

## Different Ocular Manifestations that Could be Linked to COVID-19 among a Sample of Egyptian Population

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### Abstract

**Purpose:** To find out any ocular manifestations that could be, in one way or another, linked to COVID 19, studying how they presented, how they progressed.

**Design:** This is a cross sectional study.

**Methods:** All Ophthalmologists received a questionnaire which was generated and sent through Google Forms. The primary outcome measures were ocular manifestations that could be linked to COVID-19 either directly or indirectly, or even linked to COVID-19 treatment.

**Results:** 159 Ophthalmologists responded to the questionnaire, most of them in the age group from 31 to 40 years of age (36.5%), and also most of them are cataract and refractive specialists (45.9%). Regarding COVID-19 direct effects; about 73.2% have seen cases of follicular conjunctivitis that could be linked to COVID, 19.3% have seen cases of viral keratitis, 43.9% have seen cases of retinal vascular occlusions (mainly as RVO), 33.7% have seen cases of uveitis (mainly anterior uveitis), 34.5% have seen cases of ocular neurological disorders, 20.5% have seen cases of external eye and orbital disease (mainly as orbital cellulitis), and 50% have operated on post-COVID cases. Regarding COVID indirect effects; around 60.4% have noticed deterioration of chronic cases because of lack of follow up visits, 59.1% have noticed advanced cases on initial presentation.

**Conclusion:** A lot of Ophthalmologists have seen patients infected with COVID-19 at a certain point of the disease. Some of these patients have presented with different ocular manifestations that were synchronous with their COVID-19 infection, raising the suspicion that it could be linked to COVID somehow. However, this needs further investigations to confirm this correlation.

**Keywords:** Anti-COVID Drugs; Conjunctivitis; COVID-19; Keratitis; Ocular Manifestations; Ocular Neurological; Orbital Disease; Retinal Vascular; Uveitis

### Introduction

A global epidemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has broken out with more than 4 million cases and 280,000 deaths worldwide. This disease has been named

"COVID-19" (where "CO" is corona, "VI" virus, "D" disease and "19" is the year in which it occurred; 2019) [1].

Apart from SARS-CoV-2, two human CoVs previously appeared, causing respiratory failure: SARS-CoV and Middle East Respiratory

Syndrome (MERS)-CoV. There are no reported ocular manifestations associated with SARS-CoV infection. Only one case report describes SARS-CoV positivity of a tear sample analyzed via polymerase chain reaction (PCR). As far as MERSCoV is concerned, there was no report of ocular manifestations or viral load in tear samples [2].

### Aim of the Study

In this study we aimed to find out any ocular manifestations that could be, in one way or another, linked to COVID 19, studying how they presented, how they progressed and how they ended up.

### Patients and Methods

This study was conducted according to the Declaration of Helsinki, with applicable institutional research regulations. It was approved by Kasr Al Ainy Ophthalmology Department. All Ophthalmologists received a questionnaire which was generated and sent through Google Forms.

This is a cross sectional study at Kasr Al-Ainy teaching hospital, Cairo University. Kasr Al Ainy hospital is a central university hospital in Cairo and it is the center for referral from most of the governorates in Egypt.

The questionnaire included the following questions.

#### Section I: Personal questions:

- Age group and field of interest (Subspecialty).
- Seeing patients, deferring them or triaging by phone.
- Percentage reduction of patient flow, percentage of elective patients attending clinic, using phone to communicate with patients, and having protocol for flagged patient.

#### Section II: Ocular manifestations that could be linked to COVID For each manifestation:

##### COVID-related questions:

- Its link to COVID.
- How COVID diagnosis was confirmed (Clinical, Lab tests, Chest CT, or PCR).
- When the suspected case was seen (during active disease or after treatment).
- Type of treatment for COVID, if known [Anti-malarial, anti-viral, immune-modulatory drugs (Interferon, Interleukin inhibitors), steroids, or unknown] and if the patient was previ-

ously hospitalized, and if so, was he admitted to ICU and put on ventilator (CPAP).

#### Ocular-related questions:

- Number of cases seen.
- Pattern of presentation.
- Was it treated as usual or did it deteriorate.

#### First: Manifestations due to COVID direct effect:

##### 1. Anterior segment

- a. Follicular conjunctivitis.
- b. Viral keratitis.

##### 2. Posterior segment

- a. Retinal vascular occlusion (CRAO, BRAO, cilioretinal artery, ophthalmic artery, carotid artery, CRVO, BRVO, hemiretinal vein, papillophlebitis).
- b. Retinal ischemia [Retinal hemorrhages, exudates, cotton-wool spots, retinal edema, microaneurysms, neovascularization, IRMA, anterior segment manifestations (flare, NVI, cataract)].
- c. Kawasaki disease.

##### 3. Uveitis: (Anterior, posterior, intermediate, endogenous endophthalmitis, panophthalmitis).

##### 4. Neuro-ophthalmology (Single or multiple nerve palsy, AION, papilledema, other optic neuropathy, abnormal pupillary reactions, cortical blindness, or unexplained visual loss).

##### 5. Secondary glaucoma.

##### 6. Surgical

- a. Operating on a post-COVID case?
- b. Postoperative complications (conjunctivitis, keratitis, reaction/ uveitis, orbital inflammatory reaction, retinal vascular occlusion or ischemia, ischemic optic neuropathy).

##### 7. External eye diseases and orbit (scleritis/episcleritis, pre-septal/orbital cellulitis, orbital myositis, lacrimal adenitis/dacryocystitis, Tolosa-Hunt syndrome, Wegener granulomatosis, cavernous sinus thrombosis)

##### 8. Other ocular presentations (case you could not reach a final diagnosis)

#### Second: Manifestations due to COVID indirect effect:

- I. Due to absence of medical care:

- a. Deterioration of chronic cases because of lack of follow up visits fearing from coming to the clinics.
  - b. Advanced cases on initial presentation due to late presentation fearing from going to the clinics.
- II. Related to ICU admission due to COVID:
- A) Ocular surface disorders.
  - B) Rare complications:
    - i. Valsalva retinopathy.
    - ii. Acute angle-closure glaucoma.
    - iii. Horner syndrome.
    - iv. Endogenous endophthalmitis.

### Third: Manifestations due to anti-COVID drugs:

- I. Anti-malarial drugs: Corneal epithelial deposits, posterior subcapsular cataract, ciliary body dysfunction, maculopathy.
- II. Anti-viral drugs: Macular retinal pigment epitheliopathy, cotton wool spots.
- III. Immune-modulatory drugs: Retinal hemorrhages, cotton wool spots, papilledema, nystagmus.
- IV. Steroids: Glaucoma, cataract, ocular infection.

### Statistical methods

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 20. The quantitative data were presented as mean, standard deviation while qualitative data were presented as number and percentage. The comparison between two independent groups with qualitative data was done using Chi-square test. The comparison between two independent groups with quantitative data and parametric distribution was done using Independent t-test. The confidence interval is set to 95% and the margin of error accepted is set to 5%. So, the P-value is considered significant as the following:  $P < 0.05$  and highly significant at  $p < 0.01$ .

### Results

This study was conducted during the time interval Feb-Mar 2021, during which 159 Ophthalmologists responded to the questionnaire, with the majority of them in the age group from 31 to 40 years of age (36.5%), and also with most of them having cataract and refractive as a subspecialty (45.9%). Table 1 shows their response to section I questions (personal questions).

About 88.5% of our candidates prefer seeing their patients than deferring or triaging them by phone. About 49.4% have a reduction

of 25 - 50% of patients flow in their clinics and 29.3% have around 25 - 50% of their patients as elective. About 54.8% of them would use phone or video calls to communicate with their patients and 59.2% are intending to use telemedicine in the future, while 65% are willing to examine a patient with COVID as 50.6% have a protocol for a flagged patient as a COVID suspect (Table 1).

Questions	Results
<b>Age group</b>	7.1%
1. 20 - 30	36.5%
2. 31-40	27.6%
3. 41-50	17.3%
4. 51-60	11.5%
5. 60+	
<b>Seeing patients or deferring them or doing triaging for patients by phone before their appointment</b>	88.5%
1. Seeing	3.2%
2. Deferring	8.3%
3. Triaging by phone	
<b>Percentage reduction of patient flow</b>	32.7%
1. 0 - 25	49.4%
2. 25 - 50	17.9%
3. 50 - 75	0%
4. 75 - 100	
<b>Percentage of elective patients you are currently seeing in your clinic</b>	20.4%
1. 0 - 25	29.3%
2. 25 - 50	25.5%
3. 50 - 75	24.8%
4. 75 - 100	
Use of phone or video calls to communicate with patients	54.8%
Willing to do emergency surgery on a COVID-19 patient	65%
Having a protocol for flagged patient as suspects of being COVID-19 positive	50.6%

<b>On scale from 0 (No anxiety) to 5 (Extremely anxious) rating patients' psychic concern as it relates to the pandemic</b>	
- 0	1.9%
- 1	12.7%
- 2	37.6%
- 3	36.9%
- 4	8.3%
- 5	2.5%
Considering Telemedicine in your practice later on	59.2%
<b>Field of interest (Subspecialty) (More than one choice is allowed)</b>	
1. Vitreo-Retinal surgery	25.5%
2. Glaucoma	21.7%
3. Oculoplastic and Orbit	6.4%
4. Pediatric	19.1%
5. Cornea and External Eye Disease	26.8%
6. Cataract and Refractive	45.9%
7. Neuro-ophthalmology	5.7%
8. Uveitis and Immunology	14%
9. Ocular Oncology	6.4%
10. Investigative	23.6%

**Table 1:** Section I: Personal questions.

When the candidates finished this section of personal questions, they were shifted to section II questions regarding "COVID Direct Ocular Manifestations" (Table 2). About 53.2% have seen cases that could be directly linked to COVID. The rest who haven't seen, were automatically shifted to section III questions of ocular manifestations that could be indirectly related to COVID and those that could be related to anti-COVID drugs. Of those who have seen cases that could be directly related to COVID:

- About 73.2% have seen cases of follicular conjunctivitis that could be linked to COVID, of which 70.5% said it was the usual presentation and 96.6% said it was treated.

- About 19.3% have seen cases of viral keratitis that could be linked to COVID, of which 57.1% said it was the usual presentation and 100% said it was treated.
- About 43.9% have seen cases of retinal vascular occlusions (mainly as RVO) that could be linked to COVID, of which 72.2% said it was the usual presentation and 74.3% said it was treated.
- About 15.7% have seen cases of retinal ischemia (mainly as hemorrhages) that could be linked to COVID, of which 69.2% said it was the usual presentation and 67.7% said it was treated.
- About 6.1% have seen cases of Kawasaki disease that could be linked to COVID, of which 100% said it was the usual presentation and 100% said it was treated.
- About 33.7% have seen cases of uveitis (mainly as anterior uveitis) that could be linked to COVID, of which 65.5% said it was the usual presentation and 70.4% said it was treated.
- About 34.5% have seen cases of ocular neurological disorders that could be linked to COVID, of which 64.3% said it was the usual presentation and 81.5% said it was treated.
- About 1.2% has seen cases of secondary glaucoma that could be linked to COVID, of which 100% said it was the usual presentation and 100% said it Has deteriorated.
- About 50% have operated on post-COVID cases with the appearance of various postoperative complications, of which 60% said they were the usual presentation and 100% said they were treated.
- About 20.5% have seen cases of external eye and orbital disease (mainly as orbital cellulitis) that could be linked to COVID, of which 52.9% said it was the usual presentation and 52.9% said it was treated.
- About 20.2% have seen cases without reaching a final diagnosis that could be linked to COVID.

Finally they were directed to section III questions of ocular manifestations that could be indirectly related to COVID and those that could be related to anti-COVID drugs (Table 3). Regarding indirect COVID manifestations:

- Around 60.4% have noticed deterioration of chronic cases because of lack of follow up visits.
- Around 59.1% have noticed advanced cases on initial presentation due to late presentation.

Questions	Results
Have you seen a case with ocular presentation suspected to be due to COVID-19 direct effect? Yes	53.2%
<b>I. Anterior segment</b>	
<b>A) Follicular Conjunctivitis:</b>	
Have you seen a case of follicular conjunctivitis that could be COVID related? Yes	73.2%
<b>COVID-related</b>	
- Could it be linked to COVID or was there another obvious cause?	88.5%
1. Linked to COVID	
2. Another obvious cause	11.5%
- How was COVID diagnosis confirmed? (More than one choice is allowed)	
1. Clinical presentation	59.3
2. Lab tests	39%
3. Chest CT	
4. PCR	42.4%
- Did you see the suspected case during active disease or after treatment? (More than one choice is allowed)	
1. During COVID	64.4%
2. After treatment	
- Type of treatment the COVID patient received (if known): (More than one choice is allowed)	50%
1. Anti-malarial drugs	68.3%
2. Anti-viral drugs	
3. Immune-modulatory drugs (Interferon, Interleukin inhibitors)	20.3%
4. Steroids	
5. Don't know	13.6%
- Was the COVID patient previously hospitalized? Yes	6.8%
- If the COVID patient was previously hospitalized, was he admitted to ICU and put on ventilator (CPAP)? Yes	
	28.8%
	64.4%
	30.5%
	12%
<b>Conjunctivitis-related</b>	5.6 7.1 (1-30)
- Number of cases you have seen	
- Was it the usual pattern of presentation? Yes	70.5%
- Was it treated as usual or did it deteriorate?	
1. Treated	
2. Deteriorated	96.6%
	3.4%
<b>B) Viral Keratitis:</b>	
Have you seen a case of viral keratitis that could be COVID related? Yes	19.3%

<b>COVID-related</b>	
- Could it be linked to COVID or was there another obvious cause?	62.5%
1. Linked to COVID	37.5%
2. Another obvious cause	68.8%
- How was COVID diagnosis confirmed? (More than one choice is allowed)	43.8%
1. Clinical presentation	31.3%
2. Lab tests	56.3%
3. Chest CT	18.8%
4. PCR	81.3%
- Did you see the suspected case during active disease or after treatment? (More than one choice is allowed)	13.3%
1. During COVID	26.7%
2. After treatment	6.7%
- Type of treatment the COVID patient received (if known): (More than one choice is allowed)	26.7%
1. Anti-malarial drugs	73.3%
2. Anti-viral drugs	33.3%
3. Immune-modulatory drugs (Interferon, Interleukin inhibitors)	15.4%
4. Steroids	
5. Don't know	
- Was the COVID patient previously hospitalized? Yes	
- If the COVID patient was previously hospitalized, was he admitted to ICU and put on ventilator (CPAP)? Yes	
<b>Keratitis-related</b>	
- Number of cases you have seen	1.5 0.7 (1-3)
- Was it the usual pattern of presentation? Yes	57.1%
- Was it treated as usual or did it deteriorate?	100%
1. Treated	0%
2. Deteriorated	
<b>II. Posterior Segment</b>	
<b>A) Retinal vascular occlusion</b>	
Have you seen a case of retinal vascular occlusion that could be COVID related? Yes	43.9%

<b>COVID-related</b>	
- Could it be linked to COVID or was there another obvious cause?	97.2%
1. Linked to COVID	2.8%
2. Another obvious cause	58.3%
- How was COVID diagnosis confirmed? (More than one choice is allowed)	63.9%
1. Clinical presentation	47.2%
2. Lab tests	77.8%
3. Chest CT	22.2%
4. PCR	88.9%
- Did you see the suspected case during active disease or after treatment? (More than one choice is allowed)	20%
1. During COVID	88.9%
2. After treatment	20%
- Type of treatment the COVID patient received (if known): (More than one choice is allowed)	25.7%
1. Anti-malarial drugs	5.7%
2. Anti-viral drugs	28.6%
3. Immune-modulatory drugs (Interferon, Interleukin inhibitors)	62.9%
4. Steroids	35.3%
5. Don't know	14.3%
- Was the COVID patient previously hospitalized? Yes	
- If the COVID patient was previously hospitalized, was he admitted to ICU and put on ventilator (CPAP)? Yes	
<b>Retinal vascular occlusion-related</b>	
- Type of vascular occlusion: (More than one choice is allowed)	25%
1. CRAO	13.9%
2. BRAO	2.8%
3. Cilioretinal artery occlusion	0%
4. Ophthalmic artery occlusion	0%
5. Carotid artery occlusion	58.3%
6. CRVO	55.6%
7. BRVO	25%
8. Hemiretinal vein occlusion	16.7%
9. Papillophlebitis	3.0 2.4 (1-10)
- Number of cases you have seen	
- Was it the usual pattern of presentation? Yes	72.2%
- Was it treated as usual or did it deteriorate?	74.3%
1. Treated	25.7%
2. Deteriorated	

<b>B) Retinal ischemia (hemorrhages, exudates and cotton wool spots)</b>	
Have you seen a case of retinal ischaemia (hemorrhages, exudates, cotton wool spots) that could be COVID related? Yes	15.7%
<b>COVID-related</b>	
- Could it be linked to COVID or was there another obvious cause?	
1. Linked to COVID	91.7%
2. Another obvious cause	8.3%
- How was COVID diagnosis confirmed? (More than one choice is allowed)	76.9%
1. Clinical presentation	69.2%
2. Lab tests	23.1%
3. Chest CT	61.5%
4. PCR	23.1%
- Did you see the suspected case during active disease or after treatment? (More than one choice is allowed)	
1. During COVID	92.3%
2. After treatment	30.8%
- Type of treatment the COVID patient received (if known): (More than one choice is allowed)	23.1%
1. Anti-malarial drugs	7.7%
2. Anti-viral drugs	30.8%
3. Immune-modulatory drugs (Interferon, Interleukin inhibitors)	61.5%
4. Steroids	46.2%
5. Don't know	22.2%
- Was the COVID patient previously hospitalized? Yes	
- If the COVID patient was previously hospitalized, was he admitted to ICU and put on ventilator (CPAP)? Yes	
<b>Retinal ischemia-related</b>	
- How did retinal ischemia present?	
1. Retinal hemorrhages	92.3%
2. Retinal exudates	53.8%
3. Cotton-wool spots	69.2%
4. Retinal edema	46.2%
5. Retinal microaneurysms	23.1%
6. Neovascularization	38.5%
7. IRMA	7.7%
8. Anterior segment manifestations (Flare, NVI, Cataract)	30.8%
9. Other	7.7%
- How was it diagnosed? (More than one choice is allowed)	
1. Clinically	84.6%
2. Imaging techniques	38.5%
- Number of cases you have seen	2.5 2.6
- Was it the usual pattern of presentation? Yes	(1-10)
- Was it treated as usual or did it deteriorate?	69.2%
1. Treated	67.7%
2. Deteriorated	33.3%



<b>C) Kawasaki disease</b>	
Have you seen a case of Kawasaki disease that could be COVID related? Yes	6.1%
	100%
	0%
<b>COVID-related</b>	
- Could it be linked to COVID or was there another obvious cause?	20%
1. Linked to COVID	0%
2. Another obvious cause	
- How was COVID diagnosis confirmed? (More than one choice is allowed)	80%
1. Clinical presentation	
2. Lab tests	0%
3. Chest CT	
4. PCR	
- Did you see the suspected case during active disease or after treatment? (More than one choice is allowed)	40%
1. During COVID	
2. After treatment	
- Type of treatment the COVID patient received (if known): (More than one choice is allowed)	60%
1. Anti-malarial drugs	
2. Anti-viral drugs	
3. Immune-modulatory drugs (Interferon, Interleukin inhibitors)	0%
4. Steroids	
5. Don't know	0%
- Was the COVID patient previously hospitalized? Yes	0%
- If the COVID patient was previously hospitalized, was he admitted to ICU and put on ventilator (CPAP)? Yes	0%
	0%
	100%
	20%
	20%
<b>Kawasaki disease-related</b>	1.2 0.4 (1-2)
- Number of cases you have seen	
- Was it the usual pattern of presentation? Yes	100%
- Was it treated as usual or did it deteriorate?	
1. Treated	
2. Deteriorated	100%
	0%
<b>III. Uveitis</b>	
Have you seen a case of uveitis that could be COVID related? Yes	33.7%

<b>COVID-related</b>	
- Could it be linked to COVID or was there another obvious cause?	
1. Linked to COVID	82.8%
2. Another obvious cause	17.2%
- How was COVID diagnosis confirmed? (More than one choice is allowed)	62.1%
1. Clinical presentation	51.7%
2. Lab tests	31%
3. Chest CT	44.8%
4. PCR	24.1%
- Did you see the suspected case during active disease or after treatment? (More than one choice is allowed)	86.2%
1. During COVID	17.2%
2. After treatment	20.7%
- Type of treatment the COVID patient received (if known): (More than one choice is allowed)	0%
1. Anti-malarial drugs	41.4%
2. Anti-viral drugs	69%
3. Immune-modulatory drugs (Interferon, Interleukin inhibitors)	46.4%
4. Steroids	33.3%
5. Don't know	
- Was the COVID patient previously hospitalized? Yes	
- If the COVID patient was previously hospitalized, was he admitted to ICU and put on ventilator (CPAP)? Yes	
<b>Uveitis-related</b>	
- Type of uveitis: (More than one choice is allowed)	62.1%
1. Anterior	31%
2. Posterior	17.2%
3. Intermediate	37.9%
4. Endogenous endophthalmitis	13.8%
5. Panophthalmitis	3.4%
6. Other	2.0 1.2 (1-5)
- Number of cases you have seen	65.5%
- Was it the usual pattern of presentation? Yes	
- Was it treated as usual or did it deteriorate?	70.4%
1. Treated	29.6%
2. Deteriorated	
<b>IV. Neuro-ophthalmology</b>	

Have you seen a case of ocular neurological disorders that could be COVID related? Yes	34.5%
<b>COVID-related</b>	
- Could it be linked to COVID or was there another obvious cause?	
1. Linked to COVID	93.1%
2. Another obvious cause	6.9%
- How was COVID diagnosis confirmed? (More than one choice is allowed)	
1. Clinical presentation	58.6%
2. Lab tests	62.1%
3. Chest CT	48.3%
4. PCR	65.5%
- Did you see the suspected case during active disease or after treatment? (More than one choice is allowed)	
1. During COVID	20.7%
2. After treatment	93.1%
- Type of treatment the COVID patient received (if known): (More than one choice is allowed)	
1. Anti-malarial drugs	13.8%
2. Anti-viral drugs	10.3%
3. Immune-modulatory drugs (Interferon, Interleukin inhibitors)	6.9%
4. Steroids	17.2%
5. Don't know	75.9%
- Was the COVID patient previously hospitalized? Yes	44.8%
- If the COVID patient was previously hospitalized, was he admitted to ICU and put on ventilator (CPAP)? Yes	30.4%
<b>Neuro-ophthalmology-related</b>	
- Type of presentation: (More than one choice is allowed)	
1. Single nerve palsy	17.2%
2. Multiple nerve palsies	27.6%
3. AION	17.2%
4. Papilledema	13.8%
5. Other optic neuropathy	27.6%
6. Abnormal pupillary reactions	6.9%
7. Cortical blindness	6.9%
8. Unexplained visual loss	6.9%
9. Other	23.9%
- Number of cases you have seen	1.8 1.8 (1-10)
- Was it the usual pattern of presentation? Yes	64.3%
- Was it treated as usual or did it deteriorate?	
1. Treated	81.5%
2. Deteriorated	18.5%

<b>V. Secondary Glaucoma</b>	
Have you seen a case of secondary glaucoma that could be COVID related? Yes	1.2%
<b>COVID-related</b>	
- Could it be linked to COVID or was there another obvious cause?	
1. Linked to COVID	100%
2. Another obvious cause	0%
- How was COVID diagnosis confirmed? (More than one choice is allowed)	
1. Clinical presentation	100%
2. Lab tests	100%
3. Chest CT	100%
4. PCR	100%
- Did you see the suspected case during active disease or after treatment? (More than one choice is allowed)	
1. During COVID	0%
2. After treatment	100%%
- Type of treatment the COVID patient received (if known): (More than one choice is allowed)	
1. Anti-malarial drugs	100%
2. Anti-viral drugs	100%
3. Immune-modulatory drugs (Interferon, Interleukin inhibitors)	100%
4. Steroids	100%
5. Don't know	0%
- Was the COVID patient previously hospitalized? Yes	100%
- If the COVID patient was previously hospitalized, was he admitted to ICU and put on ventilator (CPAP)? Yes	0%
<b>Glaucoma-related</b>	
- Number of cases you have seen	1
- Was it the usual pattern of presentation? Yes	100%
- Was it treated as usual or did it deteriorate?	
1. Treated	0%
2. Deteriorated	100%
<b>VI. Surgical</b>	
Have you operated on a post-COVID case? Yes	50%

<b>COVID-related</b>	
- How was COVID diagnosis confirmed? (More than one choice is allowed)	
1. Clinical presentation	42.9%
2. Lab tests	40.5%
3. Chest CT	40.5%
4. PCR	90.5%
- Type of treatment the COVID patient received (if known): (More than one choice is allowed)	14.6%
1. Anti-malarial drugs	26.8%
2. Anti-viral drugs	9.8%
3. Immune-modulatory drugs (Interferon, Interleukin inhibitors)	31.7%
4. Steroids	65.9%
5. Don't know	34.1%
- Was the COVID patient previously hospitalized? Yes	34.1%
- If the COVID patient was previously hospitalized, was he admitted to ICU and put on ventilator (CPAP)? Yes	3.4%
<b>Surgery-related</b>	
- Did he/ she develop postoperative complications? Yes	0%
- What kind of complication did he/ she develop?	33.3%
1. Conjunctivitis	0%
2. Keratitis	33.3%
3. Reaction/ Uveitis	0%
4. Orbital inflammatory reaction	0%
5. Retinal vascular occlusion	0%
6. Retinal ischemia	0%
7. Ischemic optic neuropathy	0%
8. Other	33.4%
- Number of cases you have seen	3.8 4.0 (1-20)
- Was it the usual pattern of presentation? Yes	60%
- Was it treated as usual or did it deteriorate?	100%
1. Treated	100%
2. Deteriorated	0%
<b>VII. External Eye Diseases and Orbit</b>	
Have you seen a case of external eye/orbital disease that could be COVID related? Yes	20.5%

<b>COVID-related</b>	
- Could it be linked to COVID or was there another obvious cause?	
1. Linked to COVID	94.1%
2. Another obvious cause	5.9%
- How was COVID diagnosis confirmed? (More than one choice is allowed)	
1. Clinical presentation	41.2%
2. Lab tests	41.2%
3. Chest CT	58.8%
4. PCR	76.5%
- Did you see the suspected case during active disease or after treatment? (More than one choice is allowed)	
1. During COVID	58.8%
2. After treatment	47.1%
- Type of treatment the COVID patient received (if known): (More than one choice is allowed)	
1. Anti-malarial drugs	5.9%
2. Anti-viral drugs	11.8%
3. Immune-modulatory drugs (Interferon, Interleukin inhibitors)	0%
4. Steroids	17.6%
5. Don't know	70.6%
- Was the COVID patient previously hospitalized? Yes	70.6%
- If the COVID patient was previously hospitalized, was he admitted to ICU and put on ventilator (CPAP)? Yes	50%
<b>External eye disease and orbit related</b>	
- How did the patient with external eye/ orbital disease present?	23.5%
1. Scleritis/ episcleritis	11.8%
2. Preseptal cellulitis	64.7%
3. Orbital cellulitis	17.6%
4. Orbital myositis	0%
5. Lacrimal adenitis/ dacryocystitis	0%
6. Tolosa-Hunt syndrome	0%
7. Wegener granulomatosis	0%
8. Cavernous sinus thrombosis	29.4%
9. Other	23.6%
- Number of cases you have seen	2.2 1.4
- Was it the usual pattern of presentation of external eye/orbital disease? Yes	(1-6)
- Was external eye/orbital disease treated as usual or did it deteriorate?	52.9%
1. Treated	52.9%
2. Deteriorated	47.1%
<b>VIII. Other Ocular Presentations</b>	

Have you seen a case you could not reach a final diagnosis? Yes	20.2%
<b>COVID-related</b>	
- Could it be linked to COVID or was there another obvious cause?	
1. Linked to COVID	83.3%
2. Another obvious cause	16.7%
- How was COVID diagnosis confirmed? (More than one choice is allowed)	91.7%
1. Clinical presentation	41.7%
2. Lab tests	50%
3. Chest CT	58.3%
4. PCR	
- Did you see the suspected case during active disease or after treatment? (More than one choice is allowed)	16.7%
1. During COVID	100%
2. After treatment	16.7%
- Type of treatment the COVID patient received (if known): (More than one choice is allowed)	16.7%
1. Anti-malarial drugs	16.7%
2. Anti-viral drugs	16.7%
3. Immune-modulatory drugs (Interferon, Interleukin inhibitors)	33.3%
4. Steroids	75%
5. Don't know	50%
- Was the COVID patient previously hospitalized? Yes	33.3%
- If the COVID patient was previously hospitalized, was he admitted to ICU and put on ventilator (CPAP)? Yes	
<b>Ocular-related</b>	
- Number of cases you have seen	1.2 0.4 (1-2)
- Any investigations done: Yes	76.9%

**Table 2:** Section II: Ocular manifestations of COVID. Manifestations that could be linked to COVID direct effect.

- Around 7.1% have seen cases of ocular surface disorders that could be related to ICU admission due to COVID.
  - Around 6.6% have seen cases of valsalva retinopathy that could be related to ICU admission due to COVID.
  - Around 11.8% have seen cases of acute angle closure glaucoma that could be related to ICU admission due to COVID.
  - Around 3.2% have seen cases of Horner syndrome that could be related to ICU admission due to COVID.
  - Around 25.3% have seen cases of endogenous endophthalmitis that could be related to ICU admission due to COVID.
- Speaking about manifestations that could be somehow related to anti-COVID drugs:
- About 27.5% have seen cases that have taken anti-malarial drugs but 56.5% of them have seen no ocular toxicity.
  - About 23.1% have seen cases that have taken anti-viral drugs with various ocular toxicities.

- About 8.6% have seen cases that have taken immune-modulatory drugs with various ocular toxicities.
- About 45.4% have seen cases that have taken anti-viral drugs with various ocular complications.

## Discussion

Sars-CoV-2 is a single-stranded RNA virus that is immunologi-

cally similar to Sars-CoV-1. It is part of the beta-coronavirus family and has non-structural proteins and spike proteins that interact heavily with the receptors of angiotensin-converting enzyme 2 (ACE2) in the human body, which is more concentrated in the lung, heart, renal and intestinal tissue [3].

ACE2 is also expressed in ocular tissue; in the cornea and conjunctiva epithelial cells. This receptor is associated with the main-

Questions	Results
<b>Second: Manifestations due to COVID indirect effect</b>	
<b>I. Due to absence of medical care:</b>	
- Did you notice deterioration of chronic cases you were following up because of lack of follow up visits fearing from coming to the clinics? Yes	60.4%
- If yes, what is the number of cases you have seen?	8.3 ± 6.7 (1-30)
- Did you notice advanced cases on initial presentation due to late presentation fearing from going to the clinics? Yes	59.1%
- If yes, what is the number of cases you have seen?	6.1 ± 5.2 (1-20)
<b>II. Related to ICU admission due to COVID</b>	
<b>A) Ocular surface disorders</b>	
- Have you seen any cases? Yes	7.1%
- How did it present? (More than one choice is allowed)	
1. Dry eye	45.5%
2. Conjunctivitis	45.5%
3. Keratitis	45.5%
4. Other	18.2%
- Number of cases you have seen	13.1 ± 21.5 (1-60)
- Was it treated as usual or did it deteriorate?	
1. Treated	81.8%
2. Deteriorated	18.2%
<b>B) Rare complications</b>	
<b>i.Valsalva retinopathy</b>	
- Have you seen any cases? Yes	6.6%
- Number of cases you have seen	1.3 ± 0.5 (1-2)
- Was it treated as usual or did it deteriorate?	
1. Treated	100%
2. Deteriorated	0%
<b>i.Acute angle-closure glaucoma</b>	
- Have you seen any cases? Yes	11.8%
- Number of cases you have seen	3.6 ± 4.7 (1-20)
- Was it treated as usual or did it deteriorate?	
1. Treated	100%
2. Deteriorated	0%
<b>i.Horner syndrome</b>	
- Have you seen any cases? Yes	3.2%
- Number of cases you have seen	1
<b>v.Endogenous endophthalmitis</b>	
- Have you seen any cases? Yes	25.3%
- Number of cases you have seen	1.3 ± 0.5 (1-3)
- Was it treated as usual or did it deteriorate?	
1. Treated	53.8%
2. Deteriorated	46.2%
<b>Third: Manifestations due to anti-COVID drugs</b>	
<b>I. Anti-malarial drugs</b>	
- Has the patient been taking them for COVID? Yes	27.5%
- Type of ocular complication the patient presented with: (More than one choice is allowed)	
1. Corneal epithelial deposits	13%
2. Posterior subcapsular cataract	4.3%
3. Ciliary body dysfunction	0%
4. Maculopathy	34.8%
5. Other	4.3%
6. No ocular complication	56.5%
- Number of cases you have seen with ocular complication caused by the drug	2.4 ± 1.8 (1-5)



-	Was it reversed on cessation of drug? Yes	33.3%
<b>II. Anti-viral drugs</b>		
-	Has the patient been taking them for COVID? Yes	23.1%
-	Type of ocular complication the patient presented with: (More than one choice is allowed)	
1.	Macular retinal pigment epitheliopathy	0%
2.	Cotton wool spots	14.5%
3.	Other	59.1%
4.	No ocular complication	36.4%
-	Number of cases you have seen with ocular complication caused by the drug	1
-	Was it reversed on cessation of drug? Yes	61.5%
<b>III. Immune-modulatory drugs</b>		
-	Has the patient been taking them for COVID? Yes	8.6%
-	Type of ocular complication the patient presented with: (More than one choice is allowed)	
1.	Retinal hemorrhages	22.2%
2.	Cotton wool spots	0%
3.	Papilledema	0%
4.	Nystagmus	0%
5.	Other	44.4%
6.	No ocular complication	33.3%
-	Number of cases you have seen with ocular complication caused by the drug	2.8 ± 0.5 (2-3)
-	Was it reversed on cessation of drug? Yes	57.1%
<b>IV. Steroids</b>		
-	Has the patient been taking them for COVID? Yes	45.4%
-	Type of ocular complication the patient presented with: (More than one choice is allowed)	
1.	Glaucoma	22.6%
2.	Cataract	18.9%
3.	Ocular infection	24.5%
4.	Other	20/8%
5.	No ocular complication	28.3%
-	Number of cases you have seen with ocular complication caused by the drug	2.7 ± 2.1 (1-10)

**Table 3:** Manifestations due to COVID indirect effect and due to anti-COVID drugs.

tenance of intraocular pressure and has an important role in the pathophysiology of COVID-19 [4,5].

ACE2 plays a negative regulatory role in the renin-angiotensin system (RAS). Its functions extend beyond regulating blood pressure as it modulates inflammatory and fibrotic processes in specific tissues [6]. ACE2 was notably expressed in structures that regulate the aqueous humour dynamic which has been studied for a potential therapy for glaucoma [7]. ACE2 gene has been documented in a rodent retina, particularly in the inner nuclear layer and photoreceptors and ACE2 activity was established in the ciliary and vitreous bodies from a porcine study [8,9]. Besides, ACE2 was found to exert its anti-inflammatory effect on human retinal pigment epithelium according to a study targeting on mechanisms of retinal inflammation [10].

A search was carried out in Pubmed until March, 2020 in which the following publications were included in English: letters to the editor, clinical cases, bibliographic reviews and clinical studies. The search field included publication abstract and title. Different key words were combined, such as "SARS-Cov-2", "COVID 19", "2019-nCoV", "coronavirus 2019", "ophthalmology", "eye disease", "conjunctivitis", "ocular surface", "glaucoma", "orbit", "tears", "uveitis", "retina", "vasculitis", "ophthalmoparesis", "palsy", "optic nerve",

"anterior ischemic optic neuropathy" (AION), "retinal venous occlusion" (RVO), "retinal artery occlusion" (RAO).

#### Direct effects of COVID

In our study, about 53.2% of candidates have seen cases with ocular presentation suspected to be due to COVID-19 direct effect.

#### Anterior segment Conjunctivitis

In our work, about 73.2% have seen cases of follicular conjunctivitis that could be linked to COVID, of which 70.5% said it was the usual presentation and 96.6% said it was treated.

The first reported case of SARS-CoV-2 conjunctivitis affected a member of the Chinese panel for pneumonia in Wuhan Fever Clinic who wasn't wearing eye protection, which highlights the potential conjunctival transmission route [11].

ACE-2 receptor and cell surface protease enzyme (TMPRSS2) is responsible for binding with the virus and allows its access into host cell [12].

COVID-19 conjunctivitis clinical presentation resembles any viral conjunctivitis; follicular reaction, conjunctival hyperemia, watery discharge, and lymph node enlargement [13].

### Viral keratitis

In this work, about 19.3% have seen cases of viral keratitis that could be linked to COVID, of which 57.1% said it was the usual presentation and 100% said it was treated.

### Posterior segment

#### Retinal vascular occlusion

In our study, about 43.9% have seen cases of retinal vascular occlusions (mainly as RVO) that could be linked to COVID, of which 72.2% said it was the usual presentation and 74.3% said it was treated.

#### Retinal ischemia

We found out that about 15.7% have seen cases of retinal ischemia (mainly as hemorrhages) that could be linked to COVID, of which 69.2% said it was the usual presentation and 67.7% said it was treated.

An OCT study by Marinho, *et al.* (2020) on 12 patients who tested positive for SARS-CoV-2 infection showed hyper-reflective lesions at ganglion cell and inner plexiform layers, which was more prominent at papillomacular bundle. Results of OCT angiography and ganglion cell complex analysis appeared normal. Four patients (33%) presented subtle cotton-wool spots and microhemorrhages. No signs of intraocular inflammation or visual acuity alteration were detected [14].

Zhang, *et al.* suggest that the main factor for microcirculatory damage in COVID-19 is complement-mediated thrombotic microangiopathy (TMA) [15]. Complement system activation has been previously described in ocular vascular damage, with rare cases of atypical hemolytic uremic syndrome, leading to retinal artery and vein occlusions [16]. Also, high serum levels of C3 complement factor have also been correlated to increased risk of developing diabetic retinopathy, nephropathy, and neuropathy [17]. Immunohistochemical analysis on human eye has shown that the ciliary body, choroid, retina, and RPE express significant levels of ACE receptors [18]. Since COVID-19 is able to target vascular pericytes expressing ACE-2, it could lead to complement-mediated endothelial cell dysfunction, microvascular damage, and ocular circulation involvement [19].

### Kawasaki disease (KD)

We reported that about 6.1% have seen cases of Kawasaki disease that could be linked to COVID, of which 100% said it was the usual presentation and 100% said it was treated.

KD is an acute and usually self-limiting vasculitis of the medium caliber vessels, which mostly affects young children, and it is characterized by fever, oropharyngeal and extremity changes, polymorphous rash, and unilateral cervical lymphadenopathy.

The first described case of KD with concurrent COVID-19 infection was in a 6-month-year-old female. The baby, tested positive for COVID-19, had conjunctivitis, prominent tongue papilla, blanching, polymorphous, maculopapular rash, and swelling of the hands and lower extremities [20].

### Uveitis

We have noticed that about 33.7% have seen cases of uveitis (mainly as anterior uveitis) that could be linked to COVID, of which 65.5% said it was the usual presentation and 70.4% said it was treated.

### Neuro-ophthalmology

In our work, about 34.5% have seen cases of ocular neurological disorders that could be linked to COVID, of which 64.3% said it was the usual presentation and 81.5% said it was treated.

Cases with COVID-19 after diplopia, ophthalmoparesis and abnormal cranial nerve MRI findings have been reported. Oculomotor nerve palsy could be triggered by direct virus invasion, inflammatory mediators or secondary to neurological complications such as acute disseminated encephalomyelitis, Guillain-Barré Syndrome (GBS), or transverse myelitis [21,22].

Three articles described 5 cases with COVID-19 and ocular motor palsies. The most repeated pattern was VI cranial nerve paralysis (CP), followed by incomplete involvement of III CP. In 4 of the 5 patients, the picture was accompanied by ataxia and hyporeflexia, and they were diagnosed with Miller-Fisher syndrome (ophthalmological variant of GBS) [23-25].

There is also the possibility of increased risk of ischemic optic neuropathy due to the prone position during hospital admission and ICU stay of patients [26].

### Secondary glaucoma

We noticed that about 1.2% has seen cases of secondary glaucoma that could be linked to COVID, of which 100% said it was the usual presentation and 100% said it has deteriorated.

### Surgical

In our study, about 50% have operated on post-COVID cases with the appearance of various postoperative complications, of

which 60% said they were the usual presentation and 100% said they were treated.

### External eye disease and orbit

We reported that about 20.5% have seen cases of external eye and orbital disease (mainly as orbital cellulitis) that could be linked to COVID, of which 52.9% said it was the usual presentation and 52.9% said it was treated.

### Other ocular presentations

Furthermore about 20.2% have seen cases without reaching a final diagnosis that could be linked to COVID.

### Indirect effect of COVID

#### Due to absence of medical care

Due to the global coronavirus outbreak, many countries worldwide have adopted isolation policies. Physical inactivity and sedentary behavior may be deleterious for patients. This can lead to impaired insulin sensitivity and slower lipid metabolism, increasing visceral fat and decreasing lean body mass and worsening cardiovascular performances. This may lead to new onset or worsening of diabetes mellitus, leading to increased referrals to ophthalmologists for eye complications [27].

We realized that around 60.4% have noticed deterioration of chronic cases because of lack of follow up visits and around 59.1% have noticed advanced cases on initial presentation due to late presentation.

#### Due to ICU admission

#### Ocular surface disorders

It is the most common ocular complication in ICU (60%) and can range from mild conjunctival irritation to severe infectious keratitis. These patients have several risk factors for surface disorders, some of which related to the treatments, while others to the ICU environment itself, e.g. exposure to many potentially multi-resistant bacteria [28].

In our study, around 7.1% have seen cases of ocular surface disorders that could be related to ICU admission due to COVID.

### Rare complications

#### Valsalva retinopathy

It is usually associated with sudden increase in intrathoracic or intra-abdominal pressure. It has been reported that valsalva

retinopathy can also occur due to intubation or high positive end-expiratory pressure [29].

Around 6.6% of our candidates have seen cases of valsalva retinopathy that could be related to ICU admission due to COVID.

#### Acute angle closure glaucoma

With underlying risk factors, an acute angle closure can be triggered by prone position, and also many local and systemic drugs, such as anticholinergics, sympathomimetics, and others (sulfonamides derivatives and topiramate) [30].

Around 11.8% of our enrolled Ophthalmologists have seen cases of acute angle closure glaucoma that could be related to ICU admission due to COVID.

#### Horner syndrome

It has been rarely reported as a complication of central venous catheterization [31].

Around 3.2% in our study have seen cases of Horner syndrome that could be related to ICU admission due to COVID.

#### Endogenous endophthalmitis

It should be considered among the possible rare complications of sepsis related to COVID-19. No reports of this condition have been described in the literature [32].

Around 25.3% of our candidates have seen cases of endogenous endophthalmitis that could be related to ICU admission due to COVID.

#### Manifestations due to anti-COVID drugs

No pharmacological therapies have been approved for treatment of COVID-19. However, several drugs are currently under investigation; chloroquine (CQ) and its derivative hydroxychloroquine (HCQ), antiviral drugs, and immunomodulators [33].

#### Antimalarial

The clinical picture of HCQ and CQ ocular toxicity includes whorl-like corneal intraepithelial deposits, posterior subcapsular lens opacity, ciliary body dysfunction, and maculopathy characterized by ring of parafoveal RPE depigmentation initially sparing the fovea. Advanced cases show widespread photoreceptor loss and RPE atrophy with foveal involvement. HCQ and CQ maculopathy is not reversible and can progress even after drug cessation [34].

About 27.5% in our study have seen cases that have taken anti-malarial drugs but 56.5% of them have seen no ocular toxicity.

### Anti-viral

Authors reported adverse effects of ritonavir on human retina. Roe, *et al.* described bilateral macular retinal pigment epitheliopathy with parafoveal telangiectasias and intraretinal crystal deposits in 3 HIV positive patients on long-term ritonavir [35].

About 23.1% of our candidates have seen cases that have taken anti-viral drugs with various ocular toxicities.

### Immune-modulatory

Interferon-associated retinopathy presents with cotton-wool spots, retinal hemorrhages, and retinal microvascular irregularities; around optic nerve head and in posterior pole [36]. Interleukin-1 inhibitors (e.g., anakinra) and interleukin-6 inhibitors (e.g. sarilumab, siltuximab and tocilizumab): Studies found link between high dose of anakinra and nystagmus. A case report described retinal multifocal cotton-wool spots and hemorrhages, bilateral papilledema, HTLV-1 uveitis, viral conjunctivitis, and ophthalmic herpes zoster infection, with tocilizumab [37,38].

In this work, about 8.6% have seen cases that have taken immune-modulatory drugs with various ocular toxicities.

### Steroids

We have found out that about 45.4% have seen cases that have taken anti-viral drugs with various ocular complications.

### Conclusion

A lot of Ophthalmologists of different subspecialties have been examining a lot of patients infected with COVID-19. Some of these patients have presented with different ocular manifestations that happened to be synchronous with their COVID-19 infection. When these patients don't have other predisposing factors for their ocular manifestations, leaving them with only the COVID as a predisposing factor, this might highly raise the suspicion that it could be linked to COVID somehow. However, this is yet too early to prove this link and it needs further investigations to confirm this correlation.

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The authors report no competing interest. The authors alone are responsible for the content and writing of the paper.

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