**RESEARCH ARTICLE**

**Hyperglycemia and steroid use increase the risk of rhino-orbito-cerebral mucormycosis regardless of COVID-19 hospitalization: Case-control study, India**

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**Abstract**

**Background**

In the ongoing COVID-19 pandemic, an increased incidence of ROCM was noted in India among those infected with COVID. We determined risk factors for rhino-orbito-cerebral...
mucormycosis (ROCM) post Coronavirus disease 2019 (COVID-19) among those never and ever hospitalized for COVID-19 separately through a multicentric, hospital-based, unmatched case-control study across India.

Methods
We defined cases and controls as those with and without post-COVID ROCM, respectively. We compared their socio-demographics, co-morbidities, steroid use, glycaemic status, and practices. We calculated crude and adjusted odds ratio (AOR) with 95% confidence intervals (CI) through logistic regression. The covariates with a p-value for crude OR of less than 0.20 were considered for the regression model.

Results
Among hospitalised, we recruited 267 cases and 256 controls and 116 cases and 231 controls among never hospitalised. Risk factors (AOR; 95% CI) for post-COVID ROCM among the hospitalised were age 45–59 years (2.1; 1.4 to 3.1), having diabetes mellitus (4.9; 3.4 to 7.1), elevated plasma glucose (6.4; 2.4 to 17.2), steroid use (3.2; 2 to 5.2) and frequent nasal washing (4.8; 1.4 to 17). Among those never hospitalised, age ≥ 60 years (6.6; 3.3 to 13.3), having diabetes mellitus (6.7; 3.8 to 11.6), elevated plasma glucose (13.7; 2.2 to 84), steroid use (9.8; 5.8 to 16.6), and cloth facemask use (2.6; 1.5 to 4.5) were associated with increased risk of post-COVID ROCM.

Conclusions
Hyperglycemia, irrespective of having diabetes mellitus and steroid use, was associated with an increased risk of ROCM independent of COVID-19 hospitalisation. Rational steroid usage and glucose monitoring may reduce the risk of post-COVID.

Introduction
Mucormycosis is a rare opportunistic angio-invasive fungal infection associated with high morbidity and mortality. Several clinical presentations of mucormycosis have been described depending on the site of involvement, the most common being rhino-orbito-cerebral mucormycosis (ROCM). Globally, reported incidence (per million population) ranges from 0.005 to 1.7 in the pre-Coronavirus disease 2019 (COVID-19) era, and in India, the incidence is 140, about 80 times higher than reported in developed countries [1]. This higher burden could be due to the relatively significant burden of uncontrolled diabetes mellitus [2].

Rapid progression of Mucormycosis makes its early diagnosis and treatment critical, considering that a delay of even six days doubles 30-day fatality from 32% to 66% [3]. Tissue necrosis resulting from angioinvasion and vascular thrombosis is a hallmark of the disease but is a late sign. Patients with diabetes, on steroids, with immunocompromised states such as haematological malignancy, hematopoietic/solid organ cell transplantation, treatment with deferoxamine, acquired immunodeficiencies, trauma, and malnutrition are at high risk for mucormycosis [4, 5]. A high index of suspicion is necessary for them, especially if they report unilateral facial pain or swelling, orbital swelling or proptosis.

In the context of the ongoing COVID-19 pandemic in India, reports highlighted the increased incidence of ROCM, otherwise a rare entity [6–8]. The risk of COVID-19 associated
ROCM is reported to be higher among men, diabetics, more so with poor glycemic control, steroid users, and severe COVID-19 [5, 6, 8–11]. The usual time of diagnosis with mucormycosis among COVID–19 varied from that of a concurrent infection to even seven weeks post COVID-19 diagnosis [9]. Towards the end of June 2021, the Indian health ministry reported over 40,000 mucormycosis cases and mandated its notification while several Indian states declared it an epidemic [10]. The upsurge of mucormycosis amidst the ongoing pandemic was hypothesized to be driven by the interplay between host factors like weakened immunity following COVID-19, poorly controlled diabetes mellitus, rampant use of steroids/immunomodulators, and other factors like prolonged hospital stay, continuous oxygen support, poor hospital infection control, and nursing care practices [11]. Indian researchers documented various factors linked with COVID-19 associated mucormycosis, including steroid use, diabetes mellitus, higher serum ferritin, and hypoxemia [12, 13]. Few studies have focused on highly immunocompromised groups [14] and individual-level risk factors such as zinc supplementation [15] and mean serum iron and total iron-binding capacity [16]. However, many of these studies lacked adequate sample size, did not comprehensively evaluate the range of risk factors, and did not specifically generate evidence on differential factors operating for PC-ROCM by their COVID-19 specific hospitalization status and factors thereof. Such studies may inform ways to be prepared and thus reduce the burden of PC-ROCM. Therefore, we conducted a multicentric study to determine the risk factors for PC-ROCM separately among those ever and never-hospitalised for COVID-19 management.

Methods

Study design and setting

We designed and conducted an unmatched case-control study in 20 tertiary care hospitals from the public and private sectors providing management for COVID-19 and ROCM across India during June and July 2021.

Study participants

Test positive COVID-19. Those testing positive for Severe Acute Respiratory Syndrome (SARS)-Coronavirus (CoV)-2 through rRT-PCR/TrueNat/ GeneXpert/Rapid Antigen Test.

Post COVID rhino-orbito-cerebral mucormycosis (PC-ROCM). Individuals diagnosed with ROCM clinically and/or based on diagnostic nasal endoscopy and/or contrast-enhanced MRI/CT scan with laboratory confirmation on direct microscopy (KOH/ Calcofluor white) or culture or histopathology or molecular diagnostic methods (diagnosed after April 1, 2021) and tested positive for COVID-19 any time between 12 weeks to 1 day before ROCM diagnosis.

Case for the ever-hospitalized group. Patients who had PC-ROCM and received hospitalised COVID-19 care, irrespective of the duration of hospitalization.

Controls for the ever-hospitalized group. Patients who had the negative history of ROCM symptoms and received hospitalised COVID-19 care, irrespective of the duration of hospitalization.

Case for the never-hospitalized group. Patients who had PC-ROCM and received COVID-19 care at home/COVID care centre only.

Control for the never-hospitalized group. Patients who had a negative history of ROCM symptoms and received COVID-19 care at home/COVID care centre only.

Sample size for case-control study among ever-hospitalised for COVID-19. We needed 256 cases and controls each based on assumptions that 68% of the hospitalised COVID-19 patients were treated with steroids [17], odds ratio (OR) of at least two for steroid use, alpha error of 5%, power of 80%, 1:1 ratio of cases to controls and 25% non-response.
Sample size for case-control study among never-hospitalised for COVID-19. We needed 108 cases and 216 controls for the assumptions that 15% of the never-hospitalised COVID-19 patients were treated with steroids, expected OR of at least three for steroid use, alpha error of 5%, power of 80%, the ratio of cases: controls to be 1:2 and 25% non-response.

We used OpenEpi Online calculator version 3.01 for sample size calculation (https://www.openepi.com/SampleSize/SSCC.htm).

Selection of cases and controls
Cases were recruited from those who received care for ROCM from the study hospital. Controls were recruited from those tested positive for COVID-19 at the study hospital and on the same date as the case. We excluded those were 18 years of age, without information on COVID-19 hospitalisations/management, and who were not traceable. Each study hospital created a sampling frame of cases and controls separately for hospitalised and never-hospitalised groups (during COVID-19 illness). We selected controls through simple random sampling from the list of patients who tested positive for COVID-19 on the same date as cases through a custom-built web tool [18].

Data collection and data quality management
We developed case record forms (CRFs) to gather data on exposure (a) from the time of diagnosis of COVID-19 until discharge from the hospital/home care and (b) from the time of discharge from the hospital for COVID/19 until the development of PC-ROCM. Trained site investigators interviewed the cases in the hospital and abstracted treatment and diagnostic information from hospital records. For controls, data was collected through telephone interviews, and relevant clinical information was abstracted from hospital records/prescriptions. The filled-in CRFs were shared online with the I-MUCOR study group for data entry into Research Electronic Data Capture (REDCap) software (https://www.project-redcap.org/).

Statistical analysis
We used descriptive statistics (percentages), means (standard deviation), median (inter-quartile range) to describe cases and controls. We converted steroid dose into prednisolone equivalents [19] and used the median cumulative dose among the controls to categorize the variable into low and high steroid use. We used the median duration of hospitalisation among controls to dichotomize the cases. While evaluating the blood sugar on PC-ROCM, the glycaemic status during the COVID-19 illness is crucial, rather than HbA1C, which would depict the past control, including the period before COVID-19 infection. Hence, we defined hyperglycemia as random blood sugar value above 200 mg/dl and fasting blood sugar above 126mg/dl, at least once during COVID-19 management was considered as elevated plasma glucose.

We used logistic regression to calculate crude and adjusted odds ratios (AOR) with 95% CI. For each of the ever- and never-hospitalised groups we selected covariates with a p-value for crude OR of less 0.20 for consideration in the multiple regression model [20]. The variables rural/urban residence, type of house, and occupation were collinear. Hence occupation was chosen for further analysis.

Using these variables, we constructed directed acyclic graphs (DAG) separately for the never- and ever-hospitalized using DAGitty software (http://www.dagitty.net/) [21] to visually represent the causal relationships between various risk factors and PC-ROCM. (Fig 1) The causal relationships were assumed based on literature review, and contextual understanding arrived at by consensus among the research team, including specialists in medicine, otorhinolaryngology, epidemiology, and public health. We used the backdoor criterion to identify the
Fig 1. Directed acyclic graph of Post COVID-19 rhino-orbito-cerebral mucormycosis for (a) ever-hospitalised and (b) never-hospitalised patients.

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minimal set of covariates as potential confounders that needed to be adjusted for each risk factor separately [21]. We compared the -2 log-likelihood ratios of models with and without potential confounders to arrive at the final list of covariates to be adjusted for each risk factor using multiple logistic regression. We did not observe any difference between the effect estimates obtained with or without adjustment for ‘study site’ (data not shown). We hence did not include it in the final logistic regression model. We used Stata ver. 16 (StataCorp LLC, Texas, USA) for the analyses.

Human participants protection

The Institutional Human Ethics Committee of the lead institutions of I-MUCOR and all the study hospitals approved the study procedures. The treating physicians of the study hospitals recruited study participants after explaining the study procedures and obtaining written informed consent directly from the cases and through digital modes from the controls.

Results

Among cases and controls ever-hospitalised for COVID-19

Profile of cases and controls (Table 1). We included 267 cases and 256 controls. More cases than controls (48% vs. 35%) were 45–59 years old. The majority of cases and controls were men (67% and 62%), resided in a city or town (63% vs. 72%), had completed secondary education.

| Characteristics | Ever-hospitalised for COVID-19 | | | | Never-hospitalised for COVID-19 | | | |
|-----------------|-------------------------------|--|--|---|-----------------|---|---|
| | Cases (N = 267) | Controls (N = 256) | p value | Cases (N = 116) | Controls (N = 231) | p value |
| | n (%) | n (%) | | n (%) | n (%) | |
| Age group [5] (in years) | | | | | | |
| 18–44 | 75 (28-1) | 108 (42-4) | 0.002 | 37 (31-9) | 169 (73-2) | <0-001 |
| 45–59 | 129 (48-3) | 90 (35-3) | | 53 (45-7) | 44 (19-0) | |
| ≥ 60 | 63 (23-6) | 57 (22-4) | | 26 (22-4) | 18 (7-8) | |
| Gender | | | | | | |
| Female | 89 (33-3) | 97 (37-9) | 0.2-76 | 41 (35-3) | 98 (42-4) | 0-204 |
| Male | 178 (66-7) | 159 (62-1) | | 75 (65-7) | 133 (57-6) | |
| Place of residence [6] | | | | | | |
| City or town | 168 (63-2) | 184 (71-9) | <0-001 | 66 (56-9) | 181 (78-4) | <0-001 |
| Village | 98 (36-8) | 72 (28-1) | | 50 (43-1) | 50 (21-6) | |
| Occupation [7] | | | | | | |
| Unemployed | 103 (38-8) | 96 (37-5) | 0-101 | 42 (36-2) | 79 (34-3) | 0-026 |
| Agriculture | 31 (11-6) | 17 (6-7) | | 22 (19-0) | 22 (9-6) | |
| Other types of occupation | 132 (49-6) | 143 (55-9) | | 52 (44-8) | 129 (56-1) | |
| Education [8] | | | | | | |
| No formal education | 28 (10-0) | 24 (9-0) | 0.051 | 16 (13-8) | 13 (5-6) | <0-001 * |
| Primary level | 57 (21-0) | 38 (15-0) | | 23 (19-8) | 27 (11-7) | |
| Secondary level | 81 (30-0) | 75 (29-0) | | 39 (33-6) | 55 (23-9) | |
| Graduate and above | 101 (38-0) | 118 (46-0) | | 38 (32-8) | 135 (58-7) | |
| Housing type [9] | | | | | | |
| Pucca | 249 (93-3) | 248 (96-9) | 0-057 | 98 (85-0) | 222 (97-0) | <0-001 |
| Semi-rucca / kutcha | 18 (6-7) | 8 (3-1) | | 18 (15-0) | 8 (3-0) | |

Missing values:

* Age for 1 control in ever-hospitalised group;
† Place of residence for 1 case in ever-hospitalised group;
‡ occupation for 1 case in ever-hospitalised and 1 control in never-hospitalised groups;
§ education for 1 control each in ever and never-hospitalised groups;
* Housing type for 1 control in never-hospitalised group, pucca house indicates solid and permanent structure, kutcha house indicates temporary structure.

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and graduate education (68% vs. 75%), and lived in pucca (solid and permanent structure) house (93% vs. 97%).

**Analysis of risk factors for PC-ROCM (Table 2).** A significantly higher proportion of cases had a known history of diabetes mellitus (71% vs. 33%) than controls. Participants with diabetes mellitus were five times more likely to have PC-ROCM (AOR = 4·9; 95% CI = 3·4 to 7·1). A substantial number of non-diabetic cases and controls had elevated plasma glucose levels (97% and 53%, respectively, data not shown in the table). Hence, it necessitated the inclusion of plasma glucose as an independent variable in the multiple regression model. Elevated plasma glucose was six times more likely to be associated with PC-ROCM after adjusting for diabetes mellitus and steroid use (AOR = 6·4; 95% CI = 2·4 to 17·2; Fig 1). After adjusting for confounders, hypertension, occupation, duration of hospitalization, receipt of oxygen support, use of antibiotics, remdesivir, and ivermectin were not associated with PC-ROCM.

Steroid use, irrespective of the cumulative dose, was significantly associated with PC-ROCM (OR = 3·2; 95% CI: 2·0 to 5·2) (Table 2). No dose-response relationship was documented between the amount of steroid use and duration of hospitalization with PC-ROCM. After adjustment for age, diabetes mellitus, and hypertension, the oxygen support was not associated with PC-ROCM (AOR = 1·0; 95% CI = 0·7 to 1·5). Among the cases who received oxygen support, nearly one-third (32%; n = 57) received it through cylinders. Cases had three times higher odds of receiving oxygen support through cylinders (AOR = 3·5, 95% CI = 1·9 to 6·1) than controls. Cases had around five times higher odds of practicing frequent nasal washing than controls (AOR = 4·8, 95% CI = 1·4 to 17·0) after adjusting for age. Presence of end organ damage and type of treatment for diabetes mellitus was not associated with PC-ROCM (S1 Table).

**Among cases and controls never-hospitalized for COVID-19**

**Profile of cases and controls (Table 1).** We included 116 cases and 231 controls. The proportion aged 45–59 years and ≥60 years was significantly higher among the cases (46% and 22%) as compared to the controls (19% and 8%). The majority of the cases than the controls were men (66% vs. 58%), had completed secondary and graduate-level education (66% vs. 83%), and lived in a pucca house (85% vs. 97%). More cases were village residents (43%) than the controls (22%).

**Analysis of risk factors for PC-ROCM (Table 3).** Cases were more likely to be ≥45 years of age. Cases were seven times more likely to have had diabetes mellitus (AOR = 6·7; 95% CI = 3·8 to 11·6) than controls after adjusting for age. After adjusting for steroid usage, those with elevated plasma glucose levels were 14 times more likely to have PC-ROCM (AOR = 13·7; 95% CI = 2·2 to 84·0). Steroid usage was associated with PC-ROCM (AOR for above median levels = 6·1; below median levels = 4·1).

Cases had lower odds of using oxygen concentrators/humidifiers than the controls (AOR = 0·3; 95% CI = 0·1 to 0·8) after adjusting for age, diabetes mellitus, and hypertension. The odds of use of steam inhalation was also lower among the cases than in the controls (OR = 0·5; 95% CI = 0·3 to 0·8). Nasal washing, other medications such as remdesivir, ivermectin, iron/zinc supplementation, and medications from the traditional medical system were not associated with PC-ROCM.

**Discussion**

The results of this pan-India case-control study indicates that older age, hyperglycemia, diabetes mellitus, and steroid usage were associated with PC-ROCM, irrespective of hospitalization for COVID-19. Frequent nasal wash and use of oxygen from cylinders were additional risk
## Table 2. Risk factors for mucormycosis among ever-hospitalised COVID-19 patients, multi-centric case-control study of post-COVID rhino-orbital-cerebral mucormycosis, India, 2021.

| Characteristics | Cases (N = 267) | Controls (N = 256) | Odds Ratio (95% CI) |
|-----------------|-----------------|-------------------|---------------------|
| **Socio-Demographic** |                 |                   |                     |
| Age group (years)† | 18–44           | 108 (42.4)        | Reference           |
|                  | 45–59           | 90 (35.3)         | 2.1 (1.4 to 3.1)    |
|                  | ≥ 60            | 57 (22.4)         | 1.6 (1.0 to 2.5)    |
| Occupation§     | Agricultural    | 17 (6.6)          | 1.8 (1.0 to 3.4)    |
| Non-agricultural occupations & unemployed | 239 (93.4) |                  |                      |
| **Co-Morbidity** |                 |                   |                     |
| Presence of Diabetes Mellitus‡ | 84 (32.8) | 11.5 (4.6 to 28.5) | <0.001 |
| Presence of Hypertension§ | 60 (23.4) | 1.6 (1.1 to 2.3) | 0.026 |
| Presence of any other comorbidities | 24 (9.0) | 0.9 (0.5 to 1.7) | 0.873 |
| **Clinical Status/Management** |                 |                   |                     |
| Elevated plasma glucose level¶ | 80 (70.2) | 11.5 (4.6 to 28.5) | <0.001 |
| Median Serum ferritin in µg/L (IQR) | 578 (297–796) | 474 (166–723) | 0.122 |
| **Steroid use††** | 239 (89.5) | 186 (72.7) | 3.2 (2.0 to 5.2) |
| More than 480 mg prednisolone equivalent [Median dose among controls] | 124 (46.4) | 89 (34.8) | 3.5 (2.1 to 5.8) |
| Less than 480 mg prednisolone equivalent [Median dose among controls] | 93 (36.3) | 2.8 (1.7 to 4.7) |
| Unknown dose | 11 (4.1) | 4 (1.6) | 6.9 (2.0 to 23.4) |
| No steroid use | 70 (27.3) | Reference |
| **Antibiotic use†‡** | 237 (88.8) | 213 (83.2) | 1.6 (1.0 to 2.6) |
| More than 9 days of hospitalization‡ [Median among controls] | 120 (46.9) | 1.3 (0.9 to 1.8) |
| **Received Oxygen support** * | 156 (60.9) | 1.3 (0.9 to 1.8) |
| **Source of Oxygen support among those who received oxygen support (n = 333)††** | 177 (66.3) | 203 (61.4) | 1.0 (0.7 to 1.5) |
| Oxygen cylinder | 57 (32.2) | 19 (12.1) | 3.5 (1.9 to 6.1) |
| Other sources of oxygen | 120 (67.8) | 137 (87.9) | Reference |
| **Used other medications** |                 |                   |                     |
| Remdesivir | 126 (47.2) | 123 (48.1) | 1.0 (0.7 to 1.4) |
| Ivermectin | 103 (38.6) | 95 (37.1) | 1.1 (0.7 to 1.5) |
| Hydroxychloroquine | 3 (1.1) | 0 | - |
| Tocilizumab | 2 (0.7) | 2 (0.8) | 1.0 (0.1 to 6.8) |
| Iron supplements | 12 (4.5) | 7 (2.7) | 1.7 (0.6 to 4.3) |
| Zinc containing vitamin supplements* | 211 (82.4) | 0.7 (0.5 to 1.1) |
| Indian traditional medicines (Ayush) | 8 (3.1) | 1.1 (0.4 to 2.8) |
| **Nasal wash†** |                 |                   |                     |
| Did many times in a day | 15 (5.6) | 3 (1.2) | 5.1 (1.5 to 17.9) |
| Once a day | 17 (6.4) | 12 (4.7) | 1.5 (0.7 to 3.1) |
| Never done | 235 (88.0) | 241 (94.1) | Reference |
| **Never practiced steam inhalation** | 186 (69.7) | 189 (73.8) | 1.2 (0.8 to 1.8) |
| Under home isolation prior to hospitalization | 119 (44.6) | 106 (41.4) | 1.1 (0.8 to 1.6) |
| Median (IQR) days of home isolation | 3 (2.6) | 4 (2.6) | 0.835 |
| Oxygen use at home | 14 (5.2) | 14 (5.5) | 1.0 (0.4 to 2.0) |
| **Mask Use†** |                 |                   |                     |
| Prior to onset of COVID-19 | Reference |

(Continued)
factors among those ever-hospitalised. In the never-hospitalised group, individuals reporting the use of oxygen through concentrators/humidifiers and practice of steam inhalation were at a lower risk for PC-ROCM.

Hyperglycemia as an independent risk factor for PC-ROCM, irrespective of hospitalization for COVID-19, merits attention. Published reports indicate that COVID-19 is associated with hyperglycemia in general. Hyperglycemia or new-onset diabetes mellitus has been observed with COVID-19 [22] and is hypothesized to predispose to ROCM through phagocyte dysfunction, defective chemotaxis, and impaired intracellular killing of Mucorales [11, 23]. Hyperglycaemia during COVID-19 could be due to SARS-CoV-2 infection per se [11] and steroid usage during treatment of COVID-19 [23, 24]. Therefore, it is critical to distinguish the influence of prior diabetic status and hyperglycemia induced by steroid/COVID-19 on PC-ROCM. This emphasises tight monitoring of plasma glucose even among non-diabetic COVID-19 patients.

Diabetes mellitus as a risk factor for ROCM is well documented during the pre-COVID era [5, 25]. In COVID-19 pandemic, pre-existing diabetes could worsen glycaemic control, thereby causing ketoacidosis and increasing the risk of mucormycosis [26, 27]. Our finding is consistent with published studies reporting a higher risk of mucormycosis among people with diabetes and more so after COVID-19 [4, 9, 11, 24, 26–28].

In this study steroid usage was associated with PC-ROCM independent of hospitalisation, irrespective of cumulative dose. We documented substantial steroid usage among all COVID-19 patients and more so among the never-hospitalised group indicating irrational and unmonitored use. Poor adherence to the guidelines on steroid use for COVID-19 has been reported

| Characteristics | Cases (N = 267) | Controls (N = 256) | Odds Ratio (95% CI) |
|-----------------|----------------|-------------------|---------------------|
|                 | n (%)          | n (%)             | Crude estimate | p value | Adjusted estimate | p value |
| Cloth masks only | 105 (39.3) | 98 (38.3) | 0.7 (0.3 to 1.5) | 0.374 | -                |
| Surgical masks only | 102 (38.2) | 112 (43.7) | 0.6 (0.3 to 1.3) | 0.198 | -                |
| Both Cloth and Surgical mask | 43 (16.1) | 35 (13.7) | 0.8 (0.3 to 1.9) | 0.609 | -                |
| No masks | 17 (6.4) | 11 (4.3) | Reference | - |
| **After hospitalisation** | | | | |
| Cloth masks only | 59 (22.9) | 67 (26.6) | 0.6 (0.2 to 1.7) | 0.356 | -                |
| Surgical masks only | 151 (58.5) | 152 (60.3) | 0.7 (0.3 to 1.9) | 0.473 | -                |
| Both Cloth and Surgical mask | 38 (14.7) | 26 (10.3) | 1.0 (0.3 to 3.0) | 0.967 | -                |
| No masks | 10 (3.8) | 7 (2.8) | Reference | - |

* 1 missing data among cases;  † No confounders identified;  ‡ Adjusted for age;  § 1 missing data among cases;  †† Adjusted for age and diabetes mellitus;  ‡‡ Adjusted for diabetes mellitus, and Steroid use;  ‡‡‡ data missing for 99 cases and 142 controls;  ††† data missing for 9 cases and 4 controls;  ‡‡‡‡ Adjusted for diabetes mellitus, hypertension, and steroid use;  ‡‡‡‡‡ Adjusted for age, diabetes mellitus, and hypertension;  †††† Missing values, n = 90;  †††† Missing values, n = 105;  ¥ co-morbidities includes heart disease, chronic kidney disease, cancer, organ transplant, HIV/AIDS, chronic sinusitis

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### Table 3. Risk factors for mucormycosis among never-hospitalised COVID-19 patients, multi-centric case-control study of post-COVID rhino-orbito-cerebral mucormycosis, India, 2021.

| Characteristics | Cases (N = 116) | Controls (N = 231) | Odds Ratio (95% CI) |
|-----------------|----------------|-------------------|---------------------|
| **SOCIO-DEMOGRAPHIC** |                |                   |                     |
| Age group (years)* |                |                   |                     |
| 18–44           | 37 (31.9)      | 169 (73.2)        | Reference           |
| 45–59           | 53 (45.7)      | 44 (19.0)         | 5.5 (3.2 to 9.4)    | <0.001 | - |
| ≥ 60            | 26 (22.4)      | 18 (7.8)          | 6.6 (3.3 to 13.3)   | 0.001  | - |
| Occupation†§‡   |                |                   |                     |
| Agricultural    | 22 (19.0)      | 22 (9.6)          | 2.2 (1.2 to 4.2)    | 0.015  | 1.8 (0.9 to 3.7) 0.093 |
| Non-agricultural occupations & unemployed | 94 (81.0) | 208 (90.4) | Reference |
| **CO-MORBIDITY** |                |                   |                     |
| Presence of Diabetes Mellitus† | 74 (63.8) | 36 (15.6) | 9.5 (5.7 to 16.0) | <0.001 | 6.7 (3.8 to 11.6) <0.001 |
| Presence of Hypertension† | 34 (29.3) | 26 (11.3) | 3.3 (1.8 to 5.8) | <0.001 | 1.2 (0.6 to 2.4) 0.623 |
| Presence of any other comorbidities§ | 10 (8.6) | 14 (6.1) | 1.4 (0.6 to 3.4) | 0.384  | - |
| **CLINICAL STATUS/MANAGEMENT** |                |                   |                     |
| Elevated plasma glucose level§ | 44 (38.9) | 15 (6.2) | 5.3 (1.5 to 18.3) | 0.009  | 13.7 (2.2 to 84.0) 0.005 |
| Median (IQR) Serum ferritin in μg/L |  |  |  |
| Ever used steroids | 74 (63.8) | 35 (15.2) | 9.8 (5.8 to 16.6) | <0.001 | - |
| More than 480 mg prednisolone equivalent [Median dose among controls] | 57 (49.1) | 16 (6.9) | 16.6 (8.7 to 31.7) | <0.001 | - |
| Less than 480 mg prednisolone equivalent [Median dose among controls] | 14 (12.1) | 16 (6.9) | 4.1 (1.9 to 9.0) | <0.001 | - |
| Unknown dose | 3 (2.6) | 3 (1.3) | 4.7 (0.9 to 23.9) | 0.065  | - |
| No steroid use | 42 (36.2) | 196 (84.9) | Reference |
| **Antibiotic use†** |                |                   |                     |
| Ever used | 94 (81.0) | 188 (81.4) | 1.0 (0.6 to 1.7) | 0.937  | - |
| More than 9 days of hospitalization [Median among controls] | 141 (52.8) | 120 (46.9) | 1.3 (0.9 to 1.8) | 0.175  | 0.8 (0.5 to 1.2) 0.241 |
| **Used other medications** |                |                   |                     |
| Remdesivir | 0 | 0 | - |
| Ivermectin | 57 (49.1) | 92 (39.8) | 1.5 (0.9 to 2.3) | 0.108  | - |
| Hydroxychloroquine | 1 (0.9) | 6 (2.6) | 0.3 (0.04 to 2.7) | 0.431  | - |
| Tocilizumab | 0 | 0 | - |
| Iron supplements | 3 (2.6) | 3 (1.3) | 2.0 (0.4 to 10.2) | 0.406  | - |
| Zinc containing vitamin supplements§ | 71 (61.2) | 160 (69.3) | 0.7 (0.4 to 1.1) | 0.134  | - |
| Indian traditional medicines (Ayush) | 21 (17.7) | 3 (1.3) | 0.6 (0.1 to 2.7) | 0.723  | - |
| **Mask use prior to onset of COVID-19** |                |                   |                     |
| Cloth masks only | 50 (43.1) | 61 (26.4) | 2.6 (1.5 to 4.5) | <0.001 | - |
| Surgical masks only | 34 (29.3) | 109 (47.2) | Reference |
| Both Cloth and Surgical mask | 24 (20.7) | 61 (26.4) | 1.3 (0.7 to 2.3) | 0.455  | - |
| No masks | 8 (6.9) | 0 | Omitted |
| **Oxygen use at home through oxygen concentrator/humidifier‡** |                |                   |                     |
| Ever used | 7 (6.0) | 13 (5.6) | 1.1 (0.4 to 2.8) | 0.878  | 0.3 (0.1 to 0.8) 0.017 |
| Practiced nasal washing§ | 7 (6.0) | 6 (2.6) | 2.4 (0.8 to 7.3) | 0.122  | 2.8 (0.8 to 10.1) 0.116 |
| Practiced steam inhalation§ | 52 (44.8) | 139 (60.2) | 0.5 (0.3 to 0.8) | 0.007  | - |

* No confounders identified;
† Adjusted for age;
‡ Adjusted for age and diabetes mellitus;
§ Missing data in controls;
¶ Data missing for 67 cases and 207 controls;
§§ Adjusted for steroid use;
¶¶ Adjusted for age, diabetes mellitus, and hypertension;
≠ Adjusted for age, and steam inhalation,

†† co-morbidities includes heart disease, chronic kidney disease, cancer, organ transplant, HIV/AIDS, chronic sinusitis

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widely in India [29–32]. Hyperglycemia is a known side effect of steroid intake [33, 34]. Before the emergence of COVID-19, steroid usage was not seen as an independent risk factor for mucormycosis [5]. However, studies on COVID-19 associated mucormycosis have reported steroids as an important predisposing factor [4, 8, 22, 24, 25, 28, 35]. The occurrence of mucormycosis among steroid users is mediated through macrophages/neutrophil dysfunction or hyperglycemia [5]. The viral-induced lymphopenia and endothelitis add to the favorable environment produced by steroids, diabetes mellitus, and hyperglycemia in causing COVID-19 associated ROCM. Therefore, COVID-19 patients on steroid treatment need to be monitored for their glycaemic status and educated to recognize and report symptoms and signs of ROCM. Further, prescribing steroids for COVID-19 patients in home isolation or non-hospital care centres needs to be done rationally, along with stringent monitoring and control of plasma glucose levels.

Similar to the widely reported use of steroids, antibiotic overuse and consequent secondary bacterial infections were documented [30, 31]. Antibiotics could potentially eliminate the normal nasal flora and favour fungal growth. However, there was no established association in the present study, where antibiotic usage was high.

In India, people use nasal irrigation with warm saline water at home (either before/after hospitalisation) for symptom relief based on the traditional Indian systems of medicine. Among the ever-hospitalised group, frequent nasal wash (many times a day) was associated with PC-ROCM despite being reported by a small subset. It is possible that repeated nasal washing depletes the commensal organisms of the nasal mucosa and thus allowing the fungus to thrive uninterrupted [32]. Poor maintenance of cloth masks, especially in the humid environment of India, could add to fungus friendly environment, although not specifically explored in this study.

Oxygen requirement during COVID-19 reflects the severity of pneumonia caused by SARS-CoV-2. During the pandemic’s peak, receipt of oxygen and its type depended entirely on the availability of hospital beds. Acute shortage of hospital beds with oxygen support could have been the reason for higher case fatality among severe COVID-19. Hence, it is likely that our participants could have had mild to moderate COVID-19, and such survival bias might have obscured any reported association with oxygen requirement. Among those who received oxygen, we documented a higher likelihood of PC-ROCM among those receiving through oxygen cylinder, albeit based on small sample size. Oxygen cylinders were used when the health care system was overwhelmed over and above that which could be met by piped oxygen supply. We hypothesize that a breach in the infection control practices during these periods could have contributed to the higher risk for PC-ROCM. During the same period, increased use of industrial oxygen for medical purposes was also implicated in the rise of mucormycosis among hospitalised patients [35]. This is contrary to the fact that a high concentration of oxygen does not sustain the growth of fungi [36].

The practise of steam inhalation and the use of oxygen concentrators/humidifiers seemed to reduce the likelihood of PC-ROCM among those isolated at home or in non-hospital settings in our study. A large proportion of study participants reported the practice of steam inhalation. The Indian Ministry of AYUSH (exclusive to India’s traditional medicine) recommended steam inhalation once a day for symptomatic relief during COVID-19 [37]. We did not document any benefit of steam inhalation among the hospitalised participants [25]. Nevertheless, steam inhalation and use of oxygen in non-hospitalised settings could reflect better adherence to COVID-19 protocols and home management. The participants had mild COVID-19, and thus they were not hospitalised. Further, recall of such practices is likely to be better among the non-hospitalised than those hospitalised, attributable to their health-seeking behaviour. Finally, we cannot rule out bias in the effect estimates due to unmeasured or unknown confounders and residual confounding.
Strengths of our study

We did a multicentric study with representation from all regions of India to strengthen the generalisability of our findings. Internal validity of the study was ensured by systematic training and monitoring of the site investigators and assessment of risk separately in ever- and never-hospitalized groups. We used an unmatched design since matching may complicate the enrolment of the study participants. Instead, we identified confounders (through DAG) and estimated adjusted measures of association. We analysed the role of an exhaustive set of factors linked to PC-ROCM, such as plasma glucose, steroid dose, and behavioural factors, that were hitherto not commonly examined. Statistical analysis of risk factors was based on an a-priori causal framework guided by directed acyclic graphs for the relationship between PC-ROCM and other variables. Thus each of the associations was adjusted separately for the relevant confounders only, which prevented over adjustment by covariates that are not confounders that would have resulted in potentially biased effect estimates due to induced confounding.

Limitations of our study

Our study had a few limitations. Firstly, the selection of cases could suffer from survival bias as those who survived ROCM were more likely to be recruited. This could bias our estimates in either direction. To increase representativeness and reduce selection bias, the study included individuals from both private and public health facilities, as well as two groups of people participants (never and ever hospitalized), to also include the persons who did not seek medical care for COVID-19. Secondly, although recruited from within the same hospital, many of the cases and controls in the ever-hospitalised group had received COVID-19 treatment elsewhere before their hospitalization for ROCM management. Hence, we could have missed certain risk factors from earlier hospitalization. However, we included only those individuals wherever complete information was available. In addition, misclassification could have occurred for certain factors such as plasma glycaemic status and steroid usage among the ever-hospitalised group. However, that is likely to be non-differential, leading to the association being biased towards the null. Despite this, we could calculate the odds ratios with reasonable precision. Thirdly, among the never-hospitalised group, recall bias and unverifiable level of practices leading to misclassification of key risk factors could have resulted in biased estimates in either direction. Fourthly, we could not directly measure the association of PC-ROCM with the severity of COVID-19 on account of a lack of uniformity in severity grading and irregular documentation across the multiple hospitals where cases and controls were managed. Finally, we could not incorporate factors like HbA1C and BMI, due to substantial missing values.

Conclusions and recommendations

We concluded that in COVID-19, hyperglycaemia irrespective of pre-existing diabetes mellitus and high steroid usage, was associated with the occurrence of PC-ROCM regardless of hospitalisation for COVID-19. To reduce the risk of PC-ROCM, we recommended adherence to protocols for rational use of steroids and systematic monitoring of plasma glucose levels notwithstanding the diabetic status.

Supporting information

S1 Table. Clinical status and management among those with diabetes mellitus (n, %), multi-centric case-control study of post COVID ROCM, India, 2021. (DOCX)
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References
1. Mucormycosis [Internet]. [cited 2021 Oct 28]; https://www.who.int/india/emergencies/coronavirus-disease-(covid-19)/mucormycosis

2. Prakash H, Chakraborti A. Epidemiology of Mucormycosis in India. Microorganisms 2021; 9(3):523. https://doi.org/10.3390/microorganisms9030523 PMID: 33806386

3. Chamilos G, Lewis RE, Kontoyiannis DP. Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis. Clin Infect Dis Off Publ Infect Dis Soc Am 2008; 47(4):503–9. https://doi.org/10.1086/590004 PMID: 18611163

4. Moorthy A, Gaikwad R, Krishnappa S, et al. SARS-CoV-2, Uncontrolled Diabetes and Corticosteroids—An Unholy Trinity in Invasive Fungal Infections of the Maxillofacial Region? A Retrospective, Multi-centric Analysis. J Maxillofac Oral Surg 2021;1–8.

5. Jeong W, Keighley C, Wolfe R, et al. The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis 2019; 25(1):26–34. https://doi.org/10.1016/j.cmi.2018.07.011 PMID: 30036666

6. Mishra N, Mutyaa VSS, Thomas A, et al. A case series of invasive mucormycosis in patients with COVID-19 infection. Int J Otorhinolaryngol Head Neck Surg 2021; 7(5):867–70.

7. Mehta S, Pandey A. Rhino-Orbital Mucormycosis Associated With COVID-19. Cureus 2020; 12(9):e10726. https://doi.org/10.7759/cureus.10726 PMID: 33145132
8. Placik DA, Taylor WL, Wnuk NM. Bronchopleural fistula development in the setting of novel therapies for acute respiratory distress syndrome in SARS-CoV-2 pneumonia. Radiol Case Rep 2020; 15(11):2378–81. https://doi.org/10.1016/j.radcr.2020.09.026 PMID: 32983308

9. Sen M, Honavar SG, Bansal R, et al. Epidemiology, clinical profile, management, and outcome of COVID-19-associated rhino-orbital-cerebral mucormycosis in 2826 patients in India—Collaborative OPAI-IJO Study on Mucormycosis in COVID-19 (COSMIC), Report 1. Indian J Ophthalmol 2021; 69(7):1670–92. https://doi.org/10.4103/ijo.IJO_1565_21 PMID: 34156034

10. Dr Harsh Vardhan chairs 29th meeting of Group of Ministers (GOM) on COVID-19 [Internet]. [cited 2021 Oct 20]; https://pib.gov.in/pib.gov.in/Pressreleaseshare.aspx?PRID=1730873

11. Pal R, Singh B, Bhadada SK, et al. COVID-19-associated mucormycosis: An updated systematic review of literature. Mycoses 2021. https://doi.org/10.1111/myc.13338 PMID: 34133798

12. Patel A, Agarwal R, Rudramurthy SM, et al. Multicenter Epidemiologic Study of Coronavirus Disease-Associated Mucormycosis, India. Emerg Infect Dis 2021; 27(9):2349–59. https://doi.org/10.3201/eid2709.210934 PMID: 34087089

13. Bhanuprasad K, Manesh A, Devasagayam E, et al. Risk factors associated with the mucormycosis epidemic during the COVID-19 pandemic. Int J Infect Dis IJID Off Publ Int Soc Infect Dis 2021; 111:267–70. https://doi.org/10.1016/j.ijid.2021.08.037 PMID: 34450284

14. Meshram HS, Kute VB, Chaunhan S, et al. Mucormycosis as SARS-CoV2 sequelae in kidney transplant recipients: a single-center experience from India. Int Urol Nephrol 2021. https://doi.org/10.1007/s11255-021-03057-5 PMID: 34792722

15. Muthu V, Kumar M, Paul RA, et al. Is there an association between zinc and COVID-19-associated mucormycosis? Results of an experimental and clinical study. Mycoses 2021; 64(10):1291–7. https://doi.org/10.1111/myc.13365 PMID: 34420245

16. Kumar HM, Sharma P, Rudramurthy SM, et al. Serum iron indices in COVID-19-associated mucormycosis: A case-control study. Mycoses 2022; 65(1):120–7. https://doi.org/10.1111/myc.13391 PMID: 34743358

17. Arshad S, Kilgore P, Chaudhry ZS, et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. Int J Infect Dis IJID Off Publ Int Soc Infect Dis 2020; 97:396–403.

18. I-MUCOR—Study [Internet]. [cited 2021 Oct 21]; https://imucor.netlify.app/

19. Laugesen K, Petersen I, Sørensen HT, Jørgensen JOL. Clinical indicators of adrenal insufficiency following discontinuation of oral glucocorticoid therapy: A Danish population-based self-controlled case series analysis. PLOS ONE 2019; 14(2):e0212259. https://doi.org/10.1371/journal.pone.0212259 PMID: 30779776

20. Afifi A, Clark V, May S. Regression analysis with multicollinearity ( 4th ed.). Boca Raton, FL: Chapman & Hall/CRC 2004;

21. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiol Camb Mass 1999; 10(1):37–48. PMID: 9888278

22. Waizel-Haata S, Guerrero-Paz JA, Sanchez-Hurtado L, Calleja-Alarcon S, Romero-Gutierrez L. A Case of Fatal Rhino-Orbital Mucormycosis Associated With New Onset Diabetic Ketoacidosis and COVID-19. Cureus [Internet] 2021; 13(2). Available from: https://pubmed.ncbi.nlm.nih.gov/33575155/ https://doi.org/10.7759/cureus.13163

23. Müller JA, Groß R, Conzelmann C, et al. SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. Nat Metab 2021; 3(2):149–65. https://doi.org/10.1038/s42255-021-00347-1 PMID: 33536639

24. Mishra Y, Prashar M, Sharma D, Akash, Kumar VP, Tilak TVSVGK. Diabetes, COVID 19 and mucormycosis: Clinical spectrum and outcome in a tertiary care medical center in Western India. Diabetes Metab Syndr 2021; 15(4):102196. https://doi.org/10.1016/j.dsx.2021.102196 PMID: 34246939

25. Vaezi A, Moazeni M, Rahimi MT, de Hoog S, Badali H. Mucormycosis in Iran: a systematic review. Mycoses 2016; 59(7):402–15. https://doi.org/10.1111/myc.12474 PMID: 26906121

26. Arora U, Priyadarshi M, Katiyar V, et al. Novel risk factors for Coronavirus disease-associated mucormycosis (CAM): a case control study during the outbreak in India. medRxiv 2021;2021.07.24.21261040.

27. Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. Diabetes Metab Syndr Clin Res Rev 2021; 15(4):102146. https://doi.org/10.1016/j.dsx.2021.05.019 PMID: 34192610
29. Muthu V, Rudramurthy SM, Chakrabarti A, Agarwal R. Epidemiology and Pathophysiology of COVID-19-Associated Mucormycosis: India Versus the Rest of the World. Mycopathologia 2021. https://doi.org/10.1007/s11046-021-00584-8 PMID: 34414555

30. Calderón-Parra J, Antonio M-M, Bendala-Estrada AD, et al. Inappropriate antibiotic use in the COVID-19 era: Factors associated with inappropriate prescribing and secondary complications. Analysis of the registry SEMI-COVID. PLOS ONE 2021; 16(5):e0251340. https://doi.org/10.1371/journal.pone.0251340 PMID: 33974637

31. Langford BJ, So M, Raybardon S, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis 2020; 26(12):1622–9. https://doi.org/10.1016/j.cmi.2020.07.016 PMID: 32711058

32. Mahdavinia M, Keshavarzian A, Tobin MC, Landay A, Schleimer RP. A comprehensive review of the nasal microbiome in chronic rhinosinusitis (CRS). Clin Exp Allergy J Br Soc Allergy Clin Immunol 2016; 46(1):21–41.

33. World Health Organization. Corticosteroids for COVID-19 [Internet]. https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1

34. Government of India. Ministry of Health and Family Welfare; Indian Council of Medical Research; All India Institute of Medical Sciences. Advisory for rational use of Steroids and Tocilizumab in the treatment of Covid-19 patients [Internet]. https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-

35. Bhatia M. The rise of mucormycosis in Covid-19 patients in India. Expert Rev Anti Infect Ther 2021; 0 (0):1–2. https://doi.org/10.1080/14787210.2021.1960822 PMID: 34304680

36. Baez A, Shiloach J. Effect of elevated oxygen concentration on bacteria, yeasts, and cells propagated for production of biological compounds. Microb Cell Factories 2014; 13:181.

37. Ministry of AYUSH Government of India. National Clinical Management Protocol based on ayurveda and yoga for management of COVID-19 [Internet]. www.twitter.com/moayush