

## **Retinal Manifestations of COVID -19 patients attending tertiary health care facility -Hospital based Descriptive study**

### **Abstract:**

The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had health implications of unprecedented magnitude. The infection can range from asymptomatic, mild to life threatening respiratory distress. It can affect almost every organ of the body. This study aims to study the possible retinal manifestations among COVID-19 patients.

**Material and methods:** Descriptive study was conducted among the patients attending Ophthalmology OPD in a tertiary Care Centre in Nellore with COVID-19 from April 2021 to march 2022.

**Results:** Among 100 patients with COVID-19, Diabetes Mellitus was the most common co-morbidity. The prevalence of retinal manifestations was found to be 49%. Among them around 7% of patients had Central retinal artery occlusion, 6% had diabetic retinopathy, 4% cotton wool spots, 8% had optic disc edema, 3% panophthalmitis, 2% had sub retinal exudates, 7% had central retinal vein occlusion, 4% had choroidal folds, 3% had retinal haemorrhage, 2% had central retinal artery obstruction.

### **Conclusion:**

**Keywords:** COVID-19, retinal manifestations, SARS-CoV-2, central retinal vein occlusion, central retinal artery occlusion, Mucormycosis

## **INTRODUCTION**

Since December 2019, coronavirus disease 2019 (COVID-19) has become a global pandemic caused by the highly transmissible severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>1</sup> Initially, there were several reports of eye redness and irritation in COVID-19 patients, both anecdotal and published, supporting conjunctivitis as an ocular manifestation of SARS-CoV-2 infection. Reports continue to emerge on further associations of COVID-19 with uveitic, retinovascular, and neuro-ophthalmic disease.

During the 2003 severe acute respiratory syndrome (SARS) outbreak, a study detected SARS-CoV in tear samples in SARS patients in Singapore.<sup>2</sup> Lack of eye protection was a primary risk factor of SARS-CoV transmission from SARS patients to healthcare workers in Toronto, prompting a concern that respiratory illness could be transmitted through ocular

secretions.<sup>3,4</sup> Similar concerns have been raised with SARS-CoV-2, especially among eye care providers and those on the front lines triaging what could be initial symptoms of COVID-19.

As conjunctivitis is a common eye condition, ophthalmologists may be the first medical professionals to evaluate a patient with COVID-19. Indeed, one of the first providers to voice concerns regarding the spread of coronavirus in Chinese patients was Dr. Li Wenliang, MD, an ophthalmologist. He later died from COVID-19 and was believed to have contracted the virus from an asymptomatic glaucoma patient in his clinic.<sup>5</sup>

SARS-CoV-2 is a novel enveloped, positive single-stranded RNA beta coronavirus that causes COVID-19, originally linked to an outbreak in Wuhan of China's Hubei province.<sup>1</sup> Direct contact with mucous membranes, including the eye, is a suspected route of transmission.

Coronaviruses can cause severe ocular disease in animals, including anterior uveitis, retinitis, vasculitis, and optic neuritis in feline and murine species. However, ocular manifestations in humans are typically mild and rare,<sup>6</sup> although there are increasing numbers of associated ocular findings in patients positive for the COVID-19. There are no described ocular manifestations of Middle East respiratory syndrome (MERS) or SARS, though, as previously stated, SARS-CoV-2 was isolated in ocular secretions.<sup>2</sup> Other coronaviruses have been found to cause viral conjunctivitis in humans.<sup>7</sup>

Hence the present study was done to collect the most up-to-date information on **retinal** manifestations of COVID-19.

## **Material and Methods**

**Study Design:** hospital based descriptive study

**Study setting:** COVID CARE CENTER in a tertiary Care hospital in Nellore

**Study duration:** The study period was for a period of 1 year from April 2021 to march 2022.

**Study population:** Patients attending COVID CARE CENTER in a tertiary Care hospital in Nellore during the study period.

**Inclusion criteria:**

- laboratory confirmed COVID-19 cases by RTPCR (Real Time Reverse Transcription Polymerase Chain Reaction) nasopharyngeal & throat swab with COVID
- Patients willing to participate in the study and who gave informed written consent.

**Sample size:**100 patients

**Study tool:** pre-tested semi structured questionnaire

**Study Variables:** Socio-demographic variables, Case-history, symptoms, risk factors like co-morbidities, Hospital case sheets, Lab reports, CT/ MRI report and fundus fluorescein angiography.

**Methodology:** Patients attending the COVID CARE CENTER came with the COVID -19 were included in the study. All the relevant data was collected during their stay in the hospital.

**Permissions and Ethical considerations:**

- Permission was obtained from Institutional heads ie. Superintendent of the hospital. Written informed consent was taken from patients. Institutional Ethics Committee approval was taken. Patient confidentiality was ensured.

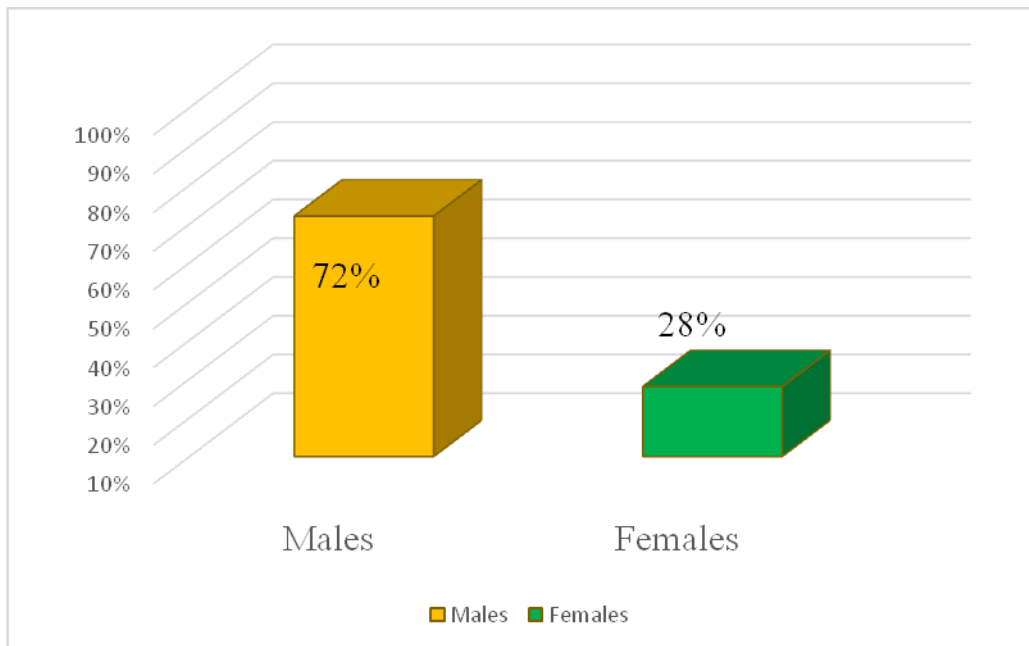
**Statistical analysis**

Data was compiled in MS Excel and analysed using SPSS ver 20.0. Descriptive statistics were presented as mean and standard deviation for quantitative variables and as frequencies with percentages for qualitative data.

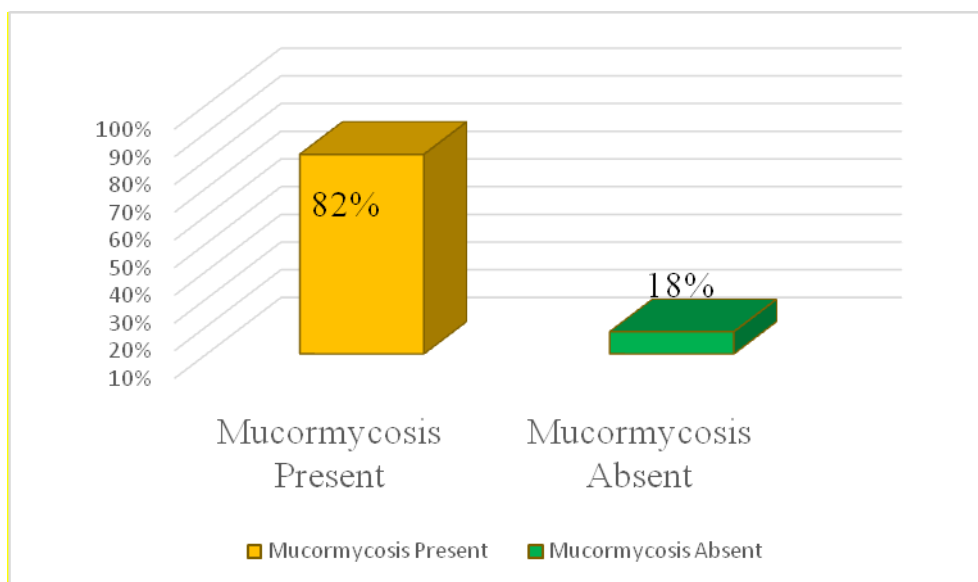
**Results:****Demography**

During the study period, 100 patients hospitalized had COVID-19.

The mean age of patients was 58.28 ( $\pm 8.57$ ) yrs. In 100 patients with COVID-19, 72% were males and the rest 28% were females as depicted in Figure:1.

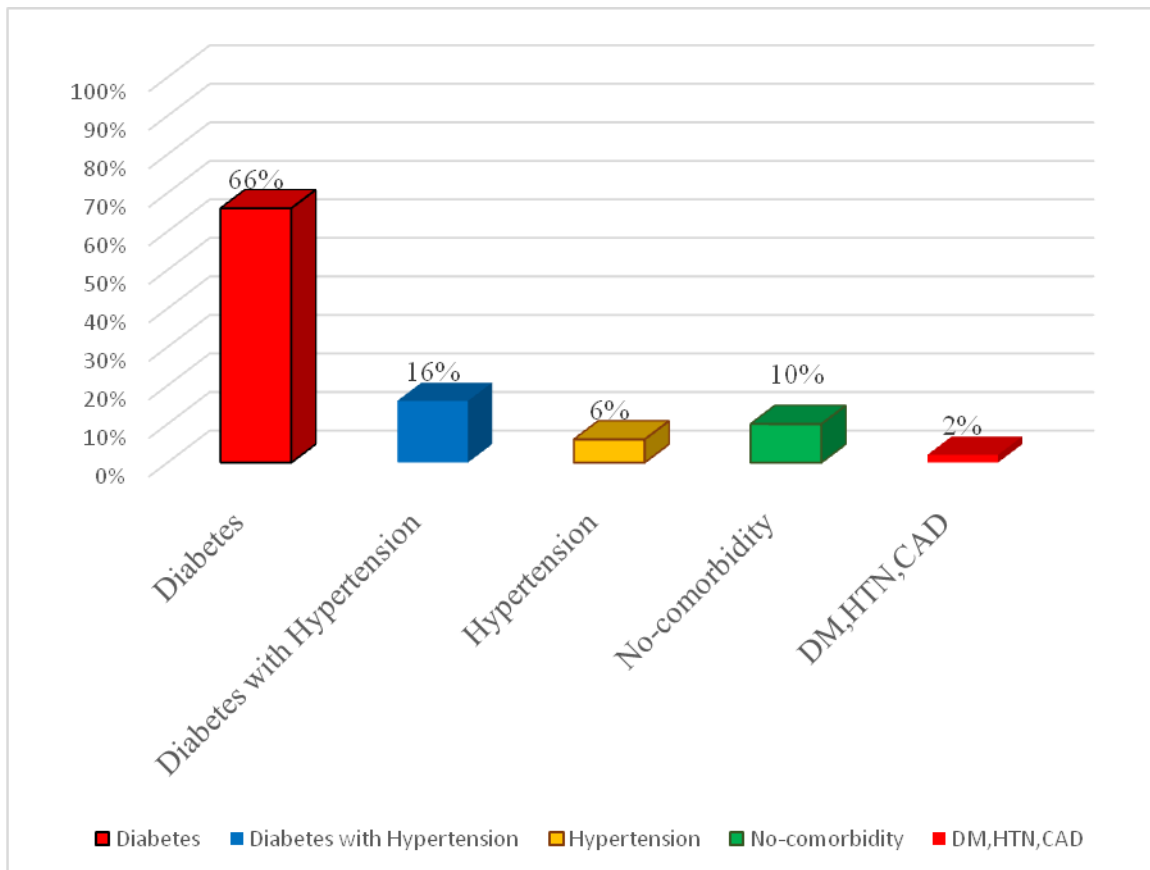


**Figure: 1 Gender wise distribution of patients with COVID-19**



**Figure: 2 Distribution of COVID-19 patients with Mucormycosis**

It was observed that mucormycosis was seen in 82% as depicted in Figure:2



**Figure:3 Distribution of Co-morbidities among the patients with mucormycosis**

In patients with COVID-19, pre-existing diabetes mellitus (DM) was present in 84% of cases while 66% had diabetes only as the most frequent co-morbidity followed by Diabetes with Hypertension among 18% and only Hypertension among 6%, 2% had coronary artery disease with Diabetes with Hypertension and 10% did not have any co-morbid conditions as depicted in figure3.

**Table:1**

Co-morbidities	No (%)
Diabetes	66(66%)
Diabetes, Hypertension	18(18%)
Hypertension	6(6%)
Diabetes, Hypertension with Coronary artery disease	2(2%)

Table: 1 show that diabetes was considered to be most common comorbidity associated with COVID -19 especially among patients with mucormycosis (76%). In patients with diabetes, mean blood glucose was 232.63 ( $\pm$ 82.81) g/dl with mean glycated haemoglobin (HbA1c) of 9.06% ( $\pm$ 2.19) at admission. There were no patients with diabetic ketoacidosis in our study.

The majority of the patients, 89% had history of steroid exposure in form of either dexamethasone and methylprednisolone. The duration and amount of exposure could not be determined as it varied due to physician preference and intake of OTC (over the counter) steroid by the patients. None of our patients received anti- IL6 therapy or monoclonal antibodies. There were no cases of malignancy, organ transplant or HIV/AIDS with Mucormycosis in the present study.

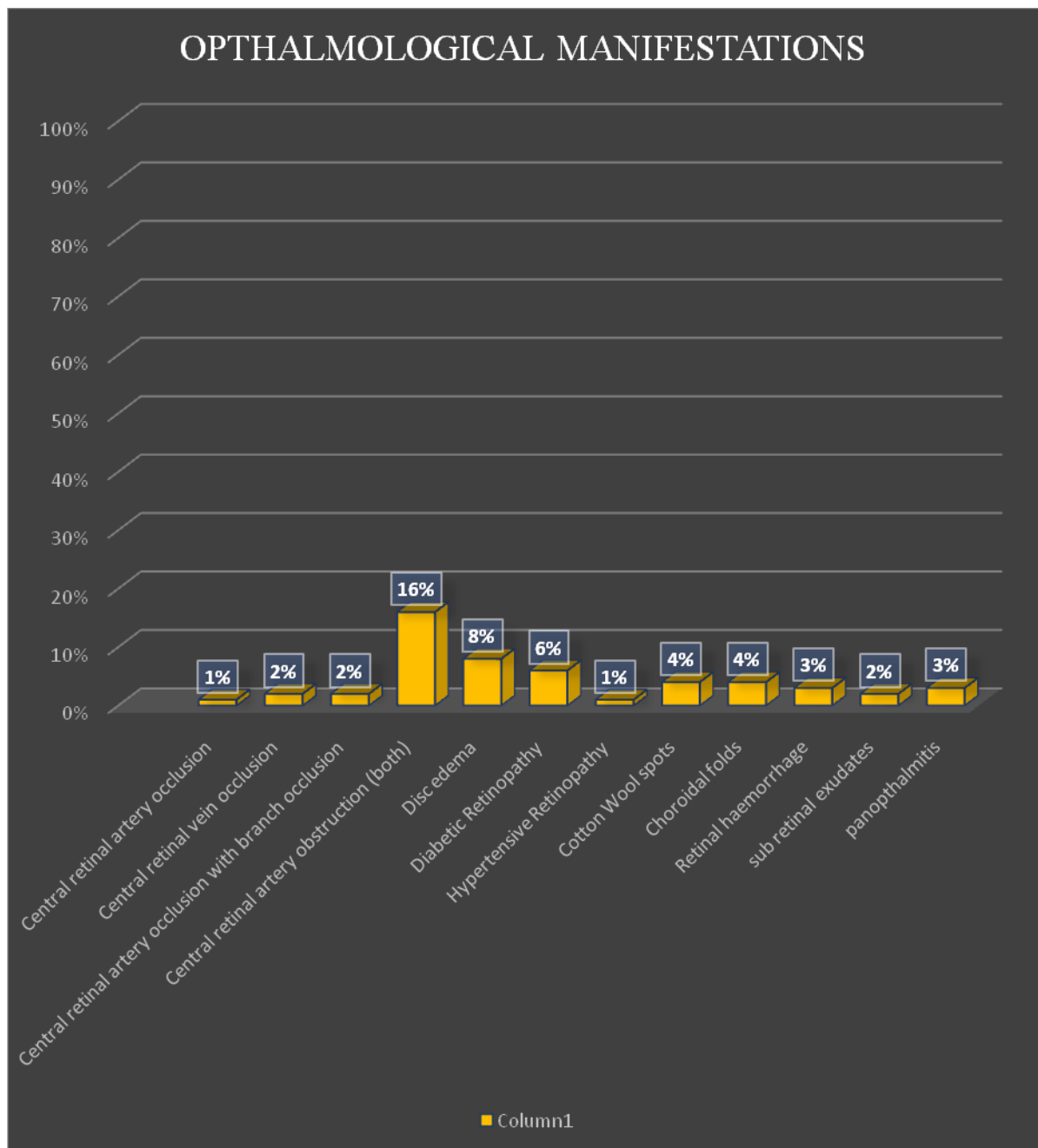
**Clinical presentation- this is not mucor mycosis – retinal mainifetations**

In Patients with COVID-19, 60% had headache, 61% had nasal symptoms in form of rhinorrhoea &49 % had eyes symptoms in form of redness or eye pain, oedema associated with facial swelling, matting of eye lashes, ptosis as depicted in figure:4.

All 82% of patients with mucormycosis were admitted and given Amphotericin IV3 doses, Posaconazole for 10 days, All patients recovered and discharged. No deaths were reported.

**Table: 2 Ophthalmic Retinal manifestations of COVID-19.**

Ophthalmic manifestations of COVID-19.	NO (%)
Central retinal artery occlusion	1(1%)
Central retinal vein occlusion	2(2%)
Central retinal artery occlusion with branch occlusion	2(1%)
Central retinal artery obstruction (both)	16(16%)
Disc oedema	8(8%)
Diabetic Retinopathy	6(6%)
Hypertensive Retinopathy	1(1%)
Cotton Wool spots	4(4%)
Choroidal folds	4(4%)
Retinal haemorrhage	3(3%)
Sub retinal exudates	2(2%)
Panopthalmitis	3(3%)
Total	49(100%)



**Figure :4 Distribution of patients based on ophthalmological manifestations**

Around 1% of patients had Central retinal artery occlusion,6% had diabetic retinopathy,4% cotton wool spots,8% had optic disc edema,3% panophthalmitis,2% had sub retinal exudates,2% had central retinal vein occlusion, 4% had choroidal folds ,3% had retinal haemorrhage,16% had central retinal artery obstruction.

**Contrast Enhanced Computed Tomography/ MRI Paranasal Sinuses** revealed 49 % with Rhino-orbital involvement. Among the Nose and Paranasal sinuses, (Maxillary and Ethmoid sinus) were predominantly involved in 51 %

cases. We had one patient with Maxillary, frontal and Ethmoid sinus and one patient with maxillary, sphenoid and ethmoidal sinus involvement.

There were no patients with cerebral, pulmonary or disseminated Mucormycosis. The diagnosis of Mucormycosis was confirmed with microscopy 85%, histopathology 80% and by culture in 27% cases.

### **Treatment and outcome**

Patients at our centre were started on liposomal amphotericin B IV and Posaconazole for 10 days with glycaemic control. In all the patients, endoscopic debridement of sinuses was done by the ENT department. All patients recovered and were discharged.

### **Discussion:**

In the present study, it was observed that mucormycosis was seen in (82%) of the patients. Among them majority of them are males (72%). Similar findings were reported from a systematic review done by **Singh AK et al in 2021<sup>8</sup>** study where mucormycosis was predominantly seen among males (78.9%).

In the present study, Diabetes was associated in our study with 84% similarly in a study done by **Y. Mishra, M. Prashar, D. Sharma et al. in 2021<sup>9</sup>**, it was reported to be 87.5%. Similar findings were reported systematic review done by **Singh AK et al in 2021<sup>8</sup>** study, where Pre-existing DM accounted for 80% of cases, while concomitant DKA was present in nearly 15% of people with mucormycosis and COVID-19.

In the present study among patients with diabetes, mean blood glucose was 232.63 ( $\pm$ 82.81) g/dl with mean glycated haemoglobin (HbA1c) of 9.06% ( $\pm$ 2.19) at admission. Similarly in a study done by **Y. Mishra, M. Prashar, D. Sharma et al. in 2021<sup>9</sup>** it was reported to 242.63 ( $\pm$ 84.81) g/dl & mean glycated haemoglobin (HbA1c) of 9.06% ( $\pm$ 2.19) at admission.

Diabetes is the most frequent co-morbidity in Mucormycosis in about 73.5% in India <sup>10</sup> However, in western countries diabetes is associated with 17% cases of Mucormycosis<sup>11</sup> Incidence of Mucormycosis is around 1.6 cases/1000 patients with diabetes<sup>12</sup>.



History of corticosteroid intake for the treatment of COVID-19 was present in 89% of the patients whereas it was 76.3% in **Singh AK et al study done in 2021**<sup>8</sup>.

**In the present study** the most prevalent ocular manifestations were dry eye or foreign body sensation (28%), redness (21%), tearing (10%), itching (10%), eye pain (15%), and discharge (16%).

Whereas in a **Systematic Review and Meta-analysis done by Naser Nasiri et al**, it was observed that among the ocular symptoms, the most common ocular manifestations were dry eye or foreign body sensation (16%), redness (13.3%), tearing (12.8%), itching (12.6%), eye pain (9.6%) and discharge (8.8%)

In the present study the prevalence of ocular manifestations among COVID-19 patients was 49%. Whereas in a **Systematic Review and Meta-analysis done by Naser Nasiri et al**<sup>13</sup> the pooled prevalence of all ocular manifestations among COVID -19 patients was 11.03%.

**Vabret et al** in a study in a French hospital, from November 2002 to April 2003, reported that ocular manifestations were 16.7% patients diagnosed with human coronavirus NL63.<sup>14</sup> **Ulhaq et al** in a systematic review study up to April 4, 2020 reported that ocular manifestations in COVID-19 patients were 5.5%.<sup>15</sup> The reason for ocular manifestations among patients diagnosed with COVID-19 and other coronaviruses could be related to the presence of ACE2 receptor, the cell receptor for coronaviruses and SARS-CoV-2, in the eye cells.<sup>16</sup>

Transmission of SARS-CoV-2 by tear is not unlikely,<sup>17</sup> and the eye can be a way for entering the infection droplets to the body.<sup>18</sup> Therefore, protecting eyes is essential for people, especially for healthcare providers to protect themselves against SARS-CoV-2.

The most important ocular manifestations in COVID-19 patients were dry eye or foreign body sensation, redness, tearing, itching, eye pain, and discharge. The mechanism of dry eye or foreign body sensation is unclear in COVID-19 patients and may not be directly associated with SARS-CoV-2. Indeed, the occurrence of dry eye during the COVID-19 epidemic could be due to wearing face masks and directing the expiratory air current toward eyes, especially when masks are loose against the face and nose. The stream of air against ocular surface causes accelerated evaporation of the tear and may create dry eye symptoms. In persons with

pre-existing dry eye or poor-quality tear film, the symptoms can be more common and prominent. Limitation of access to lubricating agents in fear of contamination of hands and drug containers also deteriorates dry eye manifestations.<sup>19,20</sup> Furthermore, since the beginning of the pandemic, people spend more time looking at screens that may exacerbate dry eye sensation.<sup>21,22</sup>

While screen watching, the rate and intensity of blinks is significantly diminished, exacerbating the dry eye symptoms. Loss of follow-up visits and reduced seeking care in patients with previous dry eye condition could be other factors that may have contributed to increased dry eye symptoms during the pandemic.<sup>19,20</sup>

In the present study, around 1% of patients had Central retinal artery occlusion, 6% had diabetic retinopathy, 4% cotton wool spots, 8% had optic disc edema, 3% panophthalmitis, 2% had sub retinal exudates, 2% had central retinal vein occlusion, 4% had choroidal folds, 3% had retinal haemorrhage, 16% had central retinal artery obstruction.

Both central retinal vein and artery occlusions have been reported in patients without classic systemic vascular risk factors. The hypothesized mechanism includes a complement-induced prothrombic and inflammatory state induced by the virus resulting in endothelial damage and microangiopathic injury. A striking example was reported by **Walinjkar et al.** with a central retinal vein occlusion (CRVO) in a 17-year-old female with COVID-19.<sup>23</sup> **Yahalomi et al.** presented a similar case in a previously healthy 33-year-old.<sup>24</sup> Several cases of central retinal artery occlusions (CRAO) have been reported, potentially related to viral-induced endothelial insult and vasculitis.<sup>25,26,27</sup>

There have been two published case reports on Purtscher-like retinopathy observed in patients with COVID-19. Bottini et al. described a 59-year-old male who presented with multiple bilateral cotton wool spots localized to the posterior pole after a month-long hospitalization for COVID-19 pneumonia associated with multiorgan failure and severe coagulopathy.<sup>28</sup>

### **Limitations:**

It was a single centre study with limited cases of COVID-19 and may not represent the full picture of the current state of the world. Moreover, we explored attributability of diabetes and

COVID-19 in the risk of **Mucormycosis** and did not have enough data for other risk factors like malignancy, neutropenia, HIV or organ transplant.

However, our study provides useful insights for demographic and ocular manifestations of COVID-19 and its relation with diabetes.

**Conclusion:** Attention to ocular manifestations in combination with other COVID-19 manifestations could help improve COVID-19 diagnosis. The main ocular manifestations were dry eye, tearing, itching, redness, eye pain, and foreign body sensation. It is recommended that healthcare providers especially ophthalmologists who are in close contacts with patients wear eye protective goggles in addition to other recommended protective equipment.

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**Declaration of competing interest:** The Authors declare there is no conflict of interest

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