Uncontrolled diabetes mellitus exacerbated by COVID-19–induced inflammation is the risk factor for COVID-19–associated rhino-orbito-cerebral mucormycosis: A matched pair case–control study

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Purpose: Amidst the ongoing coronavirus disease 2019 (COVID-19) pandemic, India experienced an epidemic of COVID-19–associated rhino-orbito-cerebral mucormycosis (ROCM). This study aimed to describe the epidemiology and elucidate the risk factors for developing COVID-19–associated ROCM, comparing the risk factors among COVID-19 patients with and without ROCM. Methods: This case–control study included all COVID-19–associated ROCM patients treated at our hospital from May 1 to July 30, 2021. Controls included age- and sex-matched COVID-19 patients without ROCM, who were treated during the same time (exact matching, in 1:2 ratio). Matched pair analysis using conditional logistic regression was performed to examine the association of various risk factors with the development of ROCM in COVID-19 patients. Results: The study included 69 patients with COVID-19–associated ROCM and 138 age- and gender-matched controls. Epidemiologically, COVID-19–associated ROCM predominantly affected males (59/69, 85%), in their early 50s (mean 52 years), with 48% (33/69) of patients being from medical resource-constrained settings. On multivariate conditional logistic regression, elevated serum glycated hemoglobin (HbA1c) (odds ratio [OR] = 1.36, 95% confidence interval [CI]: 1.03–1.78), blood glucose (OR = 1.008, 95% CI: 1.003–1.013), and C-reactive protein (CRP) (OR = 1.07, 95% CI: 1.02–1.17) were associated with increased odds of developing COVID-19–associated ROCM. Patients with undetected diabetes mellitus with increasing HbA1c (OR = 3.42, 95% CI: 1.30–9.02) and blood glucose (OR = 1.02, 95% CI: 1.005–1.03) (P = 0.02) had a higher probability of developing COVID-19–associated ROCM than patients with established DM. Conclusion: Uncontrolled DM evidenced by elevated HbA1c and blood glucose levels, exacerbated by COVID-19–induced proinflammatory state indicated by elevated CRP, is the principal independent risk factor for COVID-19–associated ROCM. Middle-aged males with undetected DM, from a resource-constraint setting, are particularly at risk.

Key words: C-reactive Protein, COVID-19 infection, epidemiology, hyperglycemia, rhino-orbito-cerebral mucormycosis, risk factors

Mucormycosis is an angioinvasive fungal infection caused by the ubiquitous fungi of the order Mucorales. It is a rare, rapidly progressive, often fatal fungal infection that can affect any organ system, with rhino-orbito-cerebral mucormycosis (ROCM) being the commonest.[1] ROCM occurs almost exclusively in the immunocompromised host.[2,3] In the pre-COVID era, uncontrolled diabetes mellitus (DM) was the commonest risk factor for ROCM in India, while hematological malignancies was the commonest risk factor in western countries.[4–5]

With the onset of the novel coronavirus disease 2019 (COVID-19) pandemic in India, there has been a surge in the incidence of invasive fungal diseases, particularly ROCM, in patients with COVID-19 infection. COVID-19 infection-associated hyperglycemia, steroid usage, severe inflammation, deranged ferritin levels, and a relative neutropenia create an ideal milieu for mucormycosis in these patients.[9]

There are many reports of ROCM in COVID-19 patients, including a large multicentric case series from India.[10–22] Sen et al., in their study of 2826 patients from across India, reported hyperglycemia and systemic steroid administration, especially among males, to be consistent risk factors for ROCM in COVID-19 patients,[19] with other studies reporting similar associations.[11–23] Though the prevalence of mucormycosis has always been much higher in India, the surge that occurred during the COVID-19 pandemic was unprecedented.[4,5] The aim of this study was to elucidate the epidemiology and risk factors for ROCM in COVID-19 patients by comparing the potential risk factors in COVID-19 patients with ROCM and without ROCM in a matched case–control study.

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Methods

Study design and participants
This retrospective, matched case–control study was conducted in a tertiary care hospital situated in Bengaluru, South India. The cases included all patients diagnosed and treated for COVID-19–associated ROCM in our hospital between May 1, 2021 and July 30, 2021. Age- and sex-matched COVID-19 patients who never had mucormycosis during the COVID-19 infection period (at least 30 days from diagnosis) were included as controls (exact matching in the ratio of 1:2). Patients with proven non-mucor fungal infections and/or mucormycosis at any other site (pulmonary/cutaneous/soft tissue) were excluded from the study. Institutional ethics review board approval for the study was obtained prior to its initiation (IEC study no. 181/2021). Waiver of consent was obtained as patient identity confidentiality was maintained. Study was carried out in accordance with the institutional ethical guidelines and tenets of Helsinki Declaration.

Management protocols
A diagnosis of COVID-19 was made using either a rapid antigen test (RAT) or molecular tests such as reverse transcriptase-polymerase chain reaction (RT-PCR), GeneXpert, or point-of-care COVID-19 assay (nucleic acid amplification test – Abbott ID now). Patients with COVID-19 were classified as mild, moderate, and severe based on the World Health Organization (WHO) classification.[23]

In patients suspected to have ROCM in the setting of concurrent COVID-19 or recently treated COVID-19 (within a period of 30 days from the diagnosis of COVID-19 infection), computed tomographic (CT) evaluation of the paranasal sinuses and magnetic resonance imaging (MRI) of brain and orbit were done immediately. Tissue for biopsy and smear/culture was obtained from the nasal cavity and paranasal sinuses either by a diagnostic nasal endoscopy or during sinus debridement surgery. The sample obtained was sent for microbiological testing including potassium hydroxide/calcofluor white staining, fungal culture, and histopathologic study. Definitive diagnosis was based on the presence of tissue invasion with aseptate fungal elements on histopathology and/or smear positivity for aseptate fungal elements and culture positivity for filamentous fungi belonging to the Mucoraceae family.

Based on the anatomical extent of the disease, evidenced both clinically and radiologically, patients with ROCM were categorized as sinonasal, rhino- orbital, rhino-orbito-cerebral, and rhinocerebral disease. All patients were treated with intravenous liposomal or conventional amphotericin B. In addition, posaconazole was given as adjunctive therapy in most patients due to erratic supply of amphoterin B formulations in the initial phase of the mucor wave. Sinonasal debridement was done at least once in all patients and more than once in most of the patients.

Patients with orbital disease were administered intraorbital amphotericin B on alternate days for a maximum of 12 injections. Orbital debridement was done in patients with significant radiological evidence of orbital infiltration. Some patients underwent orbital debridement more than once and a few underwent enucleation when needed to facilitate debridement. Those with central nervous system (CNS) disease underwent neurosurgical procedures when indicated.

Data obtained
Records of patients with ROCM treated during the study period were reviewed. Patient demographic characteristics, clinical presentation of mucormycosis such as site, extent, and so on, comorbidities, predisposing factors, treatment details, and evolutive clinical data were collected. In addition, details related to COVID-19 infection, including presentation, treatment details, and laboratory findings (serum C-reactive protein [CRP], serum ferritin, serum D-dimer levels), in both cases and controls were recorded.

Definitions
For purposes of analysis, the presence of comorbidities was defined as follows:
1. DM was defined as per the American Diabetes Association (ADA) guidelines. Patients without a history of DM fulfilling the aforementioned criteria were considered as newly diagnosed DM. Patients with a preexisting history of DM (irrespective of treatment history) were considered as known cases of DM for purposes of the study.[24]
2. Patients with diabetic ketoacidosis (DKA) were identified as those individuals with elevated plasma glucose levels (>250 mg/dL) in the presence of acidosis (pH <7.30), low serum bicarbonate levels (<18 mEq/L), ketone bodies in the serum and urine, and an anion gap >10 as per the ADA.[24]
3. Hypertension was defined as systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg following repeated examination (International Society of Hypertension Global Hypertension Practice 2020 Guidelines).[25]
4. Chronic kidney disease (CKD) was defined as abnormalities of kidney structure or function which were present for ≥3 months. A diagnosis was considered if historical/laboratory/radiological evidence of renal dysfunction for ≥3 months was present (Kidney disease Improving Global Outcomes [KDIGO] 2012 Clinical Practice Guideline).[26]

Statistical analysis
Frequency counts with percentages for categorical variables and mean (± standard deviation [SD])/median (interquartile range [IQR]) for continuous variables are reported. Conditional logistic regression analysis was performed for matched pairs with the outcome of case versus control to examine the association of various risk factors with the development of COVID-19–associated ROCM. Unadjusted and adjusted odds ratios (ORs) with 95% confidence interval are reported. Potential confounders to be considered in the multiple regression analysis were identified based on literature review. Effect modification was examined in the regression analysis by introducing an interaction term. Statistical significance was considered at P < 0.05. The data was analyzed using STATA Version 17 (StataCorp. 2021, Stata Statistical Software: Release 17; StataCorp. LLC, College Station, TX, USA).

Results
The study included 69 patients with ROCM with concurrent or recent COVID-19 infection (ROCM group). The study also included 138 age- and gender-matched controls of
COVID-19 patients without mucormycosis (control group). The patients were meticulously matched in age and gender [Table 1]. A significant male preponderance was seen in the ROCM group (male: female ratio of 6:1) [Table 1]. Forty-eight percent (33/69) of the ROCM patients were from villages and small towns where medical facilities are poor (P = 0.007).

Of the 69 patients with ROCM, 23/69 (33.33%) had sinonasal disease with the disease restricted to nasal cavity and paranasal sinuses, 27/69 (39.13%) had rhino-orbital disease, of which three had bilateral involvement, 15/69 (21.73%) had rhino-orbito-cerebral disease, and 4/69 (5.79%) had rhinocerebral disease with no evidence of orbital involvement. The median time between COVID-19 diagnosis and development of mucor symptoms was 13 days (IQR 8–18). Concurrent COVID-19 infection was seen at the time of ROCM diagnosis in 22/69 (31.88%) patients.

DM was significantly more prevalent in the ROCM group (52/69 [75.36%]) than in the controls (74/138 [53.62%]) (P = 0.003). However, all patients in the ROCM group were detected to have elevated blood sugar levels and elevated serum glycated hemoglobin (HbA1c), irrespective of their prior diabetic status, with 17/69 (24.63%) patients being newly diagnosed with DM at the time of ROCM diagnosis. The occurrence of hypertension and CKD was comparable in the two groups (P = 0.15 and P = 0.35, respectively) [Table 1]. The duration of DM, the highest recorded blood sugar level, HbA1c (P < 0.001 for all), and the occurrence of DKA (P = 0.03) were statistically significantly higher in the ROCM group than in the control group [Table 1]. There was no evidence of any other known preexisting comorbidities predisposing to mucormycosis, including chronic liver disease, hematological or solid organ malignancies, and ongoing immunosuppressive therapy.

The severity of COVID-19 infection and the treatment given were compared between the two groups [Table 2]. The proportion of patients who had severe COVID-19 infection was significantly higher in the control group (42%) compared to the ROCM group (21%) (P = 0.04). A marginally higher number of controls received oxygen therapy, compared to the ROCM group (P = 0.07). However, there was no statistical difference in the total number of patients who were administered steroids, duration of steroid therapy, and duration of oxygen administration between the two groups (P = 0.84, P = 0.35, and P = 0.21, respectively). Among the cases, 16/32 (50%) with mild COVID-19 received steroid therapy.

Blood levels of inflammatory markers such as CRP, D-dimer, ferritin, total leukocyte count, and total neutrophil count were compared between the two groups. The CRP levels alone were significantly higher in the ROCM group (P < 0.001) [Table 2].

Thus, the three main risk factors which were identified based on the comparison between ROCM and control groups and existing literature were HbA1c levels, highest random blood sugar (RBS) and CRP [Table 3]. When all three were considered together in multiple logistic regression, all variables were independently associated with ROCM, with the OR of RBS, HbA1c, and CRP being 1.008 (95% confidence interval [CI]: 1.003–1.013), 1.36 (95% CI: 1.03–1.78), and 1.09 (95% CI: 1.02–1.17), respectively [Table 4]. The effect of DKA was not independently associated with ROCM in the presence of the above variables.

We also explored the association of HbA1c and highest RBS with the DM status (known DM vs. undiagnosed DM) of the cases and controls and the probability of developing COVID-19–associated ROCM. The interaction terms of RBS (P = 0.02) and HbA1c (P = 0.02) with DM status were significant when examined in the conditional logistic regression model. The odds of ROCM with unit increase in HbA1c among patients with undiagnosed DM was 3.42 (95% CI: 1.30–9.02), while that in patients with known DM was 1.34 (95% CI: 1.12–1.61) [Fig. 1]. Similarly, the odds of ROCM with unit increase in RBS was slightly higher in patients with unknown DM (OR = 1.02, 95% CI: 1.005–1.03) compared to the odds in patients with known DM (OR = 1.01, 95% CI: 1.003–1.02). Thus, with increasing HbA1c and RBS values, the probability

**Table 1:** Demographic details and occurrence of comorbidities in COVID-19 patients with and without ROCM (cases and controls)

| Variable                      | ROCM group | Control group | Unadjusted odds ratio (95% confidence interval), P |
|-------------------------------|------------|---------------|---------------------------------------------------|
| Gender                        |            |               |                                                   |
| Males                         | 59/69 (85.5%) | 118/138 (85.5%) | 1 (0.44–2.27), P<1                                |
| Females                       | 10/63 (14.5%) | 20/138 (14.5%) |                                                   |
| Age (years)                   | 51.95 (±14.29) | 52.13 (±13.85) | 1.00 (0.98–1.02), P=0.99                         |
| Place of residence (rural)    | 33/69 (48%) | 39/138 (28%) | 0.44 (0.24–0.8), P=0.007                         |
| Hypertension (present)        | 31/67 (46.26%) | 52/137 (37.95%) | 1.58 (0.50–2.96), P=0.15                         |
| Diabetes mellitus (present)   | 52/69 (75.36%) | 74/138 (53.62%) | 3.39 (1.61–7.11), P=0.001                         |
| Diabetic ketoacidosis (present)| 9/69 (13.04%) | 5/135 (3.7%) | 3.29 (1.09–9.88), P=0.03                         |
| Chronic kidney disease (present) | 10/69 (14.49%) | 14/134 (10.44%) | 1.54 (0.62–3.83), P=0.35                         |
| Duration of DM (years)        | 5 (0-11) | 0 (0-5) | 1.12 (1.05–1.19), P=0.001                         |
| Highest RBS (mg/dL)           | 384.81 (±90.37) | 305.29 (±118.27) | 1.01 (1.00–1.01), P<0.001                         |
| HbA1c (%)                     | 10.32 (±2.37) | 8.09 (±2.38) | 1.48 (1.25–1.77), P<0.001                         |
| Serum creatinine (mg/dL)      | 0.9 (0.73–1.16) | 0.67 (0.78–1.07) | 0.95 (0.78–1.15), P=0.69                         |

CKD=chronic kidney disease, COVID-19=coronavirus disease 2019, DKA=diabetic ketoacidosis, DM=diabetes mellitus, HbA1c=glycosylated hemoglobin, RBS=random blood sugar, ROCM=rhino-orbito-cerebral mucormycosis. ROCM group=patients with ROCM and COVID-19; control group=patients with COVID-19 only. Missing data: Hypertension (HTN): cases two, control one; DKA: controls two; CKD: controls three; duration of DM: controls 20; HbA1c: controls: 27; serum creatinine: cases two
Table 2: Severity of COVID-19 infection, management, and inflammatory markers in the two groups

| Variable                        | ROCM group | Control group | Unadjusted odds ratio (95% confidence interval), P |
|---------------------------------|------------|---------------|---------------------------------------------------|
| COVID severity                  |            |               |                                                   |
| Mild                            | 32/68 (47.05%) | 51/138 (36.95%) | 0.71 (0.57-1.96), P=0.04                           |
| Moderate                        | 21/68 (30.88%) | 29/138 (21.01%) |                                                   |
| Severe                          | 14/68 (20.56%) | 58/138 (42.02%) |                                                   |
| Received steroid therapy        | 47/67 (70.14%) | 95/138 (68.84%) | 1.07 (0.57-1.96), P=0.84                           |
| Received oxygen therapy         | 35/64 (54.68%) | 87/138 (63.04%) | 0.64 (0.39-1.04), P=0.07                           |
| Duration of steroid therapy (days) | 7 (5-10)     | 6 (0-12)      | 1.01 (0.96-1.07), P=0.35                           |
| Duration of oxygen therapy (days) | 4 (0-10)     | 5 (0-11.5)    | 0.97 (0.92-1.02), P=0.21                           |
| Serum D-dimer (mg/dL)           | 503 (317-808) | 388.5 (229-744)| 1.01 (0.99-1.00), P=0.84                           |
| Serum ferritin (mg/dL)          | 778.3 (420-1053.4) | 529.2 (224.2-1056.8) | 1.00 (0.99-1.00), P=0.41                           |
| CRP (IU/dL)                     | 9.61 (4.1-20.94) | 4.57 (1.37-9.32) | 1.07 (1.03-1.12), P<0.001                           |
| Total WBC count (cells/mm³)     | 9.36 (7.58-15.57) | 8.31 (5.73-12.738) | 0.99 (0.96-1.01), P=0.41                           |
| Neutrophils (number out of 100 leukocytes counted) | 78.9 (66.65-89.7) | 79 (67-88.7) | 1.01 (0.96-1.03), P=0.49                           |

COVID-19=coronavirus disease 2019, CRP=C-reactive protein, ROCM=rhino-orbito-cerebral mucormycosis, WBC=white blood cells. ROCM group=patients with ROCM and COVID-19; control group=patients with COVID-19 only. Missing data: steroid therapy: cases two; steroid duration: cases 17, controls 13; oxygen therapy: cases five; oxygen duration: cases 14, controls six; COVID severity: case one; D-dimer: cases 10, controls six; ferritin: cases 15, controls 29; CRP cases: 14, controls nine

Table 3: Interaction of RBS and HbA1c with other variables with P<0.05 on univariate analysis

| Variable              | RBS - OR (95% CI), P  | HbA1c - OR (95% CI), P  |
|-----------------------|------------------------|-------------------------|
| Diabetes mellitus     | 1.33 (0.52-3.43), P=0.54 | 1.01 (0.38-1.74), P=0.98 |
| DKA                   | 2.9 (0.59-8.84), P=0.22  | 1.81 (0.43-7.40), P=0.41 |
| Duration of DM        | 1.07 (1.01-1.02), P=0.05  | 1.04 (0.97-1.11), P=0.27 |
| COVID severity        | 0.66 (0.45-0.95), P=0.01  | 0.55 (0.35-0.87), P=0.01  |
| CRP                   | 1.07 (1.02-1.13), P=0.01  | 1.07 (1.01-1.13), P=0.01  |

CI=confidence interval, COVID=coronavirus disease 2019, CRP=C-reactive protein, DKA=diabetes ketoacidosis, DM=diabetes mellitus, HbA1c=glycated hemoglobin, OR=odds ratio, RBS=random blood sugar

COVID-19–associated ROCM was greater in undiagnosed DM patients compared to known DM patients.

Discussion

Hyperglycemia and the use of systemic corticosteroids have been reported as the main risk factors for the development of COVID-19–associated ROCM in several previous studies.5-22 All these reports are descriptive studies or reviews. Our study is a matched pair case–control study which found that uncontrolled DM, as indicated by a high HbA1c and blood glucose, was the most important independent risk factor for developing COVID-19–associated ROCM, with elevated CRP levels being the other independent risk factor. Neither administration nor duration of steroid use was found to be a risk factor in our study.

Elevated HbA1c, with an OR of 1.36, was found to be the best predictor of COVID-19–associated ROCM. This suggests that uncontrolled DM is a far greater risk factor for ROCM than the transient hyperglycemia that may develop during COVID-19 infection due to various reasons. Although all the ROCM patients had extremely high glycemic levels at the time of ROCM diagnosis, 17/69 (25%) patients were newly diagnosed with DM. Analysis also showed that in newly diagnosed DM, increasing HbA1c and blood glucose levels had higher odds of developing COVID-19–associated ROCM, compared to
those patients known to have DM who were more likely to be on treatment.

Hyperglycemia in COVID-19 patients is multifactorial. Firstly, moderate to severe COVID-19 infection is a proinflammatory disease characterized by an excessive release of inflammatory molecules. A surge in catecholamines, cytokines, and cortisol promotes glucagon production and gluconeogenesis, resulting in hyperglycemia. Secondly, it is also well established that acute stress (here COVID-19 infection) can cause hyperglycemia, independent of an individual’s underlying DM status. Thirdly, pancreatic beta cell injury due to COVID-19 infection has also been described, which results in decreased beta cell function and apoptosis. This leads to a net decrease in the overall insulin produced, predisposing individuals (particularly patients with DM) to develop ketosis, DKA, and hyperosmolality. In our study, DKA was not an independent risk factor for the development of ROCM in COVID-19 patients.

Elevated CRP levels were also found to be an independent risk factor for developing COVID-19–associated ROCM. CRP, an acute phase protein released from hepatocytes due to interleukin (IL)-6 dysregulation in COVID-19, is a strong independent predictor of progressive disease, severity of inflammation, and poor outcomes early in COVID-19 disease. Greater degrees of inflammation can lower the pH, promote hyperglycemia (reducing normal immune activity), and impair normal endothelial function, thereby facilitating Mucorales invasion through the use of receptors like glucose-regulated protein 78 (GRP78).

Hyperglycemia and acidosis induce excessive glycosylation of carrier proteins such as transferrin and ferritin, thereby causing an increase in the serum iron, rendering it available for the fungi, and iron acquisition from the host is one of the many virulence factors in Mucorales. However, elevated serum ferritin, a proinflammatory marker in COVID-19 patients, was not a risk factor in our study. COVID-19 attacks the 1-beta chain of hemoglobin, initiating dissociation of iron from porphyrins and discharging iron into the circulation. Prospective studies on unbound serum iron could shed more light on its role in COVID-19–associated ROCM.

Steroid use was not an independent risk factor for developing mucormycosis in our study, as alluded to in other reports. Most of our patients (those with ROCM 47/69 [70%] and controls 95/138 [69%]) received steroids as part of their treatment for COVID-19 (P = 0.84). Steroids can cause an increase in glycemic levels both in normal and diabetic individuals and inhibit phagocytosis, a principal host defense mechanism against mucormycosis.

A novel host receptor GRP78 mediates invasion and damage of human endothelial cells by fungi of the order Mucorales. There is an increased expression of GRP78 protein in severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection and in patients with DKA. Spore coat protein homolog (CoTH) is a fungal ligand that mediates attachment to GRP78 during host cell invasion, an important step in the pathogenesis of mucormycosis. The role of these proteins will need to be addressed in future.

A male preponderance was seen in COVID-19–associated ROCM in our study, with similar findings being reported. One probable explanation is a preponderance of COVID-19 and DM in the male gender, though a possible biological reason needs to be explored.

Though there has been an increasing prevalence of mucormycosis, in general, in India over the years, the magnitude of the increase in numbers during the COVID-19 pandemic was enormous, with some states reporting over 500 patients in a period of 2 months. The principal reason for this is the high prevalence of DM in the Indian population. With 65 million (95% CI 58.7–71.1) prevalent cases of diabetes in India in 2016 and the projected number to be 101 million by the year 2030, India is referred to as the “diabetes capital of the world.” In addition, a significant number of patients with DM remain undiagnosed, as was seen in this study. These patients are at a higher risk of developing life-threatening complications including mucormycosis. Even in the pre-COVID period, health care was not easily accessible to most of the Indian population. Almost half the patients from the ROCM group were from villages or small towns where traditionally medical facilities are very poor. The brutal second wave of COVID-19 pandemic stretched the fragile health-care systems in India, leaving many patients without appropriate medical care. Probably the inaccessibility of health care, coupled with inappropriate use of steroids and self-medication, led to the poor glycemic control in many patients, which was further exacerbated by COVID-19–induced inflammation. This, in turn, could potentially have triggered this epidemic of invasive fungal infections in COVID-19 patients, particularly ROCM.

Incomplete data, particularly details of COVID-19 treatment among the mucormycosis patients, is an inherent limitation, given the retrospective nature of the study. The details of missing data for each variable are indicated as footnotes of the tables itself and have been accounted for while performing conditional logistic regression.

Conclusion

In conclusion, preexisting uncontrolled DM exacerbated by COVID-19–induced inflammatory response is the principal risk factor for the development of COVID-19–associated ROCM. Middle-aged males from medical resource-constraint settings with undetected diabetes were particularly at risk. Early detection of hyperglycemia, strict glycemic control, and judicious use of steroids to control COVID-19–induced inflammation will be the key for preventing another epidemic of ROCM in subsequent COVID-19 waves.

Ethics approval and consent to participate

This study was approved by the Institutional Ethics Committee of St. John’s National Academy of Health Sciences, IEC study no. 181/2021. Waiver of consent was obtained in view of the retrospective nature of the study.

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Conflicts of interest

There are no conflicts of interest.
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