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Clinical Features and Risk Factors of COVID-19-Associated Fungal Infections in Kidney Transplant Recipients

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Abstract: *Objective:* To investigate the clinical features, outcomes, and risk factors of fungal infections in kidney transplant recipients (KTRs) as a result of coronavirus disease 2019 (COVID-19). *Methods:* We retrospectively analyzed 54 KTRs with COVID-19 who were hospitalized at the China-Japan Friendship Hospital from December 1, 2022, to April 1, 2023. With a mean age of 50 ± 12 years, there were 43 men and 11 women participated. For KTRs with COVID-19, we employed multivariate logistic regression analysis to identify the risk factors. *Results:* Twenty (37.0%) patients in this study had fungal infections as a result of COVID-19. Patients with fungal infections had significantly higher rates of mortality (50.0%, 10/20 vs. 2.9%, 1/34, $P < 0.001$), acute respiratory distress syndrome (ARDS) (65.0%, 13/20 vs. 26.5%, 9/34, $P = 0.005$), and acute kidney injury (AKI) (60%, 12/20 vs. 23.5%, 8/34, $P = 0.007$) than those without fungal infections. The result of the multivariate analysis showed that the incidence of fungal infections in KTRs with COVID-19 was independently correlated with age (increased by 10 years, OR = 2.221), history of diabetes mellitus (OR = 12.293), ARDS (OR = 12.849), and bacterial co-infections (OR = 30.461). *Conclusion:* Compared to KTRs without fungal infections, those with COVID-19-related fungal infections had worse clinical courses and less favorable results. The conditions including bacterial co-infections, ARDS, older age, and comorbidity of diabetes mellitus increased the incidence of secondary fungal infections.

Keywords: COVID-19; Kidney transplant; Fungal infections; Clinical features; Risk factors

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1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has ravaged the world in recent years [1]. Even after receiving vaccination against SARS-CoV-2, kidney transplant recipients (KTRs), who are particularly vulnerable to COVID-19, remain at high risk of COVID-19-related mortality [2]. Recently, it was reported that a subset of patients were involved with fungal infections owing to COVID-19. These infections were referred to as COVID-19-associated fungal infections. At the onset of the epidemic, China was the first country to report multiple cases

of *Aspergillus* co-infections in COVID-19 patients, all of whom had negative outcomes [3]. Since then, there has been a rise in the identification of COVID-19-associated fungal infections, particularly in immunosuppressed populations, raising widespread concerns about the serious medical burden [4-7]. However, the clinical features, outcomes, and risk factors of COVID-19-associated fungal infections in KTRs were unclear.

According to reports, epithelial barrier degradation, immune system dysregulation, immunosuppressive therapy, overuse of broad-spectrum antibiotics, invasive mechanical ventilation, and host-related comorbidities have all been linked to opportunistic fungal infections associated with COVID-19 infections [8,9]. The primary pathogens were *Aspergillus*, *Candida*, and *Mucorales*, and the diagnosis could be supported by the positive results of a laborious fungal culture [10]. Fungal infections, which were frequently in COVID-19 patients, were characterized by fever, cough, and dyspnea [11]. Furthermore, the diffuse lung damage induced by SARS-CoV-2 may conceal the imaging findings of fungal disease [8,9], and the atypical computed tomography (CT) features of SARS-CoV-2, including ground-glass opacities (GGO) and nodular lesions, were similar to those of fungal infections [12]. Therefore, it was difficult to diagnose these superinfections based on clinical, pathogenic, and radiological manifestations, and it was crucial to identify high-risk individuals as soon as possible.

The treatment of COVID-19-associated fungal infections mostly consists of immunosuppression induction, antifungal drug administration, respiratory support, and human immunoglobulin utilization. The survival and outcome of the target organ were greatly enhanced by prompt diagnosis and therapy. For COVID-19 high-risk patients, antifungal prophylactic techniques were suggested as a possible treatment [13]. Before beginning antifungal therapy in KTRs, drug-drug interactions and nephrotoxicity must be taken into account, particularly in patients with acute kidney injury (AKI) [14,15].

Compared to severe COVID-19 patients without secondary fungal infections, patients with COVID-19-associated fungal infections have been documented to have longer hospital stays, greater rates of ICU admission, longer durations of mechanical ventilation, and increased death [16-18]. Trujillo *et al.* reported that KTRs as an immunosuppressive population appear to have a worse prognosis than the general population [19].

Until now, few case reports and case series have been published to describe KTRs who had secondary fungal infections after COVID-19. It was unknown what the general clinical course, outcomes, and risk factors of fungal infections associated with COVID-19 in KTRs were. Herein, we conducted a retrospective cohort study to investigate the prevalence, clinical features, prognosis, and risk factors of COVID-19-associated fungal infections in KTRs.

2. Materials and methods

2.1. Subjects and data collection

Fifty-four KTRs with COVID-19 who were hospitalized at China-Japan Friendship Hospital were retrospectively enrolled in this study between December 1, 2022, and April 1, 2023. Following the COVID-19 diagnosis, all patients were categorized into two groups: those with fungal infections (n = 20) and those without fungal infections (n = 34), based on the positive results of fungi in body fluids. The clinical characteristics, laboratory indexes, imaging features, fungi species, therapies, and prognoses of the two groups were reviewed and compared. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

2.2. Definitions

The diagnostic criteria for COVID-19 were the positive results of real-time polymerase chain reaction (RT-PCR) assay of nasopharyngeal and oropharyngeal swab specimens. Fungal/bacterial infections were diagnosed when patients had clinical symptoms and presented infections with positive pathogenic findings of fungi/bacteria in any of the following tests, including bronchoalveolar lavage culture, sputum culture, blood culture, and metagenomics next-generation sequencing of bronchoalveolar lavage.

AKI was classified according to the Kidney Disease Improving Global Outcomes (KDIGO) guideline, which was defined as any of the following conditions (not graded): increase in serum creatinine (SCr) by ≥ 0.3 mg/dl (≥ 26.5 μmol/l) within 48 hours; or increase in SCr to ≥ 1.5 times baseline, which was known or presumed to have occurred within the prior seven days; or urine volume < 0.5 ml/kg/hour for six hours [20]. Acute respiratory distress syndrome (ARDS) was defined as arterial oxygen tension < 60 mmHg or oxygenation index < 300 [21].

2.3. Statistical analysis

Data analysis was conducted using the statistical software SPSS27.0. The χ^2 test was used to compare qualitative variables that were reported as numbers (n) and percentages (%). Quantitative variables were summarized with medians and interquartile ranges [Md (IQR)] and the Mann–Whitney U test was used for comparison between the two groups. Logistic regression was used to analyze the risk factors for COVID-19-associated fungal infections in KTRs, and ROC curves were employed to assess the diagnostic value of the risk factors that were promising predictors of secondary fungal infections in patients. The *P* value of less than 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

This study comprised 54 hospitalized KTRs who had been diagnosed with COVID-19. There were 43 (79.6%) male patients. The median age and body mass index (BMI) of the enrolled patients were 50 ± 12 years and 23.2 ± 3.2 kg/m^2. The main comorbidities were hypertension (49/54, 90.7%), diabetes mellitus (25/54, 46.3%), cardiovascular disease (7/54, 11.6%), and cerebral disease (6/54, 11.1%). The median interval from kidney transplant to the COVID-19 episode was 227 (22, 565) days (**Table 1)**. Compared to KTRs without fungal co-infections, KTRs with fungal co-infections were predominantly male (100.0%, 20/20 vs. 67.7%, 23/34, $P = 0.004$) and significantly older [57 (47,60) vs. 47 (37,58) years, $P = 0.029$]. In addition, the group with fungal infections had a significantly higher rate of diabetes mellitus in the past (65.0%, 13/20 vs. 35.3%, 12/34, $P = 0.035$). There was no statistical difference between the two groups in terms of immunosuppressive therapy, the rate of acute rejection, and delayed graft function. In our study, the kidneys were obtained from deceased unrelated donors, with 75.92% coming from donation after circulatory death (DCD), 16.67% from donation after brain death (DBD), and 7.41% from donation after brain and cardiac death (DBCD).

Table 1. Clinical features of kidney transplantation recipients with COVID-19 ($N = 54$)

	Fungal infection group ($n = 20$)	Non-fungal infection group ($n = 34$)	P value
Demographics			
Male, *n* (%)	20 (100)	23 (67.7)	**0.004**
Age, years	57 (47–60)	47 (37–58)	**0.029**
Height, cm	170 (168–176)	170 (164–175)	0.264
Weight, kg	67.0 (60.8–74.0)	67.5 (60.0–75.3)	0.907
BMI, kg/m^2	22.6 (21.1–24.0)	23.2 (20.6–25.3)	0.629
Co-morbid conditions			
Hypertension, *n* (%)	19 (95.0)	30 (88.2)	0.732
Diabetes mellitus, *n* (%)	13 (65.0)	12 (35.3)	**0.035**
Cardiovascular disease, *n* (%)	4 (20.0)	3 (8.8)	0.446
Cerebral disease, *n* (%)	4 (20.0)	2 (5.9)	0.252
Transplantation characteristics			
Tacrolimus, *n* (%)	19 (95.0)	33 (97.1)	1.000
Cyclosporine, *n* (%)	1 (5.0)	1 (2.9)	1.000
Sirolimus, *n* (%)	2 (10.0)	6 (17.7)	0.713
Mycophenolate, *n* (%)	20 (100.0)	31 (91.2)	0.287
Mizoribine, *n* (%)	0 (0.0)	2 (5.9)	0.528
Steroids, *n* (%)	20 (100.0)	34 (100.0)	1.000
Delayed graft function, *n* (%)	6 (30.0)	4 (11.8)	0.193
Acute rejection, *n* (%)	9 (45.0)	8 (23.5)	0.101
Time after transplantation, days	227 (23–549)	224 (19–607)	0.778
Symptoms			
Fever, *n* (%)	18 (90.0)	32 (94.1)	0.984
Cough, *n* (%)	14 (70.0)	30 (88.2)	0.193
Dyspnea, *n* (%)	19 (95.0)	27 (79.4)	0.246
Hemoptysis, *n* (%)	3 (15.0)	1 (2.9)	0.273
Diarrhea, *n* (%)	5 (25.0)	7 (20.6)	0.706
Comorbidities and complications			
ARDS, *n* (%)	13 (65.0)	9 (26.5)	**0.005**
AKI, *n* (%)	12 (60.0)	8 (23.5)	**0.007**
Bacterial infection, *n* (%)	11 (55.0)	4 (11.8)	**< 0.001**

Abbreviations: BMI, body mass index; ARDS, acute respiratory distress syndrome; AKI, acute kidney injury.

3.2. COVID-19-associated fungal infections

A total of 20 (37%) KTRs developed COVID-19-associated fungal infections. The fungal pathogens comprised *Candida* (12/20, 60%), *Aspergillus* (11/20, 55%), and *Mucorales* (1/20, 5%). Candida mainly included *Candida albicans* (8/13, 61.5%), *Candida tropicalis* (2/13, 15.4%), *Candida paraphimosis* (2/13, 15.4%), and *Candida glabrata* (1/13, 7.7%). *Aspergillus* encompassed *Aspergillus fumigatus* (7/15, 46.7%), *Aspergillus flavus* (4/15, 26.7%), *Aspergillus niger* (3/15, 20.0%), and *Aspergillus nidulans* (1/15, 6.6%).

3.3. Clinical presentations

Fever (50/54, 92.6%), dyspnea (46/54, 85.2%), and cough (44/54, 81.5%) were the most common COVID-19-related symptoms and a proportion of patients presented diarrhea (12/54, 22.2%) and hemoptysis (4/54, 7.4%). There was no difference in clinical symptoms between the group with fungal infections and the group without fungal infections.

Twenty-two (40.7%) patients developed ARDS, 20 (37.0%) KTRs developed AKI, and 15 (27.8%) cases were diagnosed with bacterial infections. The fungal infection group had a significantly higher incidence of ARDS (65.0%, 13/20 vs. 26.5%, 9/34, $P = 0.005$), AKI (60.0%, 12/20 vs. 8/34, $P = 0.007$) and bacterial co-infections (55.0%, 11/20 vs. 11.8%, 4/34, $P < 0.001$).

3.4. Auxiliary examination

Compared with the others, KTRs with secondary fungal infections demonstrated lower lymphocyte count [0.29 (0.20–0.56) vs. 0.50 (0.36–0.99) x10^9/L, $P = 0.037$], lower albumin levels [30.1 (26.3, 32.6) vs. 33.1 (29.2, 37.9) g/L, $P = 0.008$], and higher blood urea levels [17.33 (13.65, 28.50) vs. 11.64 (8.07, 18.54) mmol/L, $P = 0.007$]. Quantitative analysis of T-lymphocytes was performed in 39 of the 54 KTRs. The $CD4^+$ T lymphocyte count [90 (51, 213) vs. 245 (90, 570)/μL, $P = 0.47$] and the $CD8^+$ T lymphocyte count [92 (69,207) vs. 266 (121, 457)/μL, $P = 0.19$] were significantly lower in the fungal infection group.

Following admission, all patients had a CT scan of the chest, and the most common radiographic findings were patch shadow (38/54, 70.4%), ground glass opacities (31/54, 57.4%), pleural effusion (22/54, 40.7%), air bronchogram (21/54, 38.9%), consolidation (15/54, 27.8%) and pleural lesions (13/54, 24.1%). The air bronchogram sign (60.0%, 12/20 vs. 44.1%, 9/34, $P = 0.015$) was more frequent in patients with secondary fungal infections (**Table 2**).

Table 2. Laboratory and imaging analysis of kidney transplantation recipients with COVID-19 ($N = 54$)

Clinical symptom	Fungal infection group ($n = 20$)	Non-fungal infection group ($n = 34$)	P value
Laboratory examination			
WBC, ×10^9/L	5.70 (3.68–8.40)	5.91 (4.10–8.19)	0.879
NEUT, ×10^9/L	4.58 (2.92–7.32)	4.49 (3.04–7.19)	0.914
LYMPH, ×10^9/L	0.29 (0.20–0.56)	0.50 (0.36–0.99)	**0.037**
NEUT %	87.9 (80.5–91.4)	83.7 (71.4–91.3)	0.452
LYMPH %	6.2 (4.1–11.7)	10.3 (4.4–17.6)	0.149
Hemoglobin, g/L	115 (97–127)	110 (96–122)	0.513
Platelet, ×10^9/L	188 (142–210)	149 (121–170)	**0.043**
CRP, mg/L	67.24 (43.37–87.01)	69.86 (22.73–120.19)	0.907
PCT, ng/ml	0.31 (0.11–0.97)	0.18 (0.10–0.68)	0.416
Albumin, g/L	30.1 (26.3–32.6)	33.1 (29.2–37.9)	**0.008**
Serum creatinine, μmol/L	232.2 (137.3–541.5)	142.5 (121.5–248.9)	0.062
eGFR, ml/min/1.73m^2	26.75 (9.72–50.10)	41.66 (23.94–57.43)	0.060
Urea, mmol/L	17.33 (13.65–28.50)	11.64 (8.07–18.54)	**0.007**
Imaging examinations, *n* (%)			
Ground glass opacity	12 (60.0)	19 (55.9)	0.768
Patch shadow	17 (85.0)	21 (61.8)	0.134
Consolidation	7 (35.0)	8 (23.5)	0.363
Pleural lesions	7 (35.0)	6 (17.6)	0.150
Air bronchogram	12 (60.0)	9 (44.1)	**0.015**
Pleural effusion	11 (55.0)	11 (32.4)	0.102

Abbreviations: WBC, white blood cell; NEUT, neutrophils; LYMPH, lymphocyte; CRP, C-reactive protein; PCT, procalcitonin; eGFR, estimated glomerular filtration rate.

3.5. Treatments

Forty (74.1%) cases received the antiviral treatment with Paxlovid, and 34 (62.9%) of the KTRs were treated with oral dexamethasone or intravenous methylprednisolone. Antibiotic therapy was given depending on the presence of confirmed or suspected bacterial infections.

Compared with patients without fungal infections, patients with secondary fungal infections were more likely to receive invasive mechanical ventilation (60.0%, 12/20 vs. 5.9%, 2/34, $P < 0.001$). We found the administration of meropenem (50.0%, 11/20 vs. 26.5%, 9/34, $P = 0.036$), piperacillin/tazobactam (50.0%, 11/20 vs. 20.6%, 7/34, $P = 0.010$), vancomycin (45.0%, 9/20 vs. 0.0%, 0/34, $P < 0.001$), and tigecycline (30.0%, 6/30 vs. 2.9%, 1/34, $P = 0.015$) were more common in KTRs with fungal co-infections than in those without fungal infections. There was no statistical difference between the two groups for intravenous corticoid therapy (**Table 3**).

Table 3. Treatment and outcomes of kidney transplantation recipients with COVID-19 ($N = 54$)

	Fungal infection group ($n = 20$)	Non-fungal infection group ($n = 34$)	*P* value
Treatments			
Invasive mechanical ventilation, *n* (%)	12 (60.0)	2 (5.9)	**< 0.001**
Paxlovid, *n* (%)	15 (75.0)	25 (73.5)	0.905
Intravenous steroid, *n* (%)	15 (75.0)	19 (55.9)	0.160
Meropenem, *n* (%)	11 (55.0)	9 (26.5)	**0.036**
Cefoperazone/sulbactam, *n* (%)	12 (60.0)	25 (73.5)	0.301
Piperacillin/tazobactam, *n* (%)	11 (55.0)	7 (20.6)	**0.010**
Fluoroquinolone, *n* (%)	9 (45.0)	12 (35.3)	0.480
Vancomycin, *n* (%)	9 (45.0)	0 (0.0)	**< 0.001**
Linezolid, *n* (%)	2 (10.0)	1 (2.9)	0.632
Tigecycline, *n* (%)	5 (25.0)	1 (2.9)	**0.015**
Sulfonamide, *n* (%)	12 (60.0)	13 (38.2)	0.121
Imipenem/cilastatin, *n* (%)	5 (25.0)	2 (5.9)	0.110
Outcomes			
ICU admission, *n* (%)	12 (60.0)	4 (11.8)	**< 0.001**
Death, *n* (%)	10 (50.0)	1 (2.9）	**< 0.001**
Length of hospital stay, days	23 (13–27)	13 (10–16)	**0.003**

Abbreviations: ICU, intensive care unit

3.6. Outcomes

The mortality rate for COVID-19-associated fungal infections was 50% (10/20), which was considerably higher when compared to those patients without fungal infections (50.0%, 10/20 vs. 2.9%, 1/34, $P < 0.001$). In addition, the group with the fungal infections had a higher rate of admission to the ICU (60.0%, 12/20 vs. 11.8%, 4/34, $P < 0.001$) and a longer hospital stay [23 (13, 27) vs. 13(10, 16) days, $P = 0.003$].

3.7. Analyses of risk factors

When COVID-19 KTRs with secondary fungal infections were compared to those without fungal infections, the results of the multivariate analysis showed that the following factors were independently related to the occurrence of COVID-19-associated fungal infections in KTRs: older age (increased by 10 years, OR = 2.221, 95% CI: 1.036–4.759), diabetes mellitus history (OR = 12.293, 95% CI: 1.485–101.758), ARDS (OR = 12.849, 95% CI: 1.487–111.012), and bacterial co-infections (OR = 30.461, 95% CI: 2.486–373.166) (**Table 4**).

Table 4. Risk factors of COVID-19-associated fungal infections in KTRs (N = 54)

	Univariate analysis			Multivariate analysis	
	Fungal infection group (n = 20)	**Non-fungal infection group (n = 34)**	***P* value**	**Odds ratio (95% CI)**	***P* value**
Age/10, years	5.7 (4.7–6.0)	4.7 (3.7–5.8)	0.029	2.221 (1.036–4.759）	**0.040**
LYMPH, $\times 10^9$/L	0.29 (0.20–0.56)	0.50 (0.36–0.99)	0.037	0.174 (0.017–1.780)	0.140
Diabetes mellitus, n (%)	13 (65.0)	12 (35.3)	0.020	12.293 (1.485–101.758)	**0.035**
ARDS, n (%)	13 (65.0)	9 (26.5)	0.005	12.849 (1.487–111.012)	**0.020**
Bacterial co-infection, n (%)	11 (55.0)	4 (11.8)	< 0.001	30.461 (2.486–373.166)	**0.008**
Air bronchogram, n (%)	12 (60.0)	9 (44.1)	0.015	0.222 (0.022–2.221)	0.200

Abbreviations: LYMPH, lymphocyte; ARDS, acute respiratory distress syndrome.

4. Discussion

In solid organ transplant (SOT) recipients, COVID-19-associated fungal infections have been reported to be especially deadly and incapacitating, resulting in longer hospital stays and increased medical expenses [2,10]. The features and risk factors of COVID-19-associated fungal co-infections have been well demonstrated in solid organ transplants, but the information available for KTRs is limited [22-25]. To the best of our knowledge, this study is the first to pinpoint the clinical traits and risk factors associated with COVID-19-associated fungal infections in KTRs in the Chinese population. We discovered that the patients had a severe clinical course, poorer kidney outcome, and worse survival, and that older age, history of diabetes mellitus, ARDS, and bacterial co-infections were independent risk factors.

This study found that COVID-19-associated fungal infections in KTRs are not rare, with an incidence of 37%. The prevalence rate was much higher than in the general population, which was between 1% and 33% [26]. In a large multicenter retrospective cohort study, the incidence of secondary fungal infections in SOT recipients with COVID-19 was reported to be 8%, which was lower than our data [22]. This may be due to the heterogeneity of patient groups and the diagnosis of fungal infections [27]. KTRs were more vulnerable to secondary fungal infections due to their long-term use of immunosuppressive drugs, especially at the second occurrence of specific infections. Additionally, we discovered that KTRs with a history of diabetes were more vulnerable to COVID-19-associated fungal infections, as the prolonged hyperglycemic state may impair neutrophil function and cause immune dysregulation [27]. Schwartz *et al.* found that a diabetic state could exacerbate the adverse effects of SARS-CoV-2 on T-lymphocytes and increase the risk of superinfections [28].

The fungal pathogens in our research were *Candida*, *Aspergillus*, and *Mucorales*, which was consistent with previous research [10]. We found that lymphocytes were significantly decreased in patients with secondary fungal infections, with $CD4^+$ and $CD8^+$ T cells being the most reduced. This phenomenon reflects the immunosuppressive state caused by the cytokine storm of COVID-19 [29]. Severe lymphocytopenia and lymphocyte dysfunction were closely associated with bacterial immune dysfunction and secondary fungal infections [10], and thrombocytopenia was a risk factor for mortality in SOT recipients with COVID-19 [30]. We discovered that patients with secondary fungal infections had a higher prevalence of hypoalbuminemia. Hypoalbuminemia was a non-specific indicator of illness severity and was associated with poor prognosis in patients with the novel coronavirus infections [31]. The synthesis of IL-10 by lymphocytes could be impaired by hypoalbuminemia and the lack of IL-10 increases the susceptibility to other infections [32]. Although the difference was not statistically significant, participants with fungal infections exhibited higher serum creatinine levels, pointing to a potential link between fungal infections and kidney damage. A larger sample size might produce more fruitful outcomes. Patients with fungal infections had platelet counts that were within normal range, but the counts were nevertheless much greater than those of uninfected patients. The activating effect of the glucosamine-glucan produced by *Aspergillus* could stimulate platelet production [33]. Imaging tests revealed that patients with secondary fungal infections have a higher frequency of bronchial symptoms. When the lung inflammation was severe, the lung parenchyma's opacity decreased, causing the bronchi to become more visible and dilated [34].

In our study, secondary fungal infections made the clinical course of COVID-19 more complicated. We found that the incidence of ARDS, AKI, and combined bacterial infections was significantly higher in patients with secondary fungal infections. The lungs of COVID-19 individuals who have experienced ARDS may be seriously damaged, necessitating the use of mechanical ventilation. However, it should be noted that mechanical ventilation may make the patients more vulnerable to fungal infections. This is especially dangerous for KTRs who are already at risk of infections [35,36]. In our study, 60% (12/20) of patients with secondary fungal infections developed AKI, significantly more than those without fungal infections. According to Yang *et al.*, in their summary of 51 studies involving 21,531 participants, the incidence of AKI caused by COVID-19 was 12.3%, with a higher rate of 38.9% among recipients of transplants [37]. According to a meta-analysis study conducted by Duarsa *et al.*, hospitalized KTRs with COVID-19 had a 3.78 times higher risk of AKI compared to the general population, often leading to worse outcomes [38]. In critically ill patients, the cytokine storms could occur in response to COVID-19 by impairing lymphocyte function through various mechanisms. This could lead to multiple organ dysfunction syndromes, including AKI [36]. Furthermore, some azole antifungal medications may inhibit cytochrome P450 3A4 (CYP3A4), and increase blood levels of tacrolimus and the risk of nephrotoxicity [39]. According to certain studies, COVID-19-induced cytokine storms may be made worse by secondary fungal infections, increasing the risk of AKI and fatality rates [36]. We discovered that individuals who developed secondary fungal infections often had mixed bacterial infections, with drug-resistant bacteria accounting for as much as 45.5% of these infections. Patients with KTRs were more susceptible to infections. When secondary infections were detected, the clinicians administered broad-spectrum antibiotics more frequently, which raised the possibility of secondary infections with drug-resistant bacteria and opportunistic pathogenic fungi [40]. Likewise, most COVID-19 patients with secondary bacterial infections were more likely to be transferred to ICU and receive invasive medical procedures, which greatly increased the risk of fungal infections [41].

We found that the air bronchogram sign was more frequent in secondary fungal infections, which could contribute to the diagnosis. Previous studies demonstrated that the diagnosis of fungal infections using biopsies and laboratory testing is often challenging and delayed. Fungal infections frequently exhibit non-specific symptoms and atypical radiographic findings, making early diagnosis difficult. Nevertheless, according to an autopsy report, 2.8% of ICU patients showed pathological signs of fungal infections. However, only 40% of these patients received a definitive diagnosis during their lifetime [42]. Therefore, it is possible that the actual incidence of these infections in KTRs is underestimated [43].

According to our research, COVID-19 KTRs with fungal infections had far greater rates of ICU admission, length of stay, and mortality than KTRs without infections. There were also significant differences between the two groups in the proportion of mechanical ventilation and antibiotic therapy. Consistent with our study findings, previous research has demonstrated that patients with COVID-19-associated fungal infections typically require more invasive ventilation and have longer hospital stays [16]. Superinfections need to be closely monitored since they have the potential to be the final cause of mortality [44]. According to a multicenter observational study by Prattes *et al.*, ICU death was nearly twice as likely to occur in patients with fungal infections compared to those without superinfections [45]. KTRs were more vulnerable to fungal coinfections, and some case reports indicated unfavorable outcomes resulting from secondary fungal infections [7,46].

In the current study, the risk factors for secondary fungal infections in KTRs with COVID-19 in this cohort were advanced age (OR = 2.221), diabetes history (OR = 12.293), ARDS (OR = 12.849), and combined bacterial co-infections (OR = 30.461). It was a well-established fact that the elderly population was highly vulnerable to COVID-19 and fungal infections, due to their compromised immune system [1,47]. Several meta-analyses demonstrated that diabetes is an independent risk factor for fungal co-infections and poor prognosis in COVID-19 patients [10,48]. In addition, severely ill COVID-19 patients with multiple comorbidities were more susceptible to secondary fungal infections [35]. As with our research findings, we found that complications of ARDS and bacterial co-infections were independent risk factors for fungal infections in COVID-19 KTRs since these patients had higher rates of receiving mechanical ventilation and high doses of antibiotics. The overuse of broad-spectrum antibiotics was a major factor contributing to the emergence of drug-resistant bacterial infections and opportunistic pathogenic fungal infections [49]. By recognizing risk factors, healthcare professionals may be able to focus more on screening procedures and perhaps prescribe antifungal prophylaxis to high-risk individuals in an effort to prevent COVID-19-associated fungal infections.

Our study has several limitations. The data presented reflected a real-life scenario for which there are no predefined standards for inpatient administration. Well-designed prospective studies at multiple centers are necessary to further substantiate this entity, as the conclusions drawn from this retrospective study at a single center may not apply to all KTRs. The sample size is limited to demonstrate the intact risk factors of COVID-19-associated fungal infections in KTRs.

5. Conclusion

To summarize, KTRs with COVID-19-associated fungal infections have a high incidence and poor outcomes. Older age, history of diabetes mellitus, ARDS, and bacterial infections were the independent risk factors for COVID-19-associated fungal infections in KTRs. Long COVID, also known as post-acute sequelae of COVID-19, affects around 10% of infected individuals [50]. Thus, studies on COVID-related fungal infections in KTRs are still crucial. Clinicians should pay special attention to secondary fungal infections in KTRs with COVID-19, especially when treating patients with multiple risk factors.

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Disclosure statement

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