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Clinical Characteristics, Pharmacotherapy, and Outcomes of Mucormycosis in Kidney Transplant Recipients Diagnosed with COVID-19: A Cross-Sectional Study at a Referral Center in Iran

Laleh Mahmoudi¹, Zahra Ebrahimi-Bidgoli², Amirreza Dehghanian³, Omid Moradi^{1*}, Iman Karimzadeh^{1*}

¹Department of Clinical Pharmacy, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran

²Student Research Committee, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran

³Department of Pathology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

ABSTRACT

Background: Mucormycosis is a rare fungal infection that affects immunocompromised individuals, with key predisposing factors including diabetes and organ transplantation. The COVID-19 pandemic led to a global increase in mucormycosis cases, but data on kidney transplant recipients (KTRs) remain limited.

Objective: This study evaluates the epidemiology and outcomes of mucormycosis in KTRs at an Iranian referral center.

Methods: This retrospective cohort study examined the clinical features, risk factors, treatment approaches, and outcomes of mucormycosis in KTRs with prior COVID-19 infection (case group) compared to KTRs with COVID-19 but without mucormycosis (control group). The study was conducted from July 2023 to August 2024 at the largest organ transplant center in Shiraz, southern Iran.

Results: The study comprised 119 participants (14 mucormycosis cases, 105 controls). Cases predominantly involved males (64.3%) aged 40–60 years, with 64.3% being overweight/obese and high rates of hypertension (50%) and diabetes (21.4%). Most mucormycosis diagnoses (64.3%) occurred within five years post-kidney transplantation, with a median baseline eGFR of 27.5 ml/min/1.73 m². Controls had a similar male predominance (67.7%), but a lower prevalence of overweight/obesity (10.5%), and a 48.1% history of COVID-19 within the past year. COVID-19 treatments included corticosteroids (78.6%) and remdesivir (39.1%). Orbital mucormycosis (45.4%) predominated, with spring being the peak diagnostic season. All cases underwent CT imaging and received antifungal treatment. Univariate analysis revealed no significant risk factors for the development of mucormycosis. Hospital mortality was 35.8% in the case group versus 18% in the control group, and the case group had a markedly longer hospital stay (24 days vs. 8 days).

Conclusion: Mucormycosis predominantly affected males aged 40–60 with high rates of comorbidities and corticosteroid use. This study is one of the few to examine KTRs with COVID-19-associated mucormycosis in Iran. Most diagnoses occurred within five years post-transplantation, with orbital mucormycosis being common. No independent risk factors for the development of mucormycosis were identified. Further research is needed to understand risk factors and improve management for KTRs.

KEYWORDS: Mucormycosis; Kidney transplantation; COVID-19; Immunocompromised Host; Antifungal agents

INTRODUCTION

Mucormycosis, a rare yet aggressive fungal infection with a highly angioinvasive nature, predominantly

affects individuals with uncontrolled diabetes or those who are immunocompromised due to conditions such as neutropenia, hematological malignancies, or the use of immunosuppressants. This infection is linked with a poor prognosis, significant morbidity and mortality rates, and considerable healthcare costs [1, 2].

The incidence of this infection ranges from 0.2% to 1.2%, with the majority of cases occur-

*Correspondence (s):

Iman Karimzadeh, PharmD, PhD & Omid Moradi, PharmD, BCCP
Department of Clinical Pharmacy, School of Pharmacy, Shiraz
University of Medical Sciences, Shiraz, Iran

ORCID: 0000-0002-8956-4528 & 0000-0001-5754-535X

E-mail: karimzadehiman@yahoo.com & O_moradi@outlook.com

ring within the first year post-transplantation [3, 4]. Kidney transplant recipients (KTRs) are vulnerable to COVID 19-associated mucormycosis due to the combined effects of chronic immunosuppression, COVID 19-induced immune dysregulation, and corticosteroid therapy. Among KTRs, rhino-cerebral mucormycosis is the most prevalent form [5]. Furthermore, the incidence of mucormycosis in KTRs increased during the pandemic, as discussed in this study.

Management involves a combination of appropriate antifungal agents, aggressive surgical interventions, and reducing or withdrawing immunosuppressive therapy [6]. Historical data from 1990 to 2010 show an overall mortality rate of 52%, varying from 30.8% for rhino-cerebral cases to nearly 100% for pulmonary cases [3].

Mucormycosis presents with symptoms including headache, fever, unilateral facial swelling, orbital cellulitis, palpebral edema, ptosis, chemosis, and ophthalmoplegia. In developed countries, 58.5% of patients exhibit pulmonary involvement, and 19.5% present with the rhino-cerebral participation. In Italy, 35% of mucormycosis cases involve the rhino-orbital-cerebral region, while 25% involve the lungs [7]. Conversely, in India, rhino-cerebral-orbital mucormycosis is the most prevalent form, with 74.7% of cases occurring in males, 77.4% in individuals over 40 years old, and 65.3% of cases developing post-COVID-19 [8, 9].

The COVID-19 pandemic has resulted in a global increase in mucormycosis cases [10]. However, the literature on COVID-19-associated mucormycosis in KTRs is limited, primarily consisting of case reports. This study aims to explore the epidemiology, clinical manifestations, risk factors, outcomes, and treatment strategies of COVID-19-associated mucormycosis in KTRs at a referral transplantation center in Iran.

MATERIALS AND METHODS

Study Design and Setting

This retrospective cohort study was conducted at a referral transplantation center affiliated with Shiraz University of Medical Sciences, Shiraz, Iran, between July 2023 and August 2024. Ethical approval was granted by the Ethical Committee of Shiraz University of Medical Sciences (Ethical ID: IR.SUMS.REC.1401.713), ensuring compliance with the Declaration of Helsinki. Written informed consent was obtained from all participants, and confidentiality and privacy were rigorously upheld.

Study Population

The study included KTRs who were hospitalized for at least 48 hours and had a confirmed diagnosis of COVID-19, as determined by positive Reverse Transcription Polymerase Chain Reaction (RT-PCR) results from nasopharyngeal and/or oropharyngeal swabs. Participants met the following inclusion criteria: being a kidney transplant recipient of any duration, aged 18 years or older, hospitalized with confirmed SARS-CoV-2 infection supported by clinical or radiological findings, and having provided written informed consent. Exclusion criteria included recipients of non-kidney solid organ transplants, patients with incomplete clinical or demographic data, those diagnosed with other invasive fungal infections during hospitalization, patients under 18, individuals with terminal illnesses or severe non-COVID-19 comorbidities unrelated to transplantation or COVID-19, and those who refused or withdrew consent. The study population was divided into two groups: the case group, comprising KTRs with documented mucormycosis, and the control group, consisting of KTRs without mucormycosis. No specific inclusion/exclusion criteria regarding the duration of kidney transplantation, type of donor, or number of kidney transplantations were considered.

Mucormycosis was diagnosed through the identification of fungal hyphae using histopathological, cytopathological, or direct microscopic examination of biopsy specimens,

along with evidence of tissue damage or positive culture results.

Data Collection

Data were collected by reviewing medical charts and the hospital's health information system (HIS). When necessary, additional information was gathered through face-to-face interviews or telephone calls with patients. Collected data included demographics (age, sex, weight, height); transplantation-related factors (donor type, duration of kidney transplantation, immunosuppressive regimen); underlying diseases; COVID-19 related factors (signs and symptoms, severity, adjustments in immunosuppressive medications, treatments received); and clinical outcomes (mortality, hospital stay duration, ICU admission, mechanical ventilation requirements, development of acute kidney injury (AKI), need for kidney replacement therapy, and acute allograft rejection) and were recorded in case report forms. For the case group, additional data on the type, clinical manifestations, laboratory findings, severity, and treatment approaches for mucormycosis were also collected.

The Severity of Mucormycosis

Mucormycosis severity was determined using both imaging findings and histopathological evidence of tissue invasion. Mucormycosis severity was classified into two categories:

Severe Mucormycosis: Extensive tissue involvement, significant morbidity, or high mortality risk, including disseminated disease, central nervous system involvement, or severe sinus / pulmonary manifestations requiring aggressive intervention.

Non-Severe Mucormycosis: Localized infections with less extensive tissue involvement, lower morbidity, and better overall prognosis, characterized by milder symptoms and a favorable response to treatment [11].

Clinical Definitions

The glomerular filtration rate (GFR) at hospital admission was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 formula [5]. COVID-19

severity was classified according to modified World Health Organization (WHO) criteria [7]. AKI was defined based on the Kidney Disease: Improving Global Outcomes (KDIGO) guideline [8]. Acute allograft rejection was confirmed via biopsy of the transplanted kidney tissue.

Statistical Analysis

Statistical analyses were conducted using SPSS version 20.0. The Kolmogorov-Smirnov test was used to assess the normal distribution of continuous variables. Qualitative data were presented as frequencies (percentages), while quantitative variables were expressed as mean $\pm$ standard deviation (SD) or median (interquartile range, IQR) for parametric and non-parametric variables, respectively. Group comparisons were performed using chi-square or Fisher's exact tests (if more than 25% of the categories have frequencies below 5) for categorical variables. Independent sample t-tests and Mann-Whitney test were used for parametric and non-parametric continuous variables, respectively. A logistic regression analysis model was used to identify potential risk factors for mucormycosis development, incorporating demographics, clinical, and laboratory characteristics. A p-value of < 0.05 was considered statistically significant.

RESULTS

In this study, a total of 119 KTRs with the diagnosis of COVID-19 were included. The study population comprised 14 patients with mucormycosis in the case group and 105 in the control group. The demographic and clinical characteristics of the participants are summarized in Table 1.

In this study, the majority of patients were male [81 (68.1%)], and the predominant age range was 40 to 60 years. Hypertension and diabetes mellitus were the most prevalent underlying conditions in both groups. More than half of the included patients presented with severe to critical COVID-19 [69 (57.9%)]. No differences were observed in demographic and baseline characteristics. On average, 33.3%

Table 1: Demographic and clinical characteristics of case and control groups.

Variables	Case Group (n= 14)	Control Group (n= 105)	P-value
Age (years)			
20-40	2 (14.3%)	25 (23.8%)	0.430
40-60	9 (64.3%)	45 (42.9%)	
60-80	3 (21.4%)	35 (33.3%)	
Sex			
Male	9 (64.3%)	72 (67.7%)	0.750
Female	5 (35.7%)	33 (31.4%)	
BMI (kg/m ²)			
<25	6 (42.9%)	48 (45.7%)	0.420
>25	5 (35.7%)	45 (42.9%)	
Unknown	3 (21.4%)	12 (11.4%)	
Concomitant disease			
Hypertension	7 (50.0%)	40 (38.1%)	0.148
Diabetes	3 (21.4%)	31 (29.5%)	
Ischemic Heart Disease	1 (7.2%)	20 (19.0%)	
Renal stone	3 (21.4%)	1 (1.0%)	
Unknown	0 (0.0%)	13 (12.4%)	
Kidney transplant time			
<5 years	9 (64.3%)	47 (44.7%)	0.177
>5 years	5 (35.7%)	58 (55.2%)	
eGFR (mL/min/1.73m ²)	27.05 (IQR= 44.8)	27.62 (IQR= 37.5)	0.790
COVID-19 severity			
Severe	6 (42.8%)	63 (60.0%)	0.940
Non-severe	8 (57.2%)	42 (40.0%)	
Anti-COVID-19 therapy			
Remdesivir	2 (14.3%)	41 (39.1%)	0.723
Non-remdesivir	12 (85.7%)	64 (60.9%)	

Abbreviations: BMI; body mass index, eGFR; estimated glomerular filtration rate, COVID-19; coronavirus disease- 2019

lung involvement was reported in the case group compared to 62% in the control group. The mean blood oxygen saturation at the time of COVID-19 diagnosis was 93%, and 3 patients (25%) in the case group presented with WBC counts greater than 12,000/ μ L and CRP levels greater than 100 mg/L.

In the case group, headache and ophthalmic symptoms, including lacrimation and eye redness, were the most prevalent signs and symptoms 5 (35.7%) and 2 (14.3%), respectively) and in the control group, combination (fever and chills, cough, dyspnea, confusion) (54.3%) was

the most common presenting symptom, followed by fever (26%) and dyspnea (18.4%).

The most commonly used antiviral was remdesivir (60.9%), while dexamethasone was the primary anti-inflammatory agent in the control group (66.7%). Corticosteroids, including dexamethasone, prednisolone, methylprednisolone, and hydrocortisone, were used in 11 (78.6%) of the patients in the case group, while 56 (53.3%) of the patients in the control group did not receive corticosteroids.

Immunosuppressive therapy adjustments were

Table 2: Adjustments of immunosuppressive agents during the course of hospital stay in the case and control groups.

Agents	Case group (%)		Control group (%)	
CNIs (CsA, Tac)	Increase	5 (38.5%)	Increase	10 (10.6%)
	Decrease	7 (53.8%)	Decrease	14 (14.9%)
	Unchanged	1 (7.7%)	Unchanged	70 (74.5%)
AZA	Increase	0 (0.0%)	Increase	0 (0.0%)
	Decrease	0 (0.0%)	Decrease	0 (0.0%)
	Unchanged	0 (0.0%)	Unchanged	7 (100.0%)
MMF	Increase	3 (42.9%)	Increase	3 (4.4%)
	Decrease	0 (0.0%)	Decrease	3 (4.4%)
	Unchanged	4 (57.1%)	Unchanged	40 (89.0%)
MPA	Increase	0 (0.0%)	Increase	1 (3.2%)
	Decrease	1 (33.3%)	Decrease	1 (3.2%)
	Unchanged	2 (66.7%)	Unchanged	29 (93.6%)

Abbreviations: CNIs; calcineurin inhibitors, CsA; cyclosporine A, Tac; tacrolimus, AZA; azathioprine, MMF; mycophenolate mofetil, MPA; mycophenolic acid

observed in both groups (Table 2). In the case group, calcineurin inhibitors were the most frequently modified agents, with dose reductions in 17.07% of patients and increases in 12.19% of patients. Antimetabolite doses were reduced in 4.4% of patients in the case group. No patient in the case group received mTOR inhibitors. In the control group, mTOR inhibitors were discontinued in all patients who were receiving the medications. Adjustments in calcineurin inhibitors and antimetabolites were observed in 39.5% and 80.2% of patients, respectively.

In the case group, orbital mucormycosis was the most common form (35.8%), followed by pulmonary (21.4%) and sinus (21.4%) involvement. The majority of cases were diagnosed in the spring season (42.8%). Diagnostic methods included computed tomography (84.6%), MRI or CT of the paranasal sinuses (46.15%), and biopsy (38.45%).

All patients in the case group received antifungal therapy with amphotericin B (conventional or liposomal). Nine patients received monotherapy, and five received a combination of amphotericin B and posaconazole. Surgical debridement was performed in all cases. The dosage regimens and duration of antifungal therapy are shown in Table 3.

Univariate logistic regression analysis revealed no independent risk factors for mucormycosis were identified in this cohort (Table 4). The incidence of acute rejection was comparable between groups (21.4% in the case group vs. 22% in the control group, $P=0.968$). The need for hemodialysis was higher in the case group (64.2%) compared to the control group (43.3%), but this difference was not statistically significant ($P=0.138$). Hospital mortality was 35.8% in the case group compared to 18% in the control group ($P=0.123$). The duration of hospital stay was significantly longer in the case group (24 (IQR=29) days vs. 8 (IQR=7) days, $P=0.01$).

DISCUSSION

This study is among the few that have explored COVID-19-associated mucormycosis (CAM) in KTRs. Out of 119 KTRs, 14 developed CAM, indicating a prevalence of 11.76%—significantly higher than the 0.07% cumulative incidence observed in a large multicenter U.S. study of solid organ transplant recipients before the pandemic. These results are consistent with global reports indicating an increase in mucormycosis cases during the pandemic, particularly in regions such as India, where the incidence rose by 2.1-fold com

Table 3: Dosage regimen of antifungal therapy in patients with mucormycosis.

Antifungal Agents	Average daily dose (mg)	Average daily dose based on weight (mg/kg)	Dosage (mg/day)	Duration of treatment
Amphotericin B conventional	65.70	1.38	35	20
			50	8
			75	1
			100	24
Amphotericin B liposomal	31.70	6.50	350	6
			100	7
			225	9
			300	15
Posaconazole	27.50	5.14	200	9
			300	7

pared to pre-pandemic times [12]. Comparing the incidence with the pre-pandemic period in transplant recipients in the US, the higher rate observed in regional disparities, including a greater prevalence of uncontrolled diabetes in our cohort, differences in healthcare access, and environmental exposure in countries such as Iran and India.

Our study aligns with demographic trends observed in the literature, indicating that middle-aged males and diabetic patients are most affected. Consistent with previous reports, the median age of affected patients in various studies ranged from 42 to 55 years [13]. Diabetes has been identified in up to 100% of CAM cases, underscoring its significant role as a risk factor [10, 13, 14]. For instance, a retrospective analysis in India found that CAM patients were predominantly male (100%) with diabetes (64%) as the most common comorbidity, and another study reported similar findings with a median age of 42 years and diabetes in 54.5% of cases [15, 16].

In contrast to previous studies, such as that by Bansal *et al.*, which identified elevated HbA1c levels and lymphopenia as significant risk factors for COVID-19-associated mucormycosis, our univariate analysis did not demonstrate statistically significant associations for these variables [15]. This discrepancy may be attributable to the limited sample size in our

study, differences in patient demographics, variations in underlying comorbidities, and differences in case definitions or diagnostic criteria.

Patients with hematologic malignancies, diabetes mellitus, transplant recipients, individuals on immunosuppressive therapy and corticosteroids are at increased risk of the disease [17]. As COVID-19 prevalence rises and corticosteroids, along with other immunosuppressive therapies, are used to treat the disease, the number of cases has significantly increased. In most cases, immunosuppressive adjustments, including dose reduction or withdrawal of calcineurin inhibitors and antimetabolites, were applied in our cohort. Optimal strategies remain a topic of ongoing debate and research [18-22].

Interestingly, more than three-quarters of CAM cases in our study emerged within the first five years following kidney transplantation, which aligns with existing literature that reports mucormycosis onset occurring between 4 and 8 years post-transplantation [15, 23, 24]. This timeline illustrates the intricate relationship between immunosuppressive therapy and corticosteroid use during COVID-19 treatment [25]. The rate of corticosteroid use among cases (78.6%) compared to controls (53.3%) was higher. This trend may indicate a contributory role in increasing susceptibility to COVID-19-associated mucor

Table 4: Logistic regression model identifying risk factors for mucormycosis diagnosis in KTRs.

Variables	Control Group N (%)	Case Group N (%)	OR	95% CI	P-value
Age (years)					
< 40 years	25 (23.8%)	2 (14.3%)	0.523	0.112-2.545	0.431
> 40 years	80 (76.2%)	12 (85.7%)			
Sex					
Male	72 (68.6%)	9 (64.2%)	0.825	0.256-2.654	0.747
Female	33 (31.4%)	5 (35.7%)			
Duration of transplantation					
< 5 years	47 (44.7%)	9 (64.3%)	2.221	0.697-7.07	0.177
> 5 years	58 (55.3%)	5 (35.7%)			
BMI (kg/m ²)					
<25	54 (51.5%)	8 (57.1%)	0.632	0.205-1.947	0.424
>25	51 (48.5%)	6 (42.8%)			
Anti-COVID-19 therapy					
Received remdesivir	10 (9.5%)	5 (35.7%)	5.278	1.478-18.844	0.150
Not received remdesivir	95 (90.5%)	9 (64.3%)			
Concomitant disease					
With diabetes	45 (42.9%)	7 (50%)	2.900	0.648-12.376	0.148
Without diabetes	60 (57.1%)	7 (50%)			
COVID-19 severity					
Severe	63 (60%)	6 (42.8%)	2.700	0.846-8.620	0.940
Non-severe	42 (40%)	8 (57.2%)			
WBC at the time of hospital admission (/μL)					
< 4000	50 (47.6%)	5 (35.7%)	0.635	0.199-2.022	0.442
> 4000	55 (52.4%)	9 (64.3%)			
eGFR at the time of hospital admission (mL/min/1.7 m ²)					
Median (IQR)	27.62 (37.5)	27.05 (44.8)	1.003	0.984-1.022	0.790

Abbreviations: KTRs; kidney transplant recipients, OR; odds ratio, CI; confidence interval, BMI; body mass index, COVID-19; coronavirus disease-2019, WBC; white blood cells, eGFR; estimated glomerular filtration rate, IQR; Interquartile range

mucormycosis and warrants consideration in clinical risk assessment.

The predominant presentation in our cohort was orbital mucormycosis. The global trends where sinonasal or rhino-orbital forms constitute the majority of CAM cases (41–74%), followed by rhino-orbitocerebral forms (8–37%) [13, 16]. The proportion of orbital mucormy-

cosis in our cohort (35.8%) was notably lower than the 74.7% rhino-orbital involvement reported in large series from India [26]. Other rare forms of the disease have been reported in KTRs and COVID-19 patients [23, 27, 28].

Systemic antifungal therapy, combined with surgical debridement, was the cornerstone of treatment in our cohort. Liposomal amphotericin B is generally preferred. However, in our

setting, shortages of liposomal formulations necessitated alternating between conventional and liposomal amphotericin B, a strategy also reported in India [23]. A combination therapy of amphotericin B and posaconazole was used in our study. While anecdotal evidence suggests potential efficacy, robust clinical data are lacking, highlighting the need for further research [15].

Interestingly, no significant associations were identified between demographics, clinical, or laboratory variables and the development of CAM in our study. This contrasts with studies like Bansal *et al.*, which found significant associations with factors such as nadir lymphocyte count, elevated inflammatory markers, and HbA1c levels [15].

Regarding outcomes, mortality rates in our cohort were comparable to those reported in the literature (15–31%). Data from India reported mortality rates of 18% to 27% among KTRs with CAM [18, 22, 23, 28]. The mortality observed in our cohort was higher than that reported in the Indian series of COVID 19–associated mucormycosis, yet remained within the range described in global solid organ transplant populations, reflecting both regional differences and the high vulnerability of this patient group.

The major limitations of the present study include the relatively small number of cases ($n = 14$), which limits the statistical power to detect potential risk factors, and the disproportionate case–control ratio (14 versus 105). The study was designed as a single-center study. The retrospective design also carries an inherent risk of incomplete or missing data, particularly for certain clinical and laboratory parameters (e.g., the time interval between COVID-19 diagnosis and mucormycosis onset, initial manifestations, lymphocyte count, HbA1c, interleukin-6 level, and d-dimer). Additionally, the follow-up period was limited to the duration of hospitalization, which precluded the assessment of long-term outcomes. Furthermore, due to the limited number of cases, multivariable regression analysis was not performed to avoid overfitting and unstable estimates.

Our findings underscore important practical implications for clinical practice and public health planning. In particular, they emphasize the importance of early ophthalmologic screening in high-risk patients to facilitate timely detection and intervention, thereby potentially preventing irreversible vision loss. Furthermore, given the potential for antifungal drug shortages during outbreaks or in resource-limited settings, our results support proactive resource planning and supply chain management to ensure uninterrupted access to essential therapies.

In conclusion, mucormycosis remains a rare but serious infection with high morbidity and mortality in KTRs, particularly during the COVID-19 pandemic. The 11.76% incidence observed in our cohort underscores the need for heightened clinical vigilance, especially in middle-aged males with diabetes or within five years post-transplantation. Orbital mucormycosis was the predominant form, emphasizing the importance of early diagnosis through imaging and biopsy. The optimal immunosuppressive strategies during treatment remain unclear and warrant further investigation.

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