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Short Communication

Risk factors associated with the mucormycosis epidemic during the COVID-19 pandemic

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ABSTRACT

This study was performed to assess the risk factors driving the epidemic of coronavirus disease 2019 (COVID-19)-associated mucormycosis (COVID–Mucor) in India that has accompanied the COVID-19 pandemic, particularly during the second wave. Risk factors were analysed among 164 participants: 132 COVID–Mucor (cases) and 32 non-COVID–Mucor (controls). Data from a prospective cohort study of mucormycosis over a period of 1 year were used. Diabetes mellitus remained a significant risk factor in both groups (97%), while uncontrolled diabetes mellitus (odds ratio (OR) 4.6; $P = 0.026$) and newly detected diabetes (OR 3.3; $P = 0.018$) were more common among the cases. Most patients with COVID–Mucor had mild COVID-19. Steroid use, often unwarranted, was highly associated with COVID–Mucor after adjusting for other risk factors (OR 28.4; $P = 0.001$). Serum ferritin was significantly higher ($P = 0.041$), while C-reactive protein was not, suggesting that alterations in iron metabolism may predispose to COVID–Mucor. Oxygen was used only in a small minority of patients with COVID–Mucor. The in-hospital mortality in both groups was low. In conclusion, the Indian COVID–Mucor epidemic has likely been driven by a convergence of interlinked risk factors: uncontrolled diabetes mellitus, unwarranted steroid use, and perhaps COVID-19 itself. Appropriate steroid use in patients with severe COVID-19 and screening and optimal control of hyperglycaemia can prevent COVID–Mucor.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic in India, having caused 29 500 000 confirmed cases and 374 000 deaths as of June 14, 2021, continues to have devastating consequences, including a large epidemic of COVID-19-associated mucormycosis (COVID–Mucor), manifesting as rhino-orbito-cerebral mucormycosis (ROCM), which has worsened the morbidity among vulnerable populations (JHU, 2021). Reports have shown a much larger surge in the incidence of COVID–Mucor during the second wave in 2021 than during the first wave (Patel et al., 2021; Moorthy et al., 2021).

This rapid rise in COVID–Mucor is probably caused by several factors. For patients with diabetes mellitus, lockdowns, travel restrictions, and restricted access to medical care have worsened glycaemic control, the central risk factor for ROCM in India (Chakrabarti et al., 2006). The extensive use of corticosteroids and the inflammation with deranged iron metabolism in COVID-19, as indicated by elevated ferritin levels, are possible risk factors (Symeonidis et al., 2009). Addressing these could reduce morbidity and mortality among vulnerable populations.

The aim of this study was to determine the risk factors for COVID–Mucor and the possible drivers of the surge in cases.

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Table 1
Risk factors for mucormycosis during the COVID-19 pandemic[a]

Variables	Total (n = 164)	Mucormycosis with COVID-19 (n = 132; 80.5%)	Mucormycosis without COVID-19(n = 32; 19.5%)	OR (95% CI)	P-value
Age (years)	50.91 ± 11.51	50.52 ± 11.66	52.53 ± 10.87	-	0.376
Sex					
Male	128 (78.0%)	101 (76.5%)	27 (84.4%)	0.60 (0.21–1.70)	0.335
Female	36 (22.0%)	31 (23.5%)	5 (15.6%)		
Comorbidity					
Chronic lung disease	6 (3.7%)	3 (2.3%)	3 (9.4%)	0.22 (0.04–1.17)	0.089
Ischemic heart disease	7 (4.3%)	5 (3.8%)	2 (6.2%)	0.59 (0.10–3.19)	0.411
Chronic kidney disease	7 (4.3%)	7 (5.3%)	0	-	0.212
Cerebrovascular events	2 (1.2%)	2 (1.5%)	0	-	0.647
Chronic liver disease	1 (0.6%)	0	1 (3.1%)	-	0.195
HIV/AIDS	2 (1.2%)	2 (1.5%)	0	-	0.647
Diabetes mellitus	159 (97.7%)	129 (97.7%)	30 (93.8%)	2.86 (0.45–17.92)	0.240
Uncontrolled diabetes mellitus	156 (95.1%)	128 (97.0%)	28 (87.5%)	4.57 (1.07–19.39)	0.026*
Newly detected diabetes mellitus	56 (35.2%)	51 (39.5%)	5 (16.7%)	3.26 (1.17–9.09)	0.018*
Diabetic ketoacidosis at presentation	6 (3.7%)	6 (4.5%)	0	-	0.266
HbA1c (%)	10.74 ± 3.39	10.84 ± 3.58	10.31 ± 2.42	-	0.426
Steroid use	74 (45.1%)	73 (55.3%)	1 (3.1%)	38.35 (5.08–289.33)	<0.001*
Serum ferritin (ng/ml)	451.75 ± 499.71	490.88 ± 521.9	290.3 ± 358.08	1.001 (1.000–1.002)	0.041
CRP (mg/L)	80.91 ± 71.99	85.05 ± 70.72	63.84 ± 75.76	-	0.135
O_2 therapy	19 (11.6%)	19 (14.4%)	0	-	0.012*
Ventilation (NIV/IMV)	3 (1.8%)	3 (2.3%)	0	-	0.519
Vaccination status					
Vaccinated	5 (3.0%)	4 (3.0%)	1 (3.1%)	0.96 (0.10–8.9)	0.667
Clinical presentation					
Acute (≤7 days)	76 (46.3%)	69 (52.3%)	7 (21.9%)	3.91 (1.58–9.66)	0.002*
Subacute (8–21 days)	88 (53.7%)	63 (47.7%)	25 (78.1%)		
Extent of involvement					
Sinus limited	164 (100.0%)	132 (100.0%)	32 (100.0%)	-	-
Orbital involvement	116 (70.7%)	93 (70.5%)	23 (71.9%)	0.93 (0.39–2.19)	0.874
CNS involvement	51 (31.1%)	39 (29.5%)	12 (37.5%)	0.69 (0.31–1.56)	0.383
Outcome					
In-hospital mortality	13 (7.9%)	13 (9.8%)	0	-	0.053

CI, confidence interval; CNS, central nervous system; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; HbA1c, haemoglobin A1c; IMV, invasive mechanical ventilation; NIV, non-invasive ventilation; OR, odds ratio. [Au?6]

[a] Data presented as n (%), or as mean±standard deviation.

* $P < 0.05$ [Au?6].

Methods

This study analysed risk factors for COVID–Mucor using data from a prospective cohort study, the POISE Mucor Study, conducted at Christian Medical College, Vellore, a 3000-bed teaching hospital in South India. The period covered was from July 1, 2020 to June 10, 2021. The study was approved by the Institutional Review Board and Ethics Committee (No. 12930/24.06.2020, with the amendment approved on July 24, 2021).

Patients aged ≥18 years with clinical and imaging features suggestive of ROCM, which was confirmed by histopathology showing broad aseptate fungal hyphae with tissue damage and/or fungal culture confirming Mucorales, were included. Cases were patients with COVID-19 confirmed by RT-PCR for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on a nasopharyngeal sample within 3 months of mucormycosis. Patients with ROCM and negative RT-PCR for SARS-CoV-2 were the controls. The study variables were compared between cases and controls using Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Statistical significance was defined as a P-value <0.05.

Results

The mean age of the 164 patients (132 cases and 32 controls) was 51 years; 78% were male and 22% were female. Details are presented in Table 1. The weekly numbers of cases and controls during the study period are shown in Figure 1. Most patients with COVID–Mucor had mild COVID-19 (76.7%); 16.3% had moderate disease and 7% had severe/critical disease, based on the severity assessment criteria (Wu Z et al., 2020).

Diabetes mellitus (present in 97%) remained a strong predisposing factor in both groups. Uncontrolled diabetes mellitus (haemoglobin A1c (HbA1c) of >7.0%), 40% of which was newly detected, was associated with COVID–Mucor (odds ratio (OR) 4.6; $P = 0.026$). Diabetic ketoacidosis was only noted in the COVID–Mucor group, but this was not statistically significant. Median HbA1c was higher in the co-infected group, but this was also not significant.

Steroid use was common, even in mild disease, and was strongly associated with COVID–Mucor (OR 38.3; $P < 0.001$). The majority of these patients (53/74; 71.6%) had received high-dose steroids (>40 mg prednisolone or equivalent), and methylprednisolone or dexamethasone was the most commonly used steroid. Oxygen use was uncommon among cases (14.4%). Serum ferritin was significantly higher among patients with COVID–Mucor ($P = 0.041$), whereas C-reactive protein was not. Acute presentation of ROCM was more common in COVID–Mucor.

Involvement of the brain and orbit was similar in the two groups. Multivariate analysis (Table 2) revealed that steroid use was independently associated with COVID–Mucor (OR 28.4; $P = 0.001$).

Discussion

India emerged as a hotspot for COVID–Mucor during the second wave of the pandemic, with more than 4000 cases documented. This study showed that while traditional risk fac-

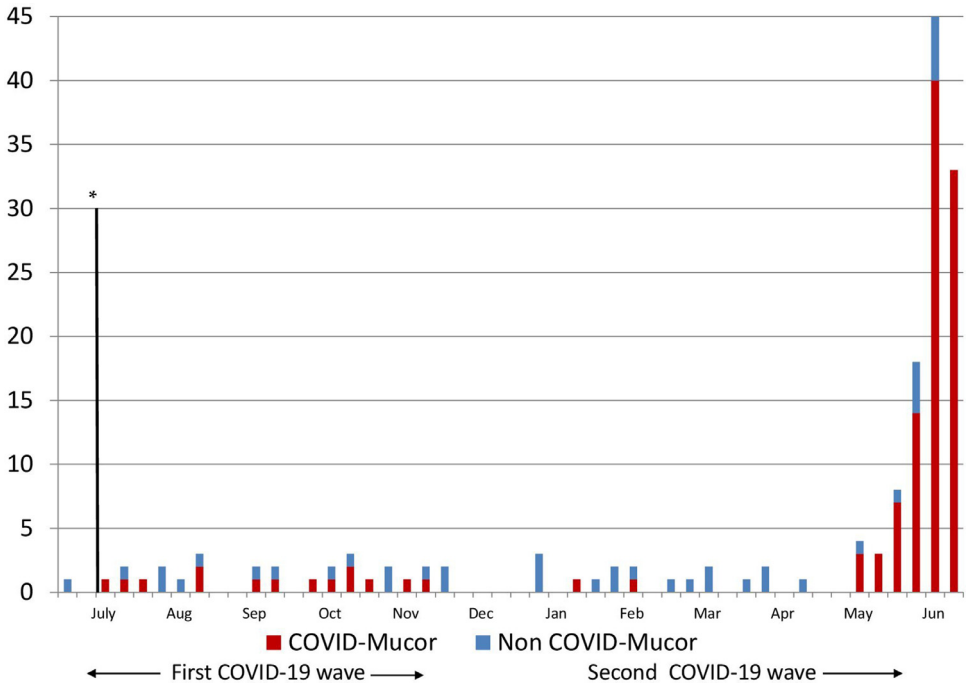

Figure 1. Weekly numbers of COVID–Mucor and non-COVID–Mucor cases from July 2020 to June 2021.*The black vertical line represents publication of the RECOVERY Trial (RECOVERY Collaborative Group, Horby P et al., 2020). [Au?3]

Table 2
Multivariate logistic regression analysis for risk factors for COVID–Mucor[a]

Variables	Total (n = 164)	Mucormycosis with COVID-19 (n = 132; 80.5%)	Mucormycosis without COVID-19 (n = 32; 19.5%)	OR (95% CI)	AOR (95% CI)	P-value
Uncontrolled DM	156 (95.1%)	128 (97.0%)	28 (87.5%)	4.57 (1.07–19.39)	3.07 (0.38–24.41)	0.289
Newly detected DM	56 (35.2%)	51 (39.5%)	5 (16.7%)	3.26 (1.17–9.09)	2.88 (0.90–9.20)	0.073
Steroid use	74 (45.1%)	73 (55.3%)	1 (3.1%)	38.35 (5.08–289.33)	28.40 (3.63–221.75)	0.001*
Serum ferritin(ng/ml)	451.75 ± 499.71	490.88 ± 521.9	290.3 ± 358.08	1.001 (1.000–1.002)	1.001 (1.000–1.002)	0.144
O_2 therapy	19 (11.6%)	19 (14.4%)	0	-	-	0.998
Clinical presentation						
Acute (≤7 days)	76 (46.3%)	69 (52.3%)	7 (21.9%)	3.91 (1.58–9.66)	2.74 (0.94–7.95)	0.063
Subacute (8–21 days)	88 (53.7%)	63 (47.7%)	25 (78.1%)			

AOR, adjusted odds ratio; CI, confidence interval; COVID-19, coronavirus disease 2019; DM, diabetes mellitus; OR, odds ratio. [Au?6]
[a] Data presented as n (%), or as mean±standard deviation.
* $P < 0.05$ [Au?6].

tors such as uncontrolled diabetes mellitus contributed, the widespread use of steroids, even for mild COVID-19, was a major driver of COVID–Mucor. Additionally, there were pointers towards a complex interaction and confluence of various determinants, including possibly the SARS-CoV-2 infection itself. High blood sugar, corticosteroids, and iron overload all lead to phagocyte dysfunction, likely the more immediate cause of mucormycosis.

The vast majority of patients, 97%, had underlying diabetes mellitus, a rate higher than that found in a multicentre COVID–Mucor study from India performed during the first wave of the COVID-19 pandemic, in which two-thirds of patients had this disease (Patel et al., 2021) [Au?2]. Hyperglycaemia lasting up to 3 months associated with COVID-19 has been reported. An aberrant cytokine milieu and insulin resistance, rather than beta cell infection, seem to be the reasons (Montefusco et al., 2021).

Steroid use also induces hyperglycaemia, and steroid use was significantly associated with mucormycosis (OR 28.4; $P = 0.001$). Despite extensive use in rheumatological diseases, the incidence of mucormycosis remains low, suggesting that steroid use in conjunction with other factors has driven the COVID–Mucor epidemic in India.

Mean serum ferritin levels, a marker of immune dysregulation and an integral part of iron metabolism, were markedly elevated among cases. In addition to hyperglycaemia and steroid use, SARS-CoV-2 infection with possible alterations in iron metabolism may have predisposed to mucormycosis (Lammaert et al., 2012; Kentaro et al., 2021).

Finally, the recent surge in COVID-19 cases was associated with an unprecedented shortage of oxygen availability in India, resulting in the use of industrial-grade oxygen in some parts of the country. Although exposure to impure oxygen was thought to be a possible risk factor, only a fraction of patients in this study required oxygen or ventilatory support, suggesting that it was unlikely a significant factor.

The diagnosis of non-COVID–Mucor in this study was based on a single negative RT-PCR. Hence there is a small chance of misclassification of controls.

In summary, the current Indian mucormycosis epidemic was precipitated by a unique confluence of risk factors: diabetes mellitus, widespread use of steroids, and perhaps SARS-CoV-2 infection itself. Restricting steroid use to patients with severe COVID-19 requiring oxygen therapy, and screening for and optimally controlling hyperglycaemia can prevent COVID–Mucor in a large majority.

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Ethics statement

This study was reviewed and approved by the Institutional Review Board and Ethics Committee of Christian Medical College, Vellore (No. 12930/24.06.2020, with the amendment approved on July 24, 2021). All patients provided written informed consent.

Declaration of Competing Interest

The authors declare no conflict of interest.

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