



# Mucormycosis as SARS-CoV2 sequelae in kidney transplant recipients: a single-center experience from India

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## Abstract

**Purpose** Coronavirus disease (COVID-19) sequelae in the transplant population are scarcely reported. Post-COVID-19 mucormycosis is one of such sequelae, which is a dreadful and rare entity. The purpose of this report was to study the full spectrum of this dual infection in kidney transplant recipients (KTR).

**Methods** We did a comprehensive analysis of 11 mucormycosis cases in KTR who recovered from COVID-19 in IKDRC, Ahmedabad, Gujarat, India during the study period from Nov 2020 to May 2021. We also looked for the risk factors for mucormycosis with a historical cohort of 157 KTR who did not develop mucormycosis.

**Results** The median age (interquartile range, range) of the cohort was 42 (33.5–50, 26–60) years with 54.5% diabetes. COVID-19 severity ranged from mild ( $n=10$ ) to severe cases ( $n=1$ ). The duration from COVID-19 recovery to presentation was 7 (7–7, 4–14) days. Ten cases were Rhino-orbital-cerebral-mucormycosis (ROCM) and one had pulmonary mucormycosis. Functional endoscopic sinus surgery (FESS) was performed in all cases of ROCM. The duration of antifungal therapy was 28 (24–30, 21–62) days. The mortality rate reported was 27%. The risk factors for post-transplant mucormycosis were diabetes (18% vs 54.5%;  $p$ -value = 0.01), lymphopenia [12 (10–18) vs 20 (12–26) %;  $p$ -value = 0.15] and a higher neutrophil-lymphocyte ratio [7 (4.6–8.3) vs 3.85 (3.3–5.8);  $p$ -value = 0.5].

**Conclusion** The morbidity and mortality with post-COVID-19 mucormycosis are high. Post-transplant patients with diabetes are more prone to this dual infection. Preparedness and early identification is the key to improve the outcomes.

**Keywords** Follow-up · Transplant · COVID-19 · Mucormycosis · Fungal infections · Readmission

## Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) has drastically impacted all the domains of humanity and solid-organ transplant recipient (SOT) is not a mere exception. However, there are enough evidence-based data to bolster the increased vulnerability of SOT with SARS-CoV2 compared to the general [1–3] and waitlisted patients [4, 5]. This fact ranks them at the top of the priority list for

the medical community. There have been a lot of speculations about the imminent threat to COVID-19 survivors even after discharge. There are a few reports of follow-up studies in the general population, but the data are limited pertaining to SOT. Mucormycosis is one such infection that has emerged as post-COVID-19 sequelae. It is regarded as an opportunistic infection before the pandemic but recently has been recognized in increasing numbers with COVID-19. The causation and association between these two are incompletely understood. As SOT is already a proven risk factor for mucormycosis [6, 7], this problem statement expands in the COVID-19 era. There is a growing need to understand the clinical spectra and management of this deadly combination to improve the outcomes in SOT, as the data are scarce. The authors have previously reported two cases of post-COVID-19 mucormycosis in kidney transplant recipients (KTR) which are included in this study as well [8]. To date, there are only a few cases reports in SOT [9, 10]

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who acquired post-COVID-19 mucormycosis. To the best of our knowledge, this remains the largest case series of post-COVID-19 mucormycosis in KTR which could serve as a learning tool for transplant physicians across the globe.

## Methodology

### Ethical statement

This was a retrospective study organized in a single center after getting an ethical approval letter from the institution (Registration number: ECRJ143/InstlGJ/2013/RR-19 with application number EC/App/20Jan21/07). The study was reported as per the Strengthening The Reporting of OBservational Studies in Epidemiology (STROBE) checklist. We followed the norms of the Transplantation of Human Organs and Tissues Act (THOTA), India; the declaration of Helsinki, and the declaration of Istanbul. The patient's privacy and confidentiality were maintained throughout the process of the study.

### Design, settings, and study population

The study was conducted at the department of nephrology and transplantation, IKDRC-ITS, Ahmedabad, Gujarat, India. All KTR with COVID-19 confirmed by SARS-CoV2 real-time polymerase chain test (RT-PCR) through nasopharyngeal swab or positive SARS-CoV2 spike protein antibody test by chemiluminescence immunoassay were included during the study period from May 2020 to May 2021. COVID-19 was defined as mild (signs of upper respiratory tract/no oxygen requirement), moderate (signs of pneumonia without the need of supplemental oxygen), and severe (severe pneumonia with oxygen saturation below 90% on room air) [11]. The cases were managed as per the availability of resources and drugs and as per the national guidelines for the management of COVID-19 [12]. The details of the 11 KTR who developed mucormycosis after COVID-19 infection were described in the study. The diagnosis of mucormycosis was confirmed by histopathological examination, KOH mount, and culture.

### Institutional immunosuppression protocols

The immunosuppression protocol for COVID-19 in the center involved stopping of antimetabolite for 7 days in mild cases and gradual reintroduction after improvement of symptoms. In cases of moderate to severe COVID-19, both antimetabolite and calcineurin inhibitors (CNI) were stopped for 7 days and were insidiously restored depending on the clinical convalescence. There was no change in drug regimen for asymptomatic cases. The immune modulation

in post-COVID-19 mucormycosis involved stopping antimetabolite and giving minimum doses of CNI in stable cases. In cases, with altered sensorium, or oxygen requirements only steroids in minimum doses were resumed. Antimetabolite was reintroduced after 2–3 weeks, and CNI was restored only after clinical recovery from mucormycosis. The immunosuppression changes were personalized depending on the clinical response and physician's discretion and we were not strict with our baseline protocol.

### The treatment regimen for mucormycosis

A dedicated room for managing mucormycosis was arranged in the hospital. The multidisciplinary team composed of nephrologists, transplant physicians, ophthalmologists, and ENT specialists was formed for managing this difficult-to-treat infection. Due to resource limitations, radiological imaging tests such as magnetic resonance imaging Para nasal sinus (MRI-PNS) or computed tomography (CT PNS) with or without contrast were performed in a different nearby imaging laboratory. Antifungal therapy was majorly composed of liposomal amphotericin B that was started with an initial dose of 1 mg/kg and gradually increased to 3–5 mg/kg after monitoring for any side effects. Posaconazole ( $n=3$ ) was less used due to limited availability and affordability. The planned duration of antifungal therapy was 21–28 days and beyond as per the clinical response. Functional endoscopic sinus surgery (FESS) was planned and performed as feasible and as early as possible.

### Data collection and analysis

Demographic and clinical data which encompass a detailed evaluation of the cases were collected by the two authors (RD and HSM) and analyzed further. Laboratory parameters were retrieved from the hospital's electronic software. The data were expressed as frequencies, percentages for categorical variables, and median interquartile range (IQR), and range for continuous variables. The comparison between historical cohort [13] which was reported recently and mucormycosis was done by Fisher test, Chi-square with Yates's correction, or  $t$  test as appropriate. A two-tailed  $p$ -value of less than 0.05 was considered statistically significant. All statistical analysis was done using SPSS software 17 version.

## Results

In the COVID-19 pandemic, we report a total of 11 post-COVID-19 mucormycosis cases were identified among KTR after COVID-19. One KTR and three liver transplant recipients with ROCM from the second wave were excluded due to incomplete details.

## Demographic characteristics of the cohort

Table 1 shows the demographic characteristics of the cohort. The median (IQR, range) of the cohort was 42 (33.5–50, 26–60) years with males ( $n = 10$ ) accounting for the bulk of cases. The gap period from the time of transplant surgery to acquiring COVID-19 was 5 (2–7.5, 2–17) years. The body mass index was 25 (23–31.5, 19–32)  $\text{kg}/\text{m}^2$ , and Charlson's co-morbidity index was 3 (2.5–3.5, 2–6) of the cohort. The blood group distribution for the study included A ( $n = 4$ ), B ( $n = 4$ ), and O ( $n = 3$ ). Only 1 case was a deceased donor, the rest others were living-related transplants. Diabetes as a co-morbidity was seen in 6 of the 11 cases. In only 2 cases, there was a history of uncontrolled blood sugars. Thymoglobulin ( $n = 8$ ) was the predominant induction used in the study. The majority of the cohort was on triple immunosuppression ( $n = 8$ ). The median tacrolimus level was 4.9 (4.45–5.15)  $\text{ng}/\text{ml}$ . There was no occupational hazard for mucormycosis. In addition, there was no history of recent trauma or antirejection therapy given. None of the cases was immunized with the SARS-CoV2 vaccine.

## COVID-19 course of the cohort before admission for mucormycosis

Table 2 exhibits the detailed clinical details during the COVID-19 admission of the cohort. Three cases were managed on an out-patient basis for the COVID-19, while others were hospitalized. Only 1 case was managed in the intensive care unit. The most common clinical manifestations during COVID-19 included fever ( $n = 11$ ), and cough ( $n = 10$ ). Anxiety ( $n = 4$ ) and depression ( $n = 4$ ) were also present in many cases. The oxygen requirement of the cohort during COVID-19 admission included home-based care ( $n = 3$ ), no oxygen therapy ( $n = 5$ ) and low flow oxygen ( $n = 2$ ), and high flow oxygen ( $n = 1$ ). No case was on mechanical ventilation. Radiological abnormalities were detected in all the cases. The laboratory derangement during COVID-19 included higher neutrophil-lymphocyte ratio [7 (4.6–8.3, 3.3–11.2)], lower lymphocyte percentage [12 (10–18, 8–25) %], higher interleukin-6 levels [94.2 (66–108, 21–114)  $\text{pg}/\text{ml}$ ], higher high sensitivity C-reactive protein [44 (38–128, 7.2–238)  $\text{mg}/\text{dl}$ ], high D-dimer [1013 (497–1359, 174–2070)  $\text{ng}/\text{ml}$ ] and serum ferritin levels [523 (423–1000, 248–1280)  $\text{ng}/\text{ml}$ ]. Most of the cases were treated with a combination of steroids, anticoagulation and remdesivir ( $n = 7$ ). The majority of the cases were treated with remdesivir, steroids and anticoagulation. The dose of steroids was 6 mg OD dexamethasone for 10 days in the three cases which required oxygen therapy. None of the cases received prophylactic antibiotics or antifungals during the COVID-19 stay. The immunosuppression management for COVID-19 is detailed

in methodology. No patient had allograft dysfunction or any other complaints at discharge.

## Clinical features and management of post-COVID-19 mucormycosis in kidney transplant recipients

The time gap between discharge from COVID-19 to the onset of symptoms of mucormycosis was 7 (7–7, 4–14) days. The clinical signs and symptoms (Table 3) described in decreasing order of frequency included facial swelling ( $n = 10$ ), headache ( $n = 10$ ), proptosis ( $n = 10$ ), nasal crusting ( $n = 10$ ), orbital cellulitis ( $n = 8$ ), chemosis ( $n = 6$ ), paresthesia ( $n = 4$ ), ophthalmoplegia ( $n = 4$ ), difficulty in vision ( $n = 3$ ), epistaxis ( $n = 3$ ), foul-smelling or black discharge from nose or throat ( $n = 3$ ), toothache ( $n = 3$ ), vision loss ( $n = 2$ ), palate crusting ( $n = 2$ ), fever ( $n = 1$ ) and sings of pneumonia ( $n = 1$ ). Most cases were classified as ROCM ( $n = 7$ ), and only a few had cerebral involvement ( $n = 3$ ) or pulmonary ( $n = 1$ ). No cutaneous, disseminated or gastrointestinal tract mucormycosis cases were reported. The confirmatory diagnosis of mucormycosis was made by KOH and HPE + biopsy in all of the cases. The culture was not isolated in any of the cases. The management involved immunosuppression drug regimen alteration which is detailed in the methodology. The antifungal therapy used was liposomal amphotericin B ( $n = 11$ ) and Posaconazole ( $n = 3$ ). FESS was performed in all of the ROCM cases. The cumulative median dose of Liposomal amphotericin B received was 280 (240–400)  $\text{mg}/\text{kg}$  for 28 (24–40, 21–62) days of treatment.

## The outcome of post-COVID-19 mucormycosis in kidney transplant recipients

Three deaths were reported in the study which corresponds to a mortality rate of 27%. In only one case (Case 1), where orbital exenteration was needed, the patient died after battling a morbid clinical course of around 2 months from the onset of COVID-19 symptoms. The pulmonary mucormycosis (Case 2) presented with ground-glass opacity initially which progressed to right lung cavitary pneumonia. He was diagnosed with mucormycosis from bronchoscopy and biopsy. Lung excision was planned but the patient perished before surgery. The only case, which was on high flow oxygen during COVID-19 (Case 3), developed ROCM with brain involvement after 7 days of COVID-19 discharge. He died even after a timely functional endoscopic sinus surgery. The entire cohort was SARS-CoV2 RT-PCR negative during the entire hospital stay. Acute kidney injury was reported in 6 (54.4%) of the cases. All three patients with mortality required hemodialysis sessions, while it was not needed in any of the survivors. The median serum creatinine value at baseline, peak value during COVID-19, and just before the diagnosis of mucormycosis was 1.3 (1.2–1.6), 1.5

**Table 1** Demographic features of the cohort

Patient number	1	2	3	4	5	6	7	8	9	10	11
Age	47	26	49	42	53	60	42	31	51	35	32
Sex	M	M	M	M	M	F	M	M	M	M	M
BMI, kg/m <sup>2</sup>	31	32	30.4	22	23	32	23	32	25	19	24
Blood group typing	A	A	B	B	B	O	O	B	A	O	A
Basic kidney disease	HTN	UE	UE	CGN	HTN	HTN	UE	UE	HTN	IgAN	RSD
Duration from transplant to COVID-19 (years)	17	2	11	2	7	5	3	2	5	8	2
Type of transplantation	LRKT	LRKT	LRKT	LRKT	LRKT	LRKT	LRKT	DKT	LRKT	LRKT	LRKT
Induction therapy	No	ATG	No	ATG	ATG	ATG	G	ATG	ATG	ATG	ATG
Co-morbidities	HTN, DM	DM	HTN	PTDM, OHA	HTN	HTN	HTN	DM, HTN, TB	DM	DM, HTN	HTN
Charlson's co-morbidity index	6	3	2	3	3	4	2	3	4	3	2
Baseline immunosuppression regimen											
Steroids	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
MMF/AZA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Tacrolimus	Y	Y	-	Y	Y	Y	Y	Y	-	Y	Y
Tacrolimus levels, ng/ml	4.6	5	-	5.2	4.4	4.2	5	NA	-	4.8	5.4
Sirolimus	-	-	-	-	-	-	-	-	Y	-	-
Others											
H/O ACEi/ARB	Y	-	-	Y	Y	Y	-	-	Y	Y	Y
H/O seasonal flu vaccination	-	-	-	-	-	-	-	-	-	Y	-
H/O uncontrolled sugars	-	-	-	Y	-	-	-	Y	-	-	-

Cases 1–3 died

BMI body mass index, MMF mycophenolate, AZA azathioprine, CNi calcineurin inhibitors, ACEi angiotensin-converting enzyme inhibitor, ARB angiotensin receptor blocker, DM diabetes, HTN hypertension, H/O history of, OHA oral hypoglycemic drugs, TB tuberculosis, ATG thymoglobulin, G grafalon, LRKT living-related kidney transplant, DKT deceased donor kidney transplant, CGN chronic glomerulonephritis, UE unknown etiology, RSD renal stone disease, IgAN IgA nephropathy, M male, F female, Y yes, NA not available

**Table 2** Detailed summary of the COVID-19 course of the cohort:

Patient number	1*	2	3	4	5	6	7	8	9	10	11*
Treatment	H	OPD	H	H	OPD	OPD	H	H	H	H	H
Cumulative clinical symptoms											
Fever	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Dyspnea	–	–	Y	–	–	–	–	–	–	Y	–
Appetite loss	Y	–	Y	–	Y	–	–	Y	–	–	–
Anosmia	Y	–	Y	–	–	–	–	–	–	–	Y
Ageusia	–	–	–	–	–	–	–	Y	–	Y	–
Cough	Y	Y	Y	Y	Y	Y	Y	Y	Y	–	Y
Disturbed sleep	–	–	–	–	–	–	Y	–	–	–	Y
Anxiety	–	–	Y	–	–	Y	–	Y	–	Y	–
Depression	–	–	Y	–	–	–	Y	–	Y	–	Y
Fatigue	–	–	Y	–	–	–	–	–	–	–	–
COVID-19 severity											
Mild	Y	Y	–	Y	Y	–	–	–	–	–	–
Moderate	–	–	–	–	–	Y	Y	Y	Y	Y	Y
Severe	–	–	Y	–	–	–	–	–	–	–	–
Laboratory findings during COVID-19											
Hemoglobin, gm/dl	–	–	12	11.6	–	15.1	12.7	12	11.3	8.6	–
TLC, per mm <sup>3</sup>	–	–	7850	8460	–	20,310	4950	13,820	8230	15,570	–
Lymphocyte, %	–	–	14	8	–	12	25	10	22	10	–
NLR, %	–	–	6	11.2	–	7	2.9	8.6	3.3	8.1	–
ALC, %	–	–	1099	676	–	2437	1237	1382	1810	1557	–
Platelet × 10 <sup>3</sup> , per mm <sup>3</sup>	–	–	243	164	–	227	230	242	232	212,000	–
IL-6, pg/ml	–	–	106.7	21.65	–	114.7	81.76	–	–	–	–
hsCRP, mg/dl	–	–	238.8	47.4	–	7.2	38	155.7	41	–	–
D-dimer, ng/ml	–	–	2070	430	–	1370	700	–	1326	174	–
Ferritin, ng/ml	–	–	248	1000	–	523	1280	–	423	–	–
PCT, ng/ml	–	–	0.24	0.05	–	0.07	–	0.8	–	–	–
SGPT, IU/ml	–	–	37	24	–	47	41	34	36	15	–
LDH, IU/l	–	–	549	252	–	326	366	–	–	–	–
COVID-19 management											
Not hospitalized	–	Y	–	–	Y	Y	–	–	–	–	–
Hospitalized, no oxygen need	–	–	–	–	–	–	Y	Y	Y	Y	Y
Low flow oxygen required	Y	–	–	Y	–	–	–	–	–	–	–
HFO/NRBM/NIV	–	–	Y	–	–	–	–	–	–	–	–
MV	–	–	–	–	–	–	–	–	–	–	–
Radiological abnormality	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Vasopressor requirement	–	–	Y	–	–	–	–	–	–	–	–
Dialysis required	–	–	–	–	–	–	–	–	–	–	–
Anti-COVID-19 therapy											
Steroid	–	–	Y	Y	–	–	Y	Y	Y	Y	Y
Anticoagulation	–	–	Y	Y	–	–	Y	Y	Y	Y	Y
Remdesivir	–	–	Y	Y	–	–	Y	Y	Y	Y	Y

Cases 1–3 died

OPD out-patient department, H hospitalized, TLC total leukocyte count, NLR neutrophil lymphocyte ratio, ALC absolute lymphocyte count, IL-6 interleukin-6, hsCRP high sensitive C reactive protein, PCT Procalcitonin, SGPT serum aspartate, LDH lactate dehydrogenase, HFO high flow oxygen, NRBM non-re-breather mask, NIV noninvasive ventilation, MV mechanical ventilation, Y yes

\* The laboratory data were not retrieved as patients were admitted in a different center for COVID-19

**Table 3** Clinical features of mucormycosis, treatment and outcome

Patient number	1	2	3	4	5	6	7	8	9	10	11
Follow-up days from COVID-19 discharge to mucormycosis symptoms	4	10	7	7	10	14	7	8	7	7	5
Classification of mucormycosis											
ROCM without brain involved	–	–	–	Y	Y	Y	Y		Y	Y	Y
ROCM with brain involved	Y	–	Y	–	–	–	–	Y	–	–	–
Pulmonary	–	Y	–	–	–	–	–	–	–	–	–
Signs and symptoms											
Proptosis	Y	–	Y	Y	Y	Y	Y	Y	Y	Y	Y
Orbital cellulitis	Y	–	Y	Y	Y	Y	–	Y	Y	–	Y
Chemosis	Y	–	Y	–	Y	Y	–	Y	Y	–	–
Epistaxis	Y	–	Y	–	Y	–	–	–	–	–	–
Ophthalmoplegia	Y	–	Y	–	Y	Y	–	–	–	–	–
Vision loss	Y	–	Y	–	–	–	–	–	–	–	–
Blurred vision	–	–	–	Y	Y	Y	–	–	–	–	–
Facial swelling	Y	–	Y	Y	Y	Y	Y	Y	Y	Y	Y
Paresthesia	Y	–	Y	–	Y	Y	–	–	–	–	–
Foul smelling discharge	Y	–	Y	–	–	Y	–	–	–	–	–
Black discharge form nose/mouth	Y	Y	Y	–	–	–	–	–	–	–	–
Unremitting fever	–	Y	–	–	–	–	–	–	–	–	–
Unresolving pneumonia	–	Y	–	–	–	–	–	–	–	–	–
Tooth ache	Y	–	Y	–	–	–	–	Y	–	–	–
Pus discharge in oral cavity	–	–	Y	–	–	–	–	–	–	–	–
Nasal crusting visible	Y	–	Y	Y	Y	Y	Y	Y	Y	Y	Y
Palate crusting visible	Y	–	Y	–	–	–	–	–	–	–	–
Headache	Y	–	Y	Y	Y	Y	Y	Y	Y	Y	Y
Treatment											
Cumulative median dose of liposomal amphotericin B (mg/kg)	290	280	280	210	240	420	400	260	240	480	210
Oral posaconazole	Y	–	–	–	–	Y	–	Y	Y	Y	–
Duration of treatment (days)	29	30	28	21	24	62	40	26	24	64	21
FESS	Y	–	Y	Y	Y	Y	Y	Y	Y	Y	Y
Outcome											
Baseline S. creatinine before COVID-19 (mg/dl)	1.3	1.4	1.6	1.4	1.2	1.8	1.1	1	1.2	1.3	2.1
Peak S. creatinine during COVID-19 (mg/dl)	2	1.5	2.1	1.9	1.2	2.3	1	1.1	1.3	1.5	3.2
AKI during COVID-19	Y	Y	Y	Y	–	Y	–	–	–	–	Y
S. creatinine before mucormycosis (mg/dl)	1.8	1.6	2.8	2.2	1.2	1.9	1.2	1.3	1.4	1.3	3.4
Peak S. creatinine during mucormycosis treatment (mg/dl)	HD	HD	HD	2.8	2.2	2.1	1.2	1.6	1.7	2.1	3.6
AKI during treatment	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N
Creatinine at last follow-up (mg/dl)	HD	HD	HD	1.5	1.3	2.1	1.1	1.2	1.4	1.3	2.6
Graft recovery	N/A	N/A	N/A	C	C	P	C	C	C	C	P
Died	Y	Y	Y	–	–	–	–	–	–	–	–
Discharged	–	–	–	Y	Y	Y	Y	Y	Y	Y	Y

*FESS* functional endoscopic sinus surgery; Case 2 was planned lung lobectomy, but died before surgery; Cases 6 and 10 are on 18th day and 17th day of amphotericin B and both are improving after FESS. Case number 1 underwent orbital exenteration; *AKI* acute kidney injury, *Y* yes, *N* no, *HD* hemodialysis, *N/A* not applicable, *C* complete (serum creatinine reached baseline at follow-up), *P* partial (serum creatinine declined but did not reach baseline levels)

(1.25–2.1), and 1.6 (1.3–2.2) mg/dl, respectively. The peak serum creatinine during mucormycosis treatment and last follow-up were 2.1 (1.67–2.65) mg/dl and 1.35 (1.27–1.95) mg/dl, respectively. All alive cases ( $n=8$ ) achieved graft recovery (two had partial and six had complete recovery).

### Comparison of COVID-19 course of the historical cohort who had not developed post-COVID-19 mucormycosis

The findings of our cohort were compared with a historical cohort of 157 KTR, in which mucormycosis was not reported (Table 4). Among the comorbidities, the presence of diabetes was associated with post-COVID-19 mucormycosis (18% vs 54.5%;  $p$ -value = 0.01). Obesity was also higher but not statistically significant (24% vs 45.5%;  $p$ -value = 0.15). Among

**Table 4** Comparison of post-COVID-19 mucormycosis with historical cohort

	Historical cohort ( $n=157$ )	Post-COVID-19 Mucor- mycosis cases ( $n=11$ )	$p$ -value
Demographic characteristics			
Median (interquartile range) age, years	43 (32–50)	42 (33.5–50)	0.80
Male sex	133 (85%)	10 (90%)	1
Obesity	38 (24%)	5 (45.5%)	0.15
Thymoglobulin induction	129 (82%)	8 (73%)	0.42
History of antirejection therapy in past	26 (17%)	2 (18%)	1
History of diabetes*	29 (18%)	6 (54.5%)	0.01
Blood group distribution, $n$ (%)			
A	37 (24%)	4 (36%)	0.46
B	61 (39%)	4 (36%)	1
AB	7 (4%)	0 (0%)	1
O	52 (33%)	4 (36%)	1
Clinical symptoms on presentation, $n$ (%)			
Fever*	91 (58%)	11 (100%)	0.003
Cough*	77 (49%)	10 (90%)	0.009
Expectoration	50 (32%)	4 (36%)	0.74
Dyspnea	46 (29%)	4 (36%)	0.73
Diarrhea	37 (23%)	1 (9%)	0.45
No symptoms	7 (4%)	0 (0%)	1
Radiological chest abnormalities			
Yes*	110 (70%)	11 (100%)	0.0001
No	47 (30%)	0 (0%)	
COVID-19 severity			
Asymptomatic	7 (4%)	0 (0%)	1
Mild	71 (45%)	8 (73%)	0.11
Moderate	48 (31%)	2 (18%)	0.50
Severe	31 (20%)	1 (9%)	0.69
Laboratory abnormalities, Median (interquartile range)			
Lymphocytes %*	20 (12–26)	12 (10–18)	0.01
Neutrophil lymphocyte ratio*	3.85 (3.3–5.8)	7 (4.6–8.3)	0.0001
High-sensitivity C-reactive protein (mg/l)	49 (19–109)	44 (38–128)	0.81
Ferritin (ng/ml)	439 (196–998)	523 (423–1000)	0.64
D-dimer ( $\mu$ g/l)	1060 (540–2330)	1013 (497–1359)	0.90
Interleukin-6 (pg/ml) *	25 (14–82)	94.2 (66–108)	0.0001
Steroids use during COVID-19	79 (50.3%)	7 (63.6%)	0.53
Allograft dysfunction during COVID-19 course	79 (50%)	5 (45.5%)	1

\* $p$ -value defined as statistically significant if value was below 0.05;  $p$ -value was measured by Chi-square with Yate's correction, Fisher test or  $T$  test as appropriate

the clinical symptoms fever (58% vs 100%;  $p$ -value = 0.003) and cough (49% vs 90%;  $p$ -value = 0.009) were reported higher in post-COVID-19 mucormycosis compared to the historical cohort. There were other differences described below which were statistically not significant. Mild cases (73% vs 43%;  $p$ -value = 0.1) were higher and there were fewer cases (20% vs 9%;  $p$ -value = 0.69) with severe COVID-19 in post-COVID-19 mucormycosis. Among the laboratory profile, lymphopenia [12 (10–18) vs 20 (12–26);  $p$ -value = 0.15] and higher neutrophil–lymphocyte ratio [7 (4.6–8.3) vs 3.85 (3.3–5.8);  $p$ -value = 0.5] was more associated with post-COVID-19 mucormycosis.

## Discussion

There is an extensive literature in the context of clinical profile and outcome of COVID-19 in SOT [14] including kidney [15–17], liver [18], lung [19], and heart [20, 21]. Transplantation activity ceased around the world during the COVID-19 peak, but it is estimated that postponing transplantation will result in excess of deaths [22] and hence depending on the COVID-19 surge and available resources, the transplantation should be resumed. There are also upcoming reports of usage of lesser potent induction and immunosuppression regimen in the COVID-19 era [23], the future implications of which is unknown.

### Need for follow-up studies in transplantation

There are various reports of follow-up studies of COVID-19 in the general population, but there are limited such reports in SOT [24, 25]. The follow-up studies have shown COVID-19 survivors to be at increased risk of adverse events [26, 27]. There have been concerning reports of readmissions and the risk of heightened clinical deterioration after discharge in COVID-19 [28–30]. In a recent report, comorbidities like diabetes are shown to be more prone to adverse events post-discharge [31, 32]. We report, our experience of readmissions for post-COVID-19 mucormycosis in KTR from India.

### Factors for the increased burden of mucormycosis in COVID-19

In a meta-analysis of 101 cases of mucormycosis associated with COVID-19 in general patients, high numbers ( $n = 82$ ) are constituted from India [33]. The exact culprit for this explosion of mucormycosis is difficult to pinpoint. A confluence of factors may be operating and are postulated for this dual infection such as overuse of steroids, uncontrolled sugars, prolonged hospital stay, and overzealous use of antibiotics, reuse of face mask, steam inhalation, zinc and iron supplementation [34, 35]. In our cohort, all the

cases had a history of mask reuse, while multivitamins such as zinc and iron were used in 4 cases, along with steam inhalation in two cases. In addition, SARS-CoV2 in itself can cause immune dysregulation and provide fertile soil for the growth of invasive fungal infections [36, 37]. We have performed an extensive comparison of KTR with COVID-19 who acquired mucormycosis compared to the cohort who did not. We found blood markers such as lymphopenia and high NLR cases to be more prone to post-COVID-19 mucormycosis. Since the advent of the pandemic, these two factors have been associated with poor prognosis and mortality in COVID-19 [38]. In addition, lymphopenia per se is an important risk factor for invasive fungal infection [39]. Another important finding is the higher proportion of diabetics and younger age compared to pre-pandemic cases. This highlights the further vulnerability of KTR for mucormycosis during the pandemic.

We also had a comparison of the outcome of mucormycosis cases in pre-pandemic times with post-COVID-19 mucormycosis. Our institute is one of the high-volume transplant centers in India, which has previously reported two to three cases of post-kidney transplant mucormycosis yearly in the pre-COVID-19 era [40]. The incidence of post-COVID-19 mucormycosis has staggeringly increased in our center compared to the pre-COVID-19 era. From 2015 to 2019, 14 cases of non-COVID-19 mucormycosis were identified in our center. Of the 14 cases, 8 (57%) patient was classified as ROCM, 5 (36%) with pulmonary mucormycosis and 1 (7%) with disseminated mucormycosis. Only 3 (21%) of the 14 cases were diabetic. The mean age of the cases was 54.7 years. One graft loss (7%) and three (21%) mortality were reported. Thus, post-COVID-19 mucormycosis in the current report are younger (44 vs 54.7) years, more frequently diabetic (54% vs 21%), and ROCM (91% vs 57%) compared to non-COVID-19 mucormycosis. In addition, the mortality reported was slightly higher in post-COVID-19 mucormycosis (27% vs 21%).

### A comparison of mucormycosis in KTR with the general population

The majority of our study had ROCM which is similar to the general population. In our report, CT scans and MRI demonstrated evidence of mucosal thickening of sinuses, orbital and intracranial involvement with maxillary and ethmoidal sinus being the most affected, which simulates the reports from the general population. Diabetes was exclusively reported in a meta-analysis of 41 general patients [41]. Our report also had half of the cases with diabetes. The reports in the general patients had severe COVID-19 and which is dissimilar to our report as the majority had either mild or moderate illness, and only one case was on oxygen therapy in our report. This observation highlights the fact



that SOT is more prone to this invasive infection compared to the general masses owing to a pre-existing chronic immunocompromised state. The mortality reported in previous reports in general patients is quite high, which emphasizes the importance of early treatment which could have relatively improved the outcome in our study of post-COVID-19 mucormycosis in SOT. Another significant concern is the graft outcome in this group of patients, where continued treatment with nephrotoxic drugs like Amphotericin B along with attenuation of maintenance IS can result in poor graft outcomes. However, in our report, only two cases had partial recovery, which was expected as IS tailoring is unavoidable in such cases. On an encouraging note, we observed that with gradual introduction and escalation of immunosuppression, creatinine level reached baseline in most cases. Thus, a favorable graft outcome was reported in the study, which is mainly attributed to maintaining a balance between immunosuppression and infection during treatment.

### How to manage post-COVID-19 mucormycosis?

Immunosuppression alteration is challenging and there is no fixed consensus in such complex cases. A personalized and low threshold for decreasing drugs was our approach which was quite successful in our report. Antifungal therapy should be started before confirmation of diagnosis even in clinically suspected cases, as early initiation of antifungal therapy is one of the most important factors responsible for survival [42]. Antifungal treatment alone is ineffective in all mucormycosis cases as there is vascular thrombosis and ischemic necrosis of tissues which prevents effective entry of antifungal drugs. Therefore, radical debridement of infected and necrotic tissue of sinuses should be performed as early as possible to improve the outcomes [35]. All of our patients underwent FESS within an average of 5 days from admission. The pulmonary mucormycosis reported in our case series succumbed before surgery, and it shows the difficulty in isolating and managing such cases. There would be many undiagnosed cases of invasive fungal infections as bronchoscopy and BAL was not done due to resource limitations in many such cases, and were treated with empirical antifungal therapies. Transplant patients with COVID-19 must have a preliminary eye, nose, oral, and cranial nerve examination for any signs such as eschar, black nasal or oral discharge, eye swelling, or cranial nerve palsy [43]. After discharge, these patients should be informed about the risk and instructed to look for any signs at home.

### Future implications

Further research in transplant settings will help in better delineating the pathogenesis and spectrum of post-COVID-19 sequelae. Eradication of COVID-19 through

vaccination or drug therapy seems far at this point. Moreover, there are reports of decreased efficacy [44] and breakthrough COVID-19 after vaccination in SOT [45, 46]. Hence, COVID-19 is still a constant menace for SOT and they should undertake adequate precautions to safeguard themselves. SOT and transplant physicians should be aware of any possibility of sequelae following COVID-19 discharge.

### Conclusion

The occurrence of mucormycosis has dramatically increased in COVID-19-recovered transplant patients. This poses additional morbidity and mortality in the follow-up of COVID-19. The strict control of blood sugars, judicious use of steroids, and balancing immunosuppression medications is essential to decrease the incidence and burden. Increased awareness on the part of the patient and physician is invariably warranted for early diagnosis and management. Prompt medical therapy along with surgical intervention is the mainstay for improving survival.

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### Declarations

**Conflict of interest** None.

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