-infections remain crucial. In Malaysia, data on IFD prevalence among COVID-19 patients are scarce. This study aims to evaluate the burden of fungal infections at our centre, offering valuable insights into local epidemiology and informing improved clinical strategies.

MATERIALS AND METHODS

Study Design and Setting

We performed a retrospective review of patient data from a healthcare facility in Kuala Lumpur, Malaysia. This tertiary teaching hospital, with a capacity of 1,000 beds, played a key role in managing COVID-19 cases during the pandemic.

Patient Selection

Using the hospital's laboratory information system, we identified patients who tested positive for COVID-19 from 2020 to 2023. We then narrowed our focus to those who had orders for mycology tests, such as blood and sterile fluid cultures, along with serological assessments like *Aspergillus* galactomannan antigen from serum and bronchoalveolar lavage, and *Candida* mannan antigen from serum. Each patient's medical records were reviewed to confirm they met our inclusion criteria.

Inclusion and Exclusion Criteria

Patients who tested positive for COVID-19 via RT-qPCR within the specified period and also had positive mycological test results were included in the study. We excluded patients whose mycology tests were conducted more than 90 days before or after their COVID-19 diagnosis. Additional exclusions included cases where COVID-19 severity was classified outside categories 4 or 5[17], cases where the relevance of fungal infection appeared doubtful, or where medical records were incomplete or unavailable.

Data Collection

We gathered demographic details including gender, age, and the interval between the initial positive COVID-19 test and the first positive mycology result. We also recorded potential risk factors for IFDs drawn from previous studies[10,18], including conditions like indwelling vascular catheters, ICU admission, mechanical ventilation, lung, kidney, or liver impairment, uncontrolled diabetes, trauma, iron overload, various malignancies, organ transplants, HIV/AIDS, and the use of certain medications (broad-spectrum antibiotics, azithromycin, corticosteroids, tocilizumab, colchicine, tofacitinib, or baricitinib). Laboratory parameters such as procalcitonin, neutrophil and lymphocyte counts, HbA1c, and serum ferritin levels collected within 48 hours of the mycology tests were also analysed.

Statistical Analysis

Data analysis was performed using online tools from Social Science Statistics (https://www.socscistatistics.com/). We first assessed the distribution of data using the Kolmogorov-Smirnov test. Continuous and categorical data were then analysed with appropriate statistical methods. A p-value of less than 0.05 was considered indicative of statistical significance.

RESULTS

Between 2020 and 2023, a total of 7,844 patients tested positive for COVID-19 using various diagnostic methods. In total, 9,105 positive test results were recorded: 5,075 from RT-qPCR, 3,065 from rapid test kits (RTK), and 965 from rapid molecular tests. Among these patients, 580 (7.4%) had mycology tests ordered, and 87 (15%) of those yielded positive mycological results. Of these 87 patients, 64 (73.6%) were excluded due to factors such as questionable relevance or weak association with COVID-19, negative RT-qPCR results, COVID-19 severity outside categories 4 or 5, a time gap exceeding 90 days between the positive COVID-19 test and positive mycology test, or missing medical records. Ultimately, 23 cases were included in the final analysis (see FIG 1).

A total of 24 positive mycology results were obtained from 23 patients, with one patient experiencing a mixed *Candida* bloodstream infection involving both *Candida albicans* and *C. glabrata*. Blood cultures accounted for the majority of positive tests (15 out of 24). Among the species identified from blood samples, *Candida tropicalis* was the most common, representing 46.7% of isolates. This was followed by *C. glabrata* at 26.7%, *C. albicans* at 13.3%, and C. *parapsilosis* at 6.7%. Additionally, *Exophiala dermatitidis*, a non-*Candida* species, was isolated from blood in 6.7% of cases. There was also one instance where *C. tropicalis* was isolated from the pleural fluid of a patient with pleural empyema. Beyond cultures, positive serological tests were recorded: serum *Aspergillus* galactomannan antigen in 75% of cases, bronchoalveolar lavage *Aspergillus* galactomannan antigen in 12.5%, and serum *Candida* mannan antigen in 12.5% (see Table 1).

The overall data followed a normal distribution, as confirmed by Kolmogorov-Smirnov tests with p-values greater than 0.05. Consequently, categorical variables were analysed using Fisher's Exact Test, while continuous variables were evaluated using the T-test for two independent means. Due to only one case of *Exophiala*, it was excluded from statistical analyses, focusing comparisons on

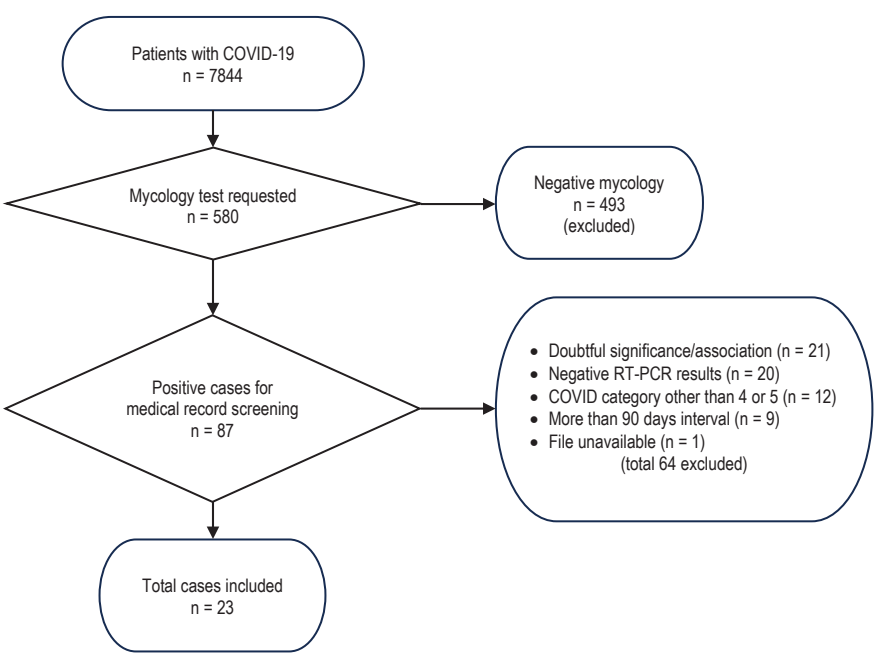

FIG 1. Flowchart of case selection

TABLE 1: Positive fungal tests from 23 patients

Fungal detection from various specimens	N (%)	Overall %
Culture – blood (n=15)		
Candida tropicalis	7 (46.7)	29.2
Candida glabrata	4 (26.7)*	16.7
Candida albicans	2 (13.3)*	8.3
Candida parapsilosis	1 (6.7)	4.2
Exophiala dermatitidis	1 (6.7)	4.2
Culture – pleural fluid (n=1)		
Candida tropicalis	1 (100.0)	4.2
Serology (n=8)		
Aspergillus antigen – serum	6 (75.0)	25
Aspergillus antigen – bronchoalveolar lavage	1 (12.5)	4.2
Candida antigen – serum	1 (12.5)	4.2
Total	24 (100.0)*	100.0

*One patient had mixed *C. albicans* and *C. glabrata* candidaemia

aspergillosis and candidiasis cases.

Male patients accounted for 73.9% of the cases, outnumbering females at 26.1%, with a male-to-female ratio of approximately 2.8:1. This gender distribution was consistent within both aspergillosis and candidiasis groups. The single *Exophiala* fungaemia case also involved a male patient. However, the higher proportion of males with IFDs was not statistically significant. Male patients tended to be younger, averaging 57.5 years, compared to females at 65.7 years, though this age difference was also not significant. The mean time from COVID-19 diagnosis to IFD detection was 13.4 days, ranging from 3 to 38 days. Aspergillosis cases had a longer average interval (16 days; 4 to 27 days) compared to candidiasis (12.6 days; 3 to 38 days) and the *Exophiala* case (6 days). These differences in timing did not reach statistical significance (see Table 2).

We examined the presence of risk factors linked to IFDs. As anticipated, the majority of IFD cases

TABLE 2: Demographic features of COVID-19-positive patients with invasive fungal diseases (IFDs)

Demographic features	All IFDs (n=23)	Asp (n=7)	Can (n=15)	Exo (n=1)	P-value
Male – n (%)	17 (73.9)	5 (71.4)	11 (73.3)	1 (100.0)	1.000
Female – n (%)	6 (26.1)	2 (28.6)	4 (26.7)	0 (0.0)	
Age – years	59.6±14.3 (26-77)	57.3±17.6 (26-75)	61.1±13.5 (27-77)	54	
Male age – years	57.5±15.2 (26-77)	55.8±19.0 (26-73)	58.6±14.8 (27-77)	54	0.578
Female age – years	65.7±10.3 (47-75)	61.0±19.8 (47-75)	68.0±5.2 (62-74)	-	
Duration between COVID-19 and IFD diagnosis – days	13.4±10.1 (3-38)	16.0±7.1 (4-27)	12.6±11.5 (3-38)	6	0.482

Plus-minus values are means±SD and unless stated otherwise, data in brackets are ranges
Asp, aspergillosis; Can, candidiasis; Exo, *Exophiala* fungaemia; IFDs, invasive fungal diseases

occurred in patients classified as Category 5, the most severe level of COVID-19 severity—71.4% for aspergillosis, 80% for candidiasis, and 100% for *Exophiala* fungaemia. Over 85% of patients with IFDs had indwelling vascular catheters, were admitted to the Intensive Care Unit (ICU), and required mechanical ventilation. Lung disease and kidney impairment were found in more than 60% of these patients, while poorly controlled diabetes and liver impairment affected over 25%. Among these, acute kidney injury was the only factor significantly linked to candidiasis development during COVID-19 infection (see Table 3). Notably, none of the patients with fungal coinfections had traditional risk factors such as hematological malignancies, solid organ or bone marrow transplants, or HIV/AIDS.

Regarding medications used during COVID-19 treatment, all patients received broad-spectrum antibiotics, more than 90% were treated with corticosteroids, about half took azithromycin, and some received immunomodulatory drugs. However, none of these therapies showed a significant association with the occurrence of IFDs. We also found no significant correlations between relevant laboratory parameters and the presence of IFDs (refer to Table 4).

We also assessed the antifungal treatments administered and patient outcomes. Most patients (73.9%) received fluconazole, typically as empirical therapy. In one instance, fluconazole was replaced with voriconazole after *Aspergillus* antigen was detected. Two additional aspergillosis cases were initially treated with voriconazole or amphotericin B. The patient with *Exophiala* fungaemia started on amphotericin B before being switched to itraconazole. The overall mortality rate was high at 91.3%, with aspergillosis and *Exophiala* fungaemia cases experiencing 100% mortality, and candidiasis cases showing an 86.7% mortality rate (see Table 5).

DISCUSSION

IFDs pose significant diagnostic challenges among COVID-19 patients, largely because their clinical signs and radiological features often overlap with those of severe COVID-19, making accurate identification difficult. In this study, among 7,844 patients testing positive for COVID-19, 87 (1.1%) had positive mycological test results. However, after detailed evaluation, 64 patients were excluded due to questionable links between the fungal infection and COVID-19. Reasons for exclusion included IFDs localised to non-systemic tissues without lung involvement, absence of antifungal treatment, likely false-positive fungal serology, uncertain or low COVID RT-PCR results, existing comorbidities independently increasing IFD risk, or fungal infections diagnosed more than 90 days after COVID-19 diagnosis. These exclusion criteria align with the Ministry of Health Malaysia's COVID-19 Management Guidelines, which categorise COVID-19 severity into five stages and exclude cases less likely to predispose to IFDs.[17]

As a result, only 23 of the 7,844 patients (0.3%) were identified with clinically significant IFDs associated with COVID-19. CAC was the most frequently observed IFD, found in 15 patients (1.91 cases per 1,000 admissions), followed by CAPA in 7 patients (0.89 cases per 1,000 admissions). There was also a single case of *Exophiala* fungaemia (0.13 cases per 1,000 admissions). Notably, no mucormycosis cases (CAM) were detected. The candidemia incidence was lower than reported in some other COVID-19 patient cohorts but exceeded rates observed in non-COVID-19 populations.[19] Similarly, CAPA incidence here was lower than in many previous reports.[20] This lower rate may reflect the strict inclusion and exclusion criteria we applied. Additionally, early in the pandemic, the absence of standardised CAPA diagnostic criteria contributed to variable reported prevalence. Before September 2020, studies on invasive pulmonary aspergillosis among ICU COVID-19 patients showed wide differences. The adoption of consensus definitions by the European Confederation of Medical Mycology (ECMM) and the International Society for Human and Animal Mycoses (ISHAM) contributed to a decline in reported CAPA rates. Nonetheless, differences between ICUs remain notable, likely influenced by regional variations in COVID treatment protocols, diagnostic accuracy, genetic predispositions, and environmental exposure to *Aspergillus*.[20]

Three particularly severe and rare cases in our study illustrate the complexity of fungal infections during COVID-19. The first involved a 68-year-old man, previously healthy, who developed *Candida tropicalis* pleural empyema alongside acute respiratory failure requiring mechanical ventilation and ICU care. Despite empirical broad-spectrum antibiotics, blood cultures and fungal serology were negative, with *Candida* isolated only from pleural fluid. Imaging

TABLE 3: Risk factors of COVID-19-positive patients with invasive fungal diseases (IFDs)

Risk factors for IFDs	All IFDs (n=23)	Asp (n=7)	Can (n=15)	Exo (n=1)	P- value
Underlying conditions					
COVID-19 category					1.000
COVID-19 category 5	18 (78.3)	5 (71.4)	12 (80.0)	1 (100.0)	
COVID-19 category 4	5 (21.7)	2 (28.6)	3 (20.0)	0 (0.0)	
Indwelling vascular catheter	22 (95.7)	7 (100.0)	12 (80.0)	1 (100.0)	0.522
ICU admission	21 (91.3)	7 (100.0)	13 (86.7)	1 (100.0)	0.545
Mechanical ventilation	20 (87.0)	6 (85.7)	13 (86.7)	1 (100.0)	1.000
Lung diseases	15 (65.2)	4 (57.1)	9 (60.0)	1 (100.0)	1.000
Pulmonary embolism	7 (30.4)	2 (28.6)	4 (26.7)	1 (100.0)	1.000
Pulmonary tuberculosis	3 (13.0)	1 (14.3)	2 (13.3)	0 (0.0)	1.000
COPD	1 (4.3)	1 (14.3)	0 (0.0)	0 (0.0)	0.318
Pneumothorax	2 (8.7)	0 (0.0)	1 (6.7)	1 (100.0)	1.000
Bronchial asthma	1 (4.3)	0 (0.0)	1 (6.7)	0 (0.0)	1.000
Pneumonia	1 (4.3)	0 (0.0)	1 (6.7)	0 (0.0)	1.000
Kidney impairment	14 (60.9)	**1 (14.3)**	**12 (80.0)**	1 (100.0)	**0.007**
Acute kidney injury	9 (39.1)	**0 (0.0)**	**8 (53.3)**	1 (100.0)	**0.022**
Chronic kidney disease	5 (21.7)	1 (14.3)	4 (26.7)	0 (0.0)	0.637
Poorly controlled diabetes	8 (34.8)	2 (28.6)	6 (40.0)	0 (0.0)	1.000
Liver impairment	6 (26.1)	0 (0.0)	5 (33.3)	1 (100.0)	0.135
Acute liver disease	3 (13.0)	0 (0.0)	3 (20.0)	0 (0.0)	0.523
Chronic liver disease	3 (13.0)	0 (0.0)	2 (13.3)	1 (100.0)	0.545
Major trauma	1 (4.3)	1 (14.3)	0 (0.0)	0 (0.0)	0.318
Solid organ malignancy	1 (4.3)	0 (0.0)	1 (6.7)	0 (0.0)	1.000
Iron overload	1 (4.3)	0 (0.0)	0 (0.0)	1 (100.0)	np
Haematological malignancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	np
Solid organ transplant	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	np
Bone marrow transplant	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	np
HIV/AIDS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	np
Drugs received					
Broad spectrum antibiotics	23 (100.0)	7 (100.0)	15 (100.0)	1 (100.0)	1.000
Corticosteroids	22 (95.7)	7 (100.0)	14 (93.3)	1 (100.0)	1.000
Azithromycin	11 (47.8)	2 (28.6)	8 (53.3)	1 (100.0)	0.371
Tocilizumab	9 (39.1)	3 (42.9)	6 (40.0)	0 (0.0)	1.000
Colchicine	3 (13.0)	0 (0.0)	2 (13.3)	1 (100.0)	0.150
Tofacitinib	2 (8.7)	2 (28.6)	0 (0.0)	0 (0.0)	0.170
Bacitinib	1 (4.3)	0 (0.0)	1 (6.7)	0 (0.0)	1.000

Data are displayed as n (%)

Asp, aspergillosis; Can, candidiasis; Exo, *Exophiala* fungaemia; IFDs, invasive fungal diseases; COPD, chronic obstructive pulmonary disease; np, not performed

TABLE 4: Laboratory findings of COVID-19-positive patients with invasive fungal diseases (IFDs)

Laboratory findings	All IFDs (n=23)*	Asp (n=7)*	Can (n=15)*	Exo (n=1)	P-value
Procalcitonin (ng/mL), n=19	9.9±15.1 (0.07-52.06)	4.1±5.3 (0.08-12.17)	8.4±14.6 (0.07-52.06)	0.4	0.373
Neutrophil count ($x10^9$/L), n=23	20.1±13.8 (3.5-61.4)	15.9±3.9 (11.6-22.0)	19.9±14.3 (3.5-61.4)	15.4	0.749
Lymphocyte count ($x10^9$/L), n=23	1.2±1.4 (0.1-5.5)	0.7±0.6 (0.1-1.7)	1.0±1.4 (0.2-5.5)	1.9	0.749
Neutrophil-lymphocyte ratio, n=23	20.1±13.8 (4.3-220.0)	65.3±78.7 (6.8-220	33.9±25.7 (4.3-93.3)	8.1	np
HbA1c (%), n=5	7.6±3.3 (4.9-11.4)	5.2±0.4 (4.9-5.4)	8.8±2.5 (6.5-11.4)	-	np
Serum ferritin (ug/L), n=20	2224.9±1638.5 (323-8612)	3055±2196.6 (487-6460)	2555.7±2478.9 (323-8612)	2487	0.529

*Data are displayed as mean ± SD (range)
Asp, aspergillosis; Can, candidiasis; Exo, *Exophiala* fungaemia; IFDs, invasive fungal diseases; np, not performed

showed necrotising pneumonia with empyema. Fluconazole was started, but the patient died. The second case was a 48-year-old man with multiple comorbidities including pulmonary tuberculosis, tension pneumothorax, diabetes, and acute kidney injury. After COVID-19 diagnosis, he was intubated and corticosteroid therapy was initiated. Although empirical fluconazole was given, blood cultures revealed mixed candidemia with *C. albicans* and *C. glabrata*. He died before echinocandin therapy could be started. The third case, reported in 2022, involved a 50-year-old COVID-19 patient with no underlying illnesses who developed fever, rapid breathing, and persistent low oxygen levels requiring intubation.[21] Chest X-ray showed diffuse bilateral lung infiltrates. Blood cultures grew *Exophiala dermatitidis*. Despite amphotericin B and itraconazole treatment, the patient died from severe pneumonia and multiorgan failure. These cases underscore the high mortality and diagnostic complexity of fungal empyema and candidemia in severely ill COVID-19 patients, regardless of comorbidities.

TABLE 5: Antifungal therapy and outcomes of COVID-19-positive patients with invasive fungal diseases (IFDs)

Antifungal therapy	All IFDs (n=23)	Asp (n=7)	Can (n=15)	Exo (n=1)	
Fluconazole, n (%)	16 (73.9)	3 (57.1)	13 (86.7)	0 (0.0)	
Fluconazole, then voriconazole, n (%)	1 (4.3)	1 (14.3)	0 (0.0)	0 (0.0)	
Voriconazole, n (%)	1 (4.3)	1 (14.3)	0 (0.0)	0 (0.0)	
Amphotericin B, n (%)	1 (4.3)	1 (14.3)	0 (0.0)	0 (0.0)	
Amphotericin B, then itraconazole, n (%)	1 (4.3)	0 (0.0)	0 (0.0)	1 (100.0)	
No antifungal therapy, n (%)	3 (13.0)	1 (14.3)	2 (13.3)	0 (0.0)	
Outcome	**All IFDs (n=23)**	**Asp (n=7)**	**Can (n=15)**	**Exo (n=1)**	**P-value**
Dead, n (%)	21 (91.3)	7 (100.0)	13 (86.7)	1 (100.0)	0.546
Alive, n (%)	2 (8.7)	0 (0.0)	2 (13.3)	0 (0.0)	

Asp, aspergillosis; Can, candidiasis; Exo, *Exophiala* fungaemia; IFDs, invasive fungal diseases

Our analysis revealed a statistically significant link between acute kidney injury (AKI) and candidiasis development in COVID-19 patients. COVID-19 profoundly affects renal function, with estimates suggesting 30-50% of patients experience AKI, which can lead to complications such as dialysis dependence and heightened risk of IFDs, especially candidiasis.[22,23] Kidney damage in COVID-19 arises from multiple mechanisms: direct viral infection of renal cells; inflammation; haemodynamic instability; hypoxia; nephrotoxic drugs including certain antibiotics (vancomycin, aminoglycosides, colistin) and antivirals (remdesivir, ritonavir); rhabdomyolysis; vascular injury from endotheliitis and microthrombosis; and immune-mediated glomerular and interstitial damage.[22,23] Moreover, COVID-19–related immunosuppression, excessive antibiotic and steroid use, and inflammatory dysregulation increase susceptibility to secondary infections including candidiasis. Additional AKI-associated factors like fluid overload, hospitalisation, mechanical ventilation, and dialysis catheter use further contribute. The cytokine storm seen in severe COVID-19 exacerbates immunosuppression, increasing secondary bacterial and fungal infection risks.[24]

Besides kidney injury, we identified other underlying conditions linked to IFD risk, though none showed statistically significant associations with specific IFD types (Table 3). Nevertheless, these comorbidities are known to impair immune defenses, potentially raising susceptibility to fungal infections.[18] Prior research has highlighted prolonged immunomodulatory treatments, including corticosteroids and various immunosuppressants, as contributors to IFD development.[10,25] In our cohort, use of immunomodulators—such as corticosteroids, azithromycin, tocilizumab, colchicine, tofacitinib, and baricitinib—showed no significant association with IFD type. Similarly, an Australian study found bacterial and fungal coinfections occurred at similar rates regardless of immunomodulator therapy, though patients receiving immunomodulators with coinfections had higher mortality (63.0%) than those without (15.4%; P = 0.038).[26] Consistent with this, our study observed higher mortality among patients with fungal coinfections (91.3%) compared to those without (56%, data not shown).

A recent study reported that elevated levels of C-reactive protein, procalcitonin, white blood cell counts, neutrophil-to-lymphocyte ratio, and systemic immune-inflammation index, along with lower albumin, were significantly associated with fungal coinfections. Although platelet counts were lower in coinfected patients, this was not statistically significant.[25] Contrastingly, our analyses did not find significant associations between these markers and IFD type (Table 4).

This study has some limitations inherent to its retrospective design, including potential confounding factors not measured (e.g., IL-6, TNF-α) and the lack of autopsy data, which limits precise determination of cause of death. Furthermore, the evolving nature of SARS-CoV-2 variants and improvements in clinical management and prevention were not accounted for. Larger, prospective studies are needed to better understand these associations.

In conclusion, COVID-19 introduces new risks for developing invasive fungal diseases through multiple mechanisms. Acute kidney injury emerged as a significant factor linked to candidiasis in these patients. Although the overall incidence of IFD was low, mortality rates remain alarmingly high. These findings highlight the urgent need for improved surveillance among patients with kidney injury and the establishment of standardized diagnostic guidelines to optimise antifungal treatment strategies.

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Author's contributions: Ding CH and Tzar MN conceptualised the study and participated in manuscript writing. Tzar MN, Wahab AA, Nordin A and Mohd Salleh AF performed literature review, data collection, data analysis and manuscript writing. Tzar MN and Ding CH reviewed and revised the manuscript.

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