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Sight-threatening ocular manifestations in the post-coronavirus pandemic era

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ABSTRACT

Background: Coronavirus disease (COVID-19) can be associated with post-recovery sight-threatening complications like optic neuritis, retinal vascular occlusions, endophthalmitis, and panophthalmitis. This study was conducted to explore the various sight-threatening post-COVID-19 ophthalmic manifestations.

Methods: This retrospective observational case series included seven patients who were diagnosed with sight-threatening manifestations post-COVID-19. They underwent detailed ophthalmic and systemic evaluation, including laboratory investigations for systemic hypercoagulable and inflammatory markers.

Results: Seven Indian patients (6 males:1 female, age range 37–66 years) presented to us with severe eye pain, acute loss of vision, redness, and watering after being diagnosed and treated for COVID-19 infection. The time from COVID-19 diagnosis to ocular sampling was 14–60 days (median 27), that of ocular symptoms to ocular sampling 1–50 days (median 4). Visual acuity ranged from no perception of light to 20/36. Three patients were pre-existing diabetics, two developed diabetes during their COVID-19 treatment. Diagnosis included one case of central retinal artery occlusion, one case of vitreous hemorrhage with retinal vasculitis, two cases of presumed bacterial endogenous endophthalmitis, one case of presumed fungal endophthalmitis, and two cases of panophthalmitis, one of them bilateral. Patients with infective intraocular inflammation were subjected to blood, ocular specimens, and urine cultures, which yielded growth in some patients. PCR of ocular specimens were positive for panfungal and/or eubacterial genome. Treatment included oral and systemic antimicrobial therapy with or without systemic steroids, with intravitreal antibiotics and/or steroids in selected cases. Final visual outcome ranged from no perception of light to 20/20.

Conclusions: Patients in this group had both vascular occlusions and infection as a cause of sight-threatening visual loss. Functional visual outcome may not be achieved in this diverse group of patients. Multi-specialty management was required in most of the cases. Larger prospective studies with controls are required to clarify pathogenesis, optimal screening, and management strategies for post-COVID-19 ocular complications.

KEYWORDS

coronavirus disease 2019, COVID-19, central retinal artery occlusion, vasculitides, infectious endophthalmitides, panophthalmitides

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INTRODUCTION

Coronavirus disease (COVID-19) has been associated with ophthalmic manifestations that can occur during or following the infection [1–17]. These include conjunctivitis, anterior uveitis, reactivation of quiescent uveitis, episcleritis, scleritis, posterior segment manifestations like cotton wool spots, retinal vascular occlusions, panuveitis, retinitis, papillophlebitis, vitritis, central serous chorioretinopathy, acute retinal necrosis, ophthalmic artery occlusion, and Adie syndrome [1–17].

Our aim was to study COVID-19 patients with sight-threatening ophthalmic manifestations.

METHODS

This retrospective consecutive case series recruited patients who presented with sight-threatening manifestations to our tertiary eye care hospital at Narayana Nethralaya and Post-Graduate Institute of Ophthalmology, Narayana Nethralaya, Bangalore, India. The Ethics Committee of our hospital approved the study (approval number C/2020/09/09). The study was conducted under the tenets of the 1964 Declaration of Helsinki and its later amendments. Patients' written informed consent for participation and publication of the study data was obtained. All patients gave consent for their images to be published.

Inclusion criteria were positive reverse transcriptase polymerase chain reaction (RT-PCR) from nasopharynx for Severe Acute Respiratory Syndrome Corona Virus (SARS- CoV-2) infection or a recent history of COVID-19 infection with presence of SARS- CoV-2 receptor-binding domain (RBD) IgM/IgG total antibodies. Demographic data, clinical examination data, and laboratory tests done for systemic inflammatory status and infective workup were recorded for analysis in all patients. This is a descriptive study with no control group of COVID-19 patients without ophthalmic manifestations.

All patients had a complete ocular examination, including assessment of best corrected visual acuity (Snellen chart, auto chart projector CP 670; Nidek Co., Ltd., Gamagori, Japan), slit lamp examination (Topcon Corporation, Tokyo, Japan) for anterior segment inflammation (SUN grading of cells and flare) [18], and intraocular pressure (IOP) (Goldmann applanation tonometer, Haag Streit, Koniz, Switzerland) and vitreous inflammation [19] documented. Dilated fundus exam with scleral indentation using indirect ophthalmoscopy (Keeler Instruments Inc., PA, USA) and a + 20 D ancillary lens (VOLK Optical Inc., Mentor, OH, USA) was done in patients where fundus evaluation was possible. Site and severity of inflammation were documented.

Ocular imaging for selected patients included anterior segment photographs with Haag Strait BX 900 (Haag-Streit AG, Koniz, Switzerland) imaging system (when there was anterior uveitis) and posterior segment imaging; fundus photographs with both Topcon fundus camera (Topcon Corp., Tokyo, Japan) and ultra-widefield fundus camera with Optos California (Optos Inc., Dunfermline, United Kingdom); spectral domain optical coherence tomography (SD-OCT) (Spectralis software, Heidelberg Engineering, Inc., Dossenheim, Germany); fundus fluorescein angiography (FFA) (Heidelberg Retinal Angiography, Heidelberg Engineering, Inc., Dossenheim, Germany) with Spectralis; and optical coherence tomography angiography (OCTA) (AngioVue-OptoVue, Inc., Fremont, CA, USA) with Optovue, Spectralis, and ultrasound B-scan Quantel Medical (Quantel Medical Inc., Cournon-d'Auvergne, France).

Demographic details, clinical characteristics, systemic and ocular findings, laboratory tests, imaging features, microbiological results, management strategies, and visual outcomes of all patients were retrospectively collected from medical records. Descriptive data were compiled and summarized in tabular form. Continuous variables are presented as observed values, medians, or means, and categorical variables are reported as frequencies and clinical descriptions. No formal statistical comparisons were performed due to the descriptive nature of this case series.

RESULTS

Seven Asian Indian patients (6 males:1 female) presented with severe eye pain, acute loss of vision, redness, and watering many days after being diagnosed and treated for COVID-19 infection. The time from COVID-19 diagnosis to ocular sampling was 14–60 days (median 27), yet the time between ocular symptoms to ocular sampling was 1–50 days (median 4). Age distribution range was 37–66 years (median 55).

Visual acuity ranged from no perception of light to 20/36. Table 1 shows the demographic and clinical diagnosis of the patients. Table 2A shows the systemic hypercoagulable and inflammatory markers done for our series. A discussion follows of two representative challenging cases that we encountered in this study.

Patient 2: A 63-year-old Asian Indian male presented with bilateral blurring of vision, severe pain, acute loss of vision, redness, and watering. He had been treated for COVID-related pneumonia at a local hospital, with chest CT findings classified as the COVID-19 Reporting and Data System (CO-RADS) category 6 and a CT severity score of 6/25, indicating mild pulmonary involvement [22, 23]. He had reticular skin rashes on limbs, nose, and body, with gangrenous changes in the nose, index finger, ankle, and foot. (Figure 1A–E). Tests for systemic vasculitis and infective profile were negative during hospitalization.

He was discharged with subcutaneous enoxaparin 40 mg once daily for the next two weeks [24]. Four days after discharge he developed the ocular symptoms. Best corrected visual acuity (BCVA) in both eyes was counting fingers close to the face; IOPs were 30 and 9 mmHg in the right and left eye, respectively. Anterior segment evaluation of the right eye showed conjunctival congestion and blood-stained cornea, with epithelial and stromal edema with hyphema covering the entire iris (Figure 2A). The pupil, lens, and anterior vitreous were not visualized. The left eye showed pigments on the corneal endothelium with anterior chamber showing flare+, cells+, and pigments, and was pseudophakic. The anterior vitreous showed few red blood cells and pigments.

Table 1. Demographic and clinical characteristics of the study participants

Patient	Age/Sex	Diagnosis	Presenting BCVA	Systemic status	COVID-19 diagnosis (d)	Onset of ocular symptoms (d)	Time to present (d)
Patient 1	66/M	CRAO OD, Panuveitis OU, Optic neuritis OU	CF 2 meters OD 20/36 OS	DM	14	7	7
Patient 2	63/M	Retinal vasculitis, vitreous haemorrhage, secondary glaucoma with systemic vasculitis OU	CF close to face OU	HTN	27	3	3
Patient 3	47/M	Endophthalmitis OD	PL OD	None	25	13	4
Patient 4	37/M	Endophthalmitis OS	HM OS	DM	60	50	50
Patient 5	65/F	Endophthalmitis OD	CF 2 meters OD	Advanced gastric carcinoma	Asymptomatic infection	2	2
Patient 6	56/M	Panophthalmitis OS	PL OS	None	45	19	19
Patient 7	55/M	Panophthalmitis OU	NPL OD PL with inability to identify projection of light rays OS	NHL (rectum), in remission for 8 years; DM	30	2	1

Abbreviations: BCVA, best-corrected visual acuity; COVID-19, coronavirus disease 2019; d, days; M, male; F, female; CRAO, central retinal artery occlusion; OD, right eye; OS, left eye; OU, both eyes; CF, counting fingers; DM, diabetes mellitus; HTN, hypertension; PL, perception of light; HM, hand movements; NPL, no perception of light; NHL, non-Hodgkin's lymphoma. Note: COVID-19 diagnosis in Patient 5 was based on serological evidence (positive COVID-19 IgM/IgG antibodies) in the absence of symptoms.

Table 2A. Blood tests of the patients showing systemic inflammatory and hypercoagulable markers and the corresponding normal values

Systemic markers (unit)	Normal biological references	Mean
D-Dimer levels (ng/mL)	**<250**	**725.14**
Prothrombin time (sec)	**11–13.4**	12.60
Partial thromboplastin time (sec)	**23-30**	27.15
Serum Ferritin (ng/mL)	**M 22–322, F 11-307**	**370.52**
Procalcitonin (ng/mL)	**<0.05**	**5.21**
Lactate dehydrogenase (U/L)	**120–246**	**413.60**
ESR (mm/hr)	**<20**	**73.00**
CRP (mg/L)	**<3**	**30.46**
Serum Vitamin D (ng/mL)	**30–50**	37.60
Fibrinogen (mg/dL)	**200–400**	381.33
Neutrophil /Lymphocyte (ratio)	**0.78–3.53 [20, 21]**	**4.79**

Abbreviations: ESR, erythrocyte sedimentation rate; CRP, C- reactive protein; ng/mL, nanograms per millilitre; U/L, units per liter; mm/hr, millimeters per hour; mg/L, milligrams per liter; mg/dL, milligrams per deciliter. Notes: Patient mean values exceeding normal biological reference ranges are shown in bold; Serum ferritin reference ranges are sex-specific (M = males; F = females).

Figure 1. Clinical manifestations in patient 2 (63-year-old Asian Indian male) during coronavirus disease 2019 (COVID-19). (A) Nasal gangrene with associated lip swelling. (B) Gangrenous changes involving the fingertips. (C) Gangrene of the index finger with a reticular rash over the dorsal aspect, suggestive of vasculitis. (D) Right ankle and foot showing petechial hemorrhagic rash with associated swelling. (E) Left foot demonstrating gangrene (black discoloration) involving the heel and dorsum. These findings are consistent with systemic vasculitic and thrombotic manifestations associated with COVID-19.
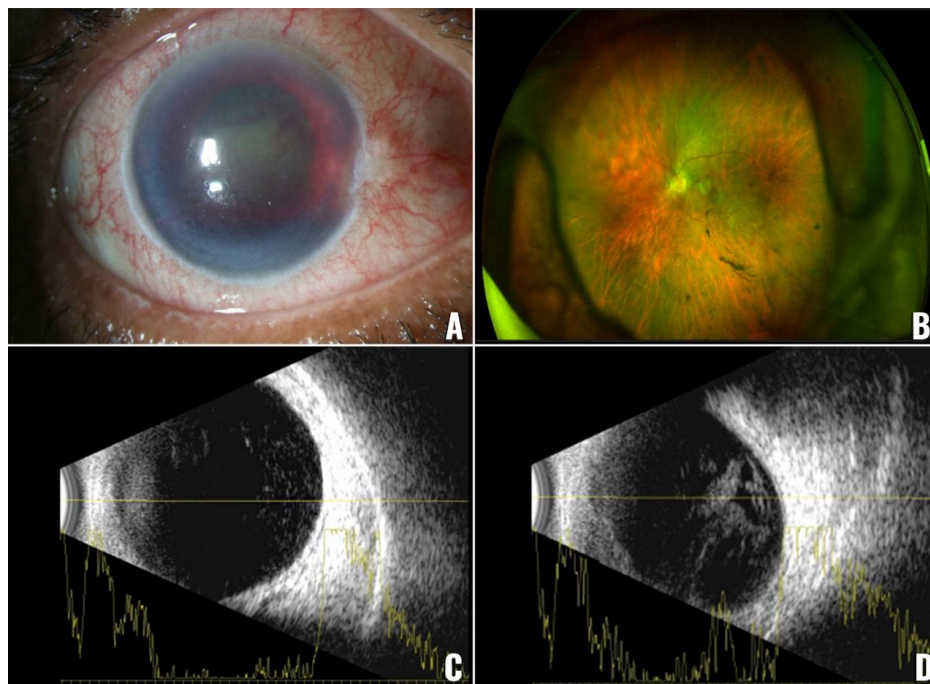

Figure 2. Ocular findings in patient 2 (63-year-old Asian Indian male) at presentation. (A) Diffuse slit-lamp photograph of the right eye demonstrating hyphema. (B) Ultra-widefield fundus image of the left eye using Optos™ (Optos Carfornia®, Optos Inc., Dunfermline, United Kingdom), showing a shadow of the intraocular lens with multiple vitreous opacities consistent with vitreous hemorrhage, along with a pale, swollen optic disc and intraretinal hemorrhages. (C) Ultrasonography (B-scan; Quantel medical™, Quantel Medical Inc., Cournon-d'Auvergne, France) of the right eye showing dense posterior vitreous opacities. (D) Ultrasonography of the left eye showing dense mid and posterior vitreous opacities with membranous echoes.

Table 2B. Laboratory tests of Patients 2 and 7

Parameter	Patient 2	Patient 7
Coagulation and inflammatory markers		
D-dimer	**1974.7 ng/mL FEU (<500)**	**401.84 ng/mL FEU (<500)**
Fibrinogen	**548 mg/dL (180–350)**	–
ESR	**120 mm/hr (0–10)**	**94 mm/1st hour (<20)**
CRP	**4.3 mg/L (<0.6)**	**73 mg/L (<5)**
Ferritin	**984.4 ng/mL (20–250)**	**609.8 ng/mL (22–435)**
Lactate dehydrogenase	188 U/L (120–246)	**494.28 U/L** at 37°C (125–220)
Hematological parameters		
Hemoglobin	**9.1 g/dL (13.5–18)**	–
RBC count	**3.01 ×10⁶/µL (4.2–6.5)**	–
PCV	**27.1% (39–54)**	–
Neutrophils	**81.7% (40–75)**	**85.1% (40–75)**
Lymphocytes	**12.2% (20–45)**	**8.1% (20–45)**
Neutrophil–lymphocyte ratio	**6.69 (0.78–3.53)**	**10.50 (0.78–3.53)**
COVID-19 related investigations		
COVID-19 serology	COVID IgM/IgG antibodies positive	–
Anti–SARS-CoV-2 RBD IgM/IgG	**>10 (cut-off <1)**	–
Anti–SARS-CoV-2 spike protein S1/S2 IgG	**74.9 AU/mL (<12)**	–
Liver function tests		
SGOT (AST)	–	**63.0 U/L (≤35)**
SGPT (ALT)	–	29.5 U/L (<45)
Renal function and electrolytes		
Serum creatinine	0.7 mg/dL (0.6–1.3)	**0.58 mg/dL (0.7–1.3)**
Blood urea	–	**14.8 mg/dL (18–55)**
Blood urea nitrogen	–	8 mg/dL (6–20)
Sodium	–	**128 mmol/L (136–145)**
Potassium	–	3.67 mmol/L (3.50–5.10)
Uric acid	–	4.4 mg/dL (3.5–7.2)
Serum calcium	–	9.1 mg/dL (8.6–10.2)
Metabolic parameters		
Random blood sugar	–	**422 mg/dL (≤140)**
PPBS	–	**250 mg/dL (90–140)**
HbA1c	–	**12.1% (≤6.0)**
Cardiac markers		
Troponin T	–	**131 pg/mL (<14)**
NT-proBNP	–	**163.10 pg/mL (<125.00)**
Coagulation profile		
Prothrombin time	13.2 sec (12.4–16.2)	**12.4 sec (9.8–12.1)**
APTT	34.3 sec (22.6–34.8)	27.5 sec (22.7–31.8)
Bleeding time	–	2.00 min (1–3)
Clotting time	–	4.00 min (2–7)
Serum Vitamin D	**60.5 ng/mL (30–50)**	–
Infectious disease screening (Patient 7)		
Hepatitis B surface antigen	–	Non-reactive
Anti–Hepatitis C virus	–	Non-reactive
HIV 1 & 2	–	Non-reactive
Treponema pallidum hemagglutination	–	Negative

Abbreviations: ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; NLR, neutrophil–lymphocyte ratio; RBC, red blood cell; PCV, packed cell volume; COVID-19, coronavirus disease 2019; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; PPBS, postprandial blood sugar; HbA1c, glycated hemoglobin; NT-proBNP, N-terminal pro–B-type natriuretic peptide; APTT, Activated partial thromboplastin time; HIV 1 & 2, Human immunodeficiency virus 1&2; ng/mL FEU, nanograms per milliliter (fibrinogen equivalent units); mg/dL, milligrams per deciliter; mm/hr, millimeters per hour; mg/L, milligrams per liter; U/L, units per liter; g/dL, grams per deciliter; ×10⁶/µL, million cells per microliter; %, percentage; AU/mL, arbitrary units per milliliter; sec, seconds; min, minutes; mmol/L, millimoles per liter; pg/mL, picograms per milliliter. **Notes:** Values outside the reference range are shown in bold; Reference ranges are provided in parentheses; D-dimer values are expressed in fibrinogen equivalent units (FEU); COVID-19 serology indicates anti–SARS-CoV-2 antibody testing.

Fundus evaluation was not possible in the right eye, and the left eye showed swollen pale optic disc (Figure 2B). Ultrasound B-scan of both eyes (Figures 2C and 2D) showed vitreous debris in the mid and posterior vitreous with low-to-medium spikes on associated vector A-scan. The left eye had coalesced vitreous membrane with presence of after movement (Figure 2D). The retina was attached in both eyes. In summary, we have a patient with unilateral hyphema, secondary glaucoma, bilateral vitreous hemorrhage, and systemic vasculitis. Table 2B shows tests done for the patient.

The patient was started on topical steroids and antibiotics (moxifloxacin 0.5% w/v + dexamethasone 0.1% w/v 4 times/day, homatropine 2% twice daily, a combination of brimonidine 0.2% + timolol 0.5% twice daily, and brinzolamide 1% thrice daily for the right eye. Moxifloxacin 0.5% w/v + dexamethasone 0.1% w/v 4 times/day were started for the left eye. Subcutaneous enoxaparin [24] was stopped in consultation with his primary physician.

The rheumatologist initiated the patient on intravenous solumedrol [25] 500 mg in 250 mL normal saline for 3 days, followed by oral prednisolone (Wysolone®) 30 mg in tapering doses over the next month, pantaprozole 40 mg, oral apixaban [26] 2.5 mg twice daily, and oral azathioprine 25 mg twice daily for 2 weeks, then increased the dose to 75 mg.

The right eye was subjected to anterior chamber washout; the sample was also sent for reverse transcriptase polymerase chain reaction (RT-PCR) for SARS-CoV-2, which was negative. Intravitreal anti-vascular endothelial growth factor bevacizumab 1.25mg/0.05mL was administered to the right eye.

One month later both eyes were subjected to panretinal photocoagulation. The right eye had persistent anterior chamber inflammation and was also a steroid responder with high IOP (26–30 mmHg). The systemic vasculitis was not improving and the rheumatologist stopped azathioprine; the patient was administered intravenous cyclophosphamide 500 mg in 250 mL normal saline over 2h for a total of 6 doses in biweekly intervals. Due to persistently high IOP he underwent trabeculectomy with mitomycin C 0.4mg/mL under conjunctiva for a minute and then washed it off. He was on oral steroids during and after surgery for about a month. A month later he had good functioning bleb with IOP 8 mmHg in the right eye.

On his final follow-up one year later he had auto-amputation of the last carpal bone of his index finger (Figure 3A) and resolution of the ankle and foot gangrene (Figure 3B), BCVA 20/25, and IOP 12 mmHg in both eyes. The right eye (Figure 3C) had resolved hyphema, a quiet anterior chamber, nuclear sclerosis 2–3, and good functioning bleb; gonioscopy had 270° peripheral anterior synechiae with no new vessels in the angle. Fundus evaluation of the right eye (Figure 3D) showed pale optic disc with cup disc ratio 0.8, few dot hemorrhages, and laser scars. The left eye had flare+, no cells, few pigments, pseudophakia, cup disc ratio 0.6 with attenuated retinal vessels, intraretinal hemorrhages, and laser scars (Figure 3E).
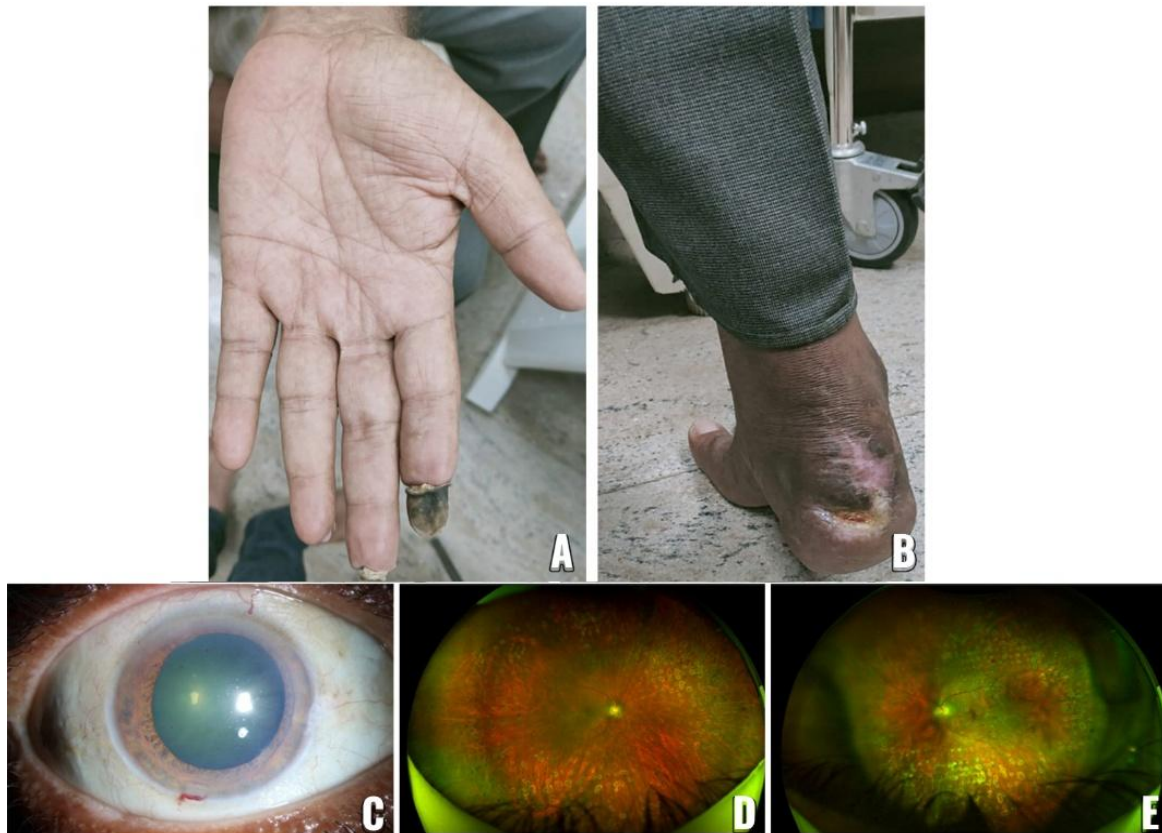

Figure 3. Clinical and ocular findings in patient 2 (63-year-old Asian Indian male) at final follow-up. (A) Palmar view of the hand showing auto-amputation of the index finger. (B) Right ankle and heel demonstrating resolution of gangrene with no residual petechial hemorrhages. (C) Diffuse slit-lamp photograph of the right eye showing resolution of hyphema. (D) Ultra-widefield fundus image of the right eye (Optos™, Optos Carfornia®, Optos Inc., Dunfermline, United Kingdom) showing a pale optic disc, scattered laser photocoagulation marks, and intraretinal hemorrhages. (E) Ultra-widefield fundus image of the left eye (Optos™) showing a pale optic disc with intraretinal hemorrhages and scattered laser photocoagulation marks.

Patient 7: A 55-year-old Asian Indian male presented with bilateral blurring of vision, severe pain, acute loss of vision, redness, and watering lasting two days. He had been diagnosed with COVID-19 a few weeks back and subsequently developed abdominal pain; he was treated symptomatically at a local hospital. At the hospital he was noted to have leucopenia with thrombocytopenia and normal renal function tests; nasal swab for SARS-Cov-2 was positive; and levels of CRP (73 mg/L, ref. < 5), lactate dehydrogenase (494.28 U/L at 37°C, ref 125–220), and serum ferritin (609.8 ng/mL, ref 22–435) were raised. He was treated with intravenous antibiotics (cefepime 1000 mg + tazobactam 125 mg); methyl prednisolone 500mg; subcutaneous enoxaparin 40 mg; remdesivir 100 mg/20 mL; remdesivir injection 100 mg two doses on day 1 and single daily doses on days 2-5; and oral ivermectin 12 mg once daily for 7 days. At the time of discharge, the patient was afebrile for at least 3 days and oxygen saturation stayed above 95% without oxygen support.

Medication at discharge was subcutaneous enoxaparin [24] 40 mg; oral prednisolone 32 mg in tapering doses (over a month); a combination of glimepiride 2mg + metformin 500 mg + voglibose 0.2 mg; cefpodoxime proxetil 200 mg for 5 days; multivitamin supplementation including zinc, vitamin C 500 mg twice daily for 10 days; and rivaroxaban 20 mg for 3 weeks.

He had type-2 diabetes mellitus with a history of non-Hodgkin lymphoma of the rectum eight years earlier, and was on remission without any symptoms. He had bilateral symptoms and signs. His visual acuity in the right eye was no perception of light, and in the left eye perception of light with inability to identify projection of light rays. On ocular evaluation of both eyes, he had matting of lashes with severe lid edema, proptosis with restriction of eyeball movements, diffuse conjunctival congestion, chemosis with central corneal haze, anterior chamber flare 4+, cells 3+, fixed dilated pupil with an inflammatory membrane (Figure 4A), and no view of the fundus. In the left eye he also had corneal epithelial defect with a 3-mm stromal infiltrate with satellite lesions (Figure 4B). He was diagnosed with bilateral panophthalmitis.

Ultrasound B scans of both eyes showed vitreous debris and membrane, retinal detachment (Figure 4C, D), increased retinochoroidal thickness, and sub-Tenon's fluid. His treatment managing team subjected the patient to systemic tests, which are shown in Tables 2B and Tables 2C. The left eye developed corneal abscess and the material was sent for stain and culture sensitivity. Subsequently both eyes developed scleral abscess (Figure 5A, B); the right eye (Figure 5C) started resolving after systemic antibiotics while the left eye developed scleral melt (Figure 5D). Oncological review showed no signs of relapse of his non-Hodgkin lymphoma.
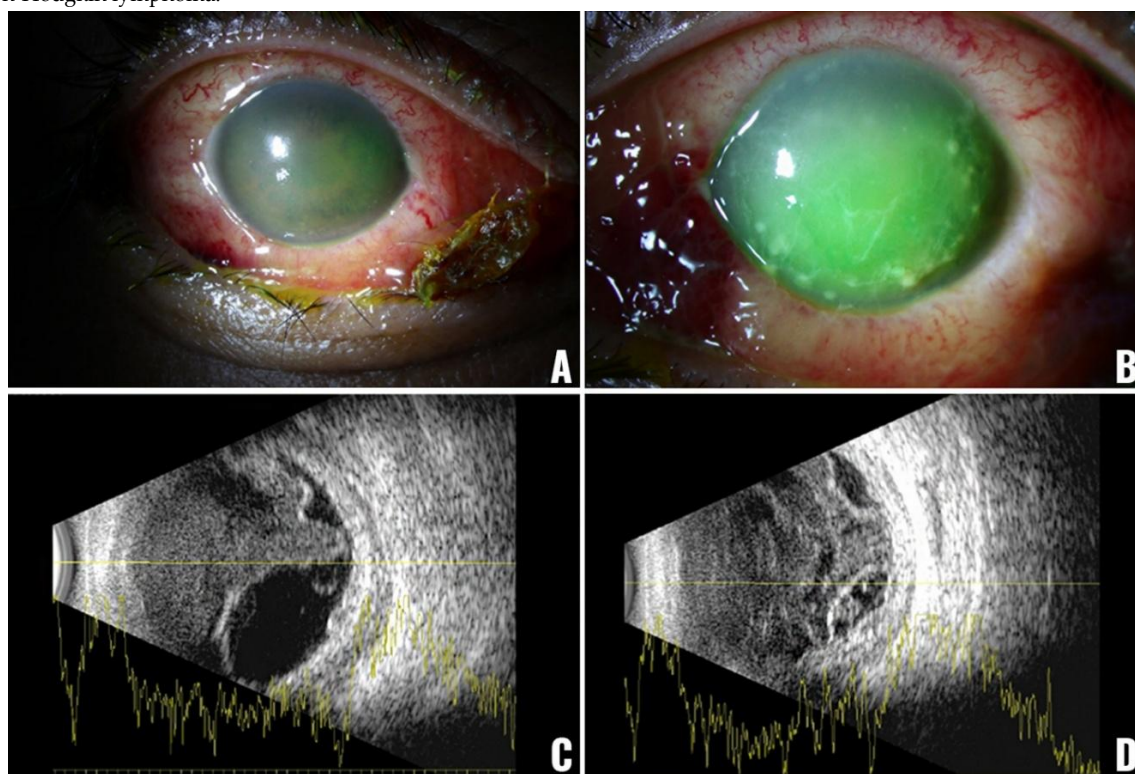

Figure 4. Anterior and posterior segment findings at presentation in patient 7 (55-year-old Asian Indian male). Panels (A) and (C) correspond to the right eye; panels (B) and (D) correspond to the left eye. (A) Diffuse slit-lamp photograph of the right eye showing marked conjunctival congestion and chemosis with central corneal haze, a fixed dilated pupil, and an inflammatory membrane. (B) Diffuse slit-lamp photograph of the left eye showing diffuse conjunctival congestion and chemosis with a corneal epithelial defect and a 3-mm stromal infiltrate with satellite lesions. (C) Ultrasonography (B-scan; Quantel medical™, Quantel Medical Inc., Cournon-d'Auvergne, France) of the right eye demonstrating dense vitreous debris with membranous echoes, retinal detachment, increased retinochoroidal thickness, and sub-Tenon's fluid. (D) Ultrasonography (B-scan) of the left eye demonstrating vitreous debris with membranes, retinal detachment, increased retinochoroidal thickness, and sub-Tenon's fluid.

Table 2C. Imaging features of Patient 7

Imaging modality	Findings
MRI of the brain (non-contrast)	• Bilateral thickening of the ethmoid sinuses and left maxillary sinus. • Flattening of the pituitary gland along the floor of the sella. • Lentiform-shaped T2 hyperintense lesions with blooming on gradient echo sequences along the medial and lateral walls of the right orbit and along the medial wall of the left orbit, with altered signal intensity in the vitreous of the posterior segments of both globes. • Mild prominence of the subarachnoid space around the optic nerves in the intracanalicular segments.
CT of the lungs	• Multiple areas of subsegmental and band atelectasis involving the posterior apical and basal segments of both lower lobes and the posterior aspects of both upper lobes. • Scattered fibrotic lesions and band atelectasis in the apical segment of the right upper lobe. • Right middle lobe bulla measuring 1.2 cm in diameter. • Small subpleural ground-glass opacities in the anterior segment of the right upper lobe, subpleural region of the left lower lobe, lateral segment of the right middle lobe, and inferior lingular segment.
Two-dimensional echocardiography	• Normal cardiac chambers with no evidence of intracardiac thrombus, mass, or vegetation.

Abbreviations: MRI, magnetic resonance imaging; CT, computed tomography. Notes: MRI was performed without contrast; CT findings are described based on axial imaging; All findings are reported as per radiology interpretation.
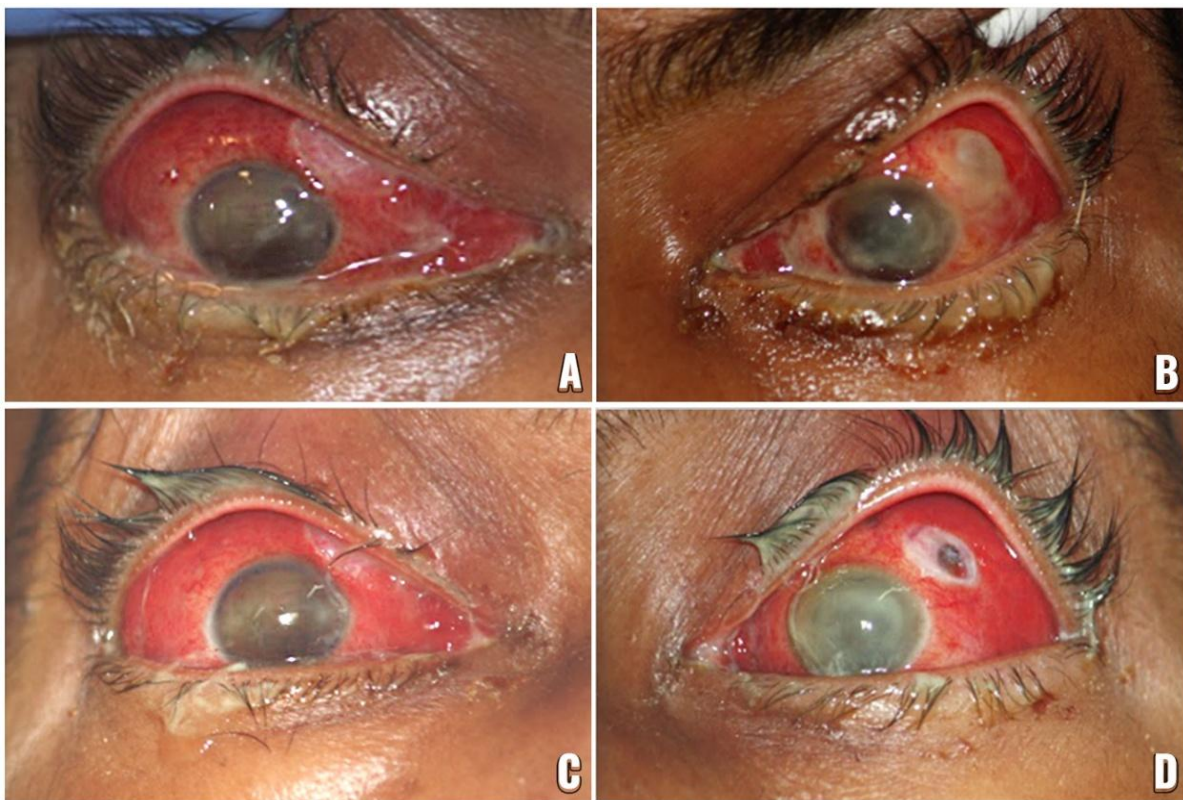

Figure 5. Scleral abscesses and clinical course in patient 7 (55-year-old Asian Indian male). Panels (A) and (C) correspond to the right eye; panels (B) and (D) correspond to the left eye. (A) Scleral abscess in the right eye at presentation. (B) Scleral abscess in the left eye at presentation. (C) Right eye showing signs of resolution of the scleral abscess following systemic antibiotic therapy. (D) Left eye showing progression of the scleral abscess to scleral melt, necessitating subsequent evisceration.

Management

Ocular

Topical steroids (prednisolone acetate 1%, 6 times/day in tapering doses), topical antibiotics (moxifloxacin 0.5%, 6 times/day), topicalcycloplegic (homatropine 2%), and intravitreal injections of antibiotics (vancomycin 1mg/0.1mL + amikacin 0.125mg/0.1mL, 7 doses in the right eye and 4 in the left eye) and voriconazole (0.01mg/0.1mL, 4 doses in the right eye and 3 in the left eye).

Systemic

- Teicoplanin 400 mg twice daily for 14 days
- Clindamycin 300 mg twice daily for 1 week
- Parenteral meropenem 1 gr every 8h for 14 days
- Insulin isophane/NPH 70% + human insulin/soluble insulin 30%, 10-0-10 units

Table 2D. Ocular microbiological tests including aqueous, vitreous, and eviscerated material

Patient	Age/Sex	Diagnosis	Sample / Site	Findings	Urine culture	Blood culture
Patient 3	47/M	Endophthalmitis OD	AC tap	Gram-positive cocci	Pseudomonas species, 10,000 CFU/mL; sensitive to amikacin and gentamicin	No growth
			Vitreous tap	Gram-positive cocci; no growth on culture; PCR for Eubacteria **positive**		
Patient 4	37/M	Endophthalmitis OS	AC tap	PCR for panfungal genome **positive**	No growth	No growth
Patient 5	65/F	Endophthalmitis OD	AC tap	Few Gram-positive cocci in singles and pairs; PCR for Eubacteria **positive**	No growth	No growth
Patient 6	56/M	Panophthalmitis OS	Ocular contents	Plenty of pus cells, cellular debris, and occasional Gram-positive cocci in singles and pairs; PCR for Eubacteria **positive**	No growth	No growth
Patient 7	55/M	Panophthalmitis OU	Vitreous tap (OD)	Gram-positive cocci and Gram-negative bacilli; *Klebsiella pneumoniae* isolated, sensitive to tobramycin, cotrimoxazole, and amikacin and resistant to all other antibiotics; PCR positive for Eubacterial genome; PCR positive for panfungal genome; SARS-CoV-2 RT-PCR negative	No growth	*Staphylococcus capitis* isolated
			Vitreous tap (OS)	Not sampled		
			Aqueous tap (OD)	Gram-positive cocci in singles and pairs; SARS-CoV-2 RT-PCR negative		
			Aqueous tap (OS)	Gram-positive cocci in singles and pairs		
			Corneal scraping (OD)	Stain and culture negative		
			Corneal scraping (OS)	Not available		
			Scleral abscess scraping (OD)	Gram-positive cocci in singles; culture negative		
			Scleral abscess scraping (OS)	Gram-positive cocci in singles; culture negative		
			Eviscerated material (OS)	*Klebsiella pneumoniae* isolated in culture		

Abbreviations: AC, anterior chamber; OD, right eye; OS, left eye; OU, both eyes; PCR, polymerase chain reaction; RT-PCR, reverse transcription polymerase chain reaction; CFU, colony-forming units; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. Notes: Positive microbiological or molecular results are highlighted in bold. PCR refers to polymerase chain reaction testing for bacterial or fungal genomes. SARS-CoV-2 testing was performed using RT-PCR where indicated.

Surgical interventions

At the local hospital, functional endoscopic sinus surgery (FESS) was performed to drain the left maxillary sinus. The sample was sent for gram stain, KOH, culture negative, and SARS- Cov-2 RT- PCR, all of which were negative.

At our center, left-eye evisceration was done due to the progression of scleral abscess. Histopathology of the eviscerated material showed disorganized eyeball contents containing retinal and lens tissue with fragments of cornea exhibiting ulcerations of lining epithelium. Sub-epithelial stroma showed proliferating blood vessels lined by plump endothelial cells surrounded by dense mixed inflammatory cell infiltrate, predominantly comprising neutrophils, few lymphocytes, and sheets of foam cells with areas of necrosis. Gomori methenamine silver stain was negative for fungal elements. Sections were negative for granulomas or malignancy.

On final follow-up one year later the diabetes was under control; visual acuity was no light perception bilaterally. The right eye had become phthisical and the left eye had a healthy socket with conformer in place.

Table 3. Presenting and final visual outcomes with a summary of management

No.	Age/Sex	Diagnosis	Clinical details and management		
			Presenting BCVA	Ocular Intervention	Final BCVA
Patient 1	66/M	CRAO OD, Panuveitis OU, Optic neuritis OU	CF 2 meters OD 20/36 OS	Topical steroids	CF 3 m OD 20/20 OS
Patient 2	63/M	Retinal vasculitis, vitreous haemorrhage, secondary glaucoma with systemic vasculitis OU	CF close to face OU	Anterior chamber washout OD Intravitreal bevacizumab (Avastin®) x 1 OD Laser photocoagulation OU Trabeculectomy OD	20/25 OU
Patient 3	47/M	Endophthalmitis OD	PL OD	Pars plana vitrectomy OD Intravitreal antibiotics OD Laser peripheral iridotomy for iris bombe OD	20/320 OD
Patient 4	37/M	Endophthalmitis OS	HM OS	Pars plana vitrectomy OS Intravitreal antibiotics OS	20/200 OS
Patient 5	65/F	Endophthalmitis OD	CF 2 meters OD	Intravitreal antibiotics OD Refused surgical intervention for RD	HM OD
Patient 6	56/M	Panophthalmitis OS	PL OS	Conservative management (no surgical intervention)	PL OS
Patient 7	55/M	Panophthalmitis OU	NPL OD PL with inability to identify projection of light rays OS	Intravitreal antibiotics OU Evisceration OS	NPL OU

Abbreviations: OD, right eye; OS, left eye; OU, both eyes; BCVA, best-corrected visual acuity; LP, light perception; NPL, no perception of light; CF, counting fingers; HM, hand movements; CRAO, central retinal artery occlusion. **Notes:** Topical steroids included prednisolone acetate 1%. Oral corticosteroid therapy consisted of prednisolone 0.5 mg/kg/day, administered with appropriate antimicrobial cover in infective cases. Systemic antibiotic therapy included ciprofloxacin 500 mg twice daily for all infective cases. Intravitreal antibiotics included vancomycin (1 mg/0.1 mL), ceftazidime (2.25 mg/0.1 mL), and voriconazole (0.01 mg/0.1 mL). Intravitreal bevacizumab (1.25 mg/0.05 mL) and dexamethasone (0.4 mg/0.1 mL) were administered where indicated. Immunosuppressive therapy included methotrexate 10 mg/week (Patient 1) and systemic corticosteroids with intravenous pulse cyclophosphamide followed by mycophenolate mofetil 1000 mg twice daily (Patient 2).

All the study patients underwent tests that included complete blood count, blood/urine culture (where appropriate), and hypercoagulable and inflammatory markers. D- Dimer, serum ferritin, lactate dehydrogenase, erythrocyte sedimentation rate, C-reactive protein, and procalcitonin were significantly raised in this cohort when compared to normal values. These results have been published [16].

Those patients with infective sight-threatening conditions like endophthalmitis and panophthalmitis underwent intraocular fluid sampling; the details are shown in Table 2D.

Oral and systemic antimicrobial therapy either with or without systemic steroids with intravitreal vancomycin/ceftazidime/voriconazole with dexamethasone was given for infected cases. Patients 1 and 2 needed additional immunosuppression. Patient 2 was treated with IV methyl prednisolone 500 mg for 3 days, oral prednisolone 30 mg along with apixaban 2.5 mg twice daily, and oral azathioprine 25 mg twice daily and then 75 mg. Since his systemic and ocular vasculitis worsened, he was started on intravenous pulse cyclophosphamide 500 mg for 4 sessions in biweekly intervals. The summary of interventions is provided in Table 3.

DISSCUSSION

Reported sight-threatening manifestations post-COVID-19 [12] are optic neuritis, optic atrophy, panuveitis, multifocal retinitis, necrotizing retinitis, central retinal artery/vein occlusion, and endogenous endophthalmitis. Bikdeli et al. [27] suggested that COVID-19 may predispose patients to arterial and venous thrombosis. Unilateral/bilateral central retinal artery occlusion (CRAO) was found secondary to COVID-19. [7, 28, 29]. In some patients with retinal vascular occlusions, markers such as interleukin-6, CRP, ferritin, fibrinogen, and D-dimer imply a prothrombotic and hypercoagulable state [2, 7, 28]. Likewise, in

our series of sight-threatening ocular manifestations associated with COVID-19 we found CRAO in the right eye of Patient 1 and retinal vasculitis bilaterally in Patient 2.

Onset of retinal vasculitis two weeks after a SARS-CoV-2 infection was reported in a patient, [29] with normal vasculitis workup including coagulation parameters, activated partial thromboplastin time, prothrombin time (PT), and international normalized ratio, while only fibrinogen (431.03 mg/dL) was elevated. He was treated with intravenous 1 g pulse steroids and subsequently with oral steroids in a dose of 1mg/kg body weight [29]. In our patient with retinal vasculitis (Patient 2), fibrinogen (548 mg /dL) was elevated too.

Coronaviruses have previously evidenced to cause retinal vasculitis, retinal degeneration, and breakdown of the blood-retinal barrier in animal models [30]. An experimental coronavirus retinopathy model has shown that the virus-induced retinal damage happens in a biphasic manner. The early phase involves retinal inflammation and infiltration by immune cells and release of inflammatory mediators, and in the next phase—which comes after the first week of infection—viral clearance occurs. Later on, autoantibodies are produced against the retina and retinal pigment epithelium cells, leading to damage of photoreceptors and the neuroretina [31]. Apart from endothelial damage by the virus, endothelial cells may also undergo inflammation, apoptosis, and dysfunction [32].

COVID-19 may sometimes lead to life-threatening thromboembolic complications, and systemic antithrombotic therapy has been suggested as a prophylactic and therapeutic management strategy for patients affected with serious systemic disease. Retinal complications are seen in both sick and apparently healthy COVID-19 patients, potentially leading to vision loss [33].

Prophylactic anticoagulation even after recovery from COVID-19 is controversial, as there is insufficient data regarding thromboembolic events after discharge [34]. Our Patient 2 with hyphema in the right eye and bilateral retinal vasculitis and vitreous hemorrhage was on enoxaparin 40 mg post-discharge, which could be a possible risk factor for intraocular bleeding.

Inflammatory CNS vasculopathy with antimyelin oligodendrocyte glycoprotein antibodies in a patient with COVID-19 showed clinical improvement after immunomodulation therapy [35]. Type-3 hypersensitivity and IL-6-mediated inflammation have been proposed as the pathophysiology of this COVID-19-induced vasculitis [36]. Both our patients 1 and 2 with retinal vascular occlusions received immunosuppression, with a favorable outcome.

Endogenous endophthalmitis is exceedingly rare in immunocompetent patients [37]. Its presence should prompt an immunologic workup to rule out underlying immune deficiencies [37, 38]. It was negative in all our patients. Three patients had pre-existing diabetes, two developed diabetes during their COVID-19 treatment. The presence of pseudomonas urinary infection in patients with immune deficiencies or debilitating disease is a well-known risk factor for endogenous endophthalmitis [39], and would explain both the mucosal lesions at the nose and the eye involvement in Patient 3. The presence of COVID-19 might as well be a fortuitous phenomenon. Still, we cannot conclude that intraocular inflammation may be related to COVID-19 even though the patient had no systemic illness otherwise. The patient did not have any symptoms suggestive of urinary tract infection.

Endophthalmitis during the COVID-19 pandemic has been reported [40–44], yet in none of the cases was it possible to conclusively prove if it was primarily due to COVID-19 or to its complications. One series presented patients with clinical features of fungal endophthalmitis, but no organism was isolated [45]. Ocular specimens from our patients with infectious endophthalmitis/panophthalmitis (Patients 3–7) did not have any bacterial or fungal growth on culture.

In a series of fungal endogenous endophthalmitis, 5 of 7 eyes grew fungus as the causative organism (*Candida sp.* in four eyes, *Aspergillus sp.* in one eye) [40]. In another series, COVID-19 patients with multifocal pneumonia were more likely to be treated with systemic steroids than the no-steroids group at admission, and it was noted that the steroids group had significantly higher rates of bacterial infection (25% versus 13.1%) and fungal infection (12.7% versus 0.7%) during hospitalization [41]. Systemic steroid administration may therefore have contributed to a predisposition for infectious endophthalmitis in our patients.

In the series of Khatwani et al. [46], patients who were COVID-positive presented after 7–30 days for an eye consultation. They all received systemic steroids, oxygen therapy, anticoagulants, and anti-viral drugs as part of their standard treatment protocol. Endophthalmitis patients underwent a pars plana vitrectomy with intravitreal antifungal injections. They were also started on systemic antimicrobial agents based on the culture sensitivity report [46]. Similarly, to our patient with panophthalmitis, they had a patient who presented with no perception of light bilaterally, bilateral pansinusitis, and endonasal biopsy showing mucromycosis [46]. Our patient's FESS sample did not show any growth or organisms.

Abdelkader et al. [47] had nine patients with a diagnosis of unilateral endophthalmitis with orbital cellulitis. RT-PCR of conjunctival swabs was positive in two patients. Microbiological testing of aqueous and vitreous aspirates on aerobic, anaerobic, and fungal media were negative. Three patients died, four patients had atrophic bulbi, and two patients retained the shape of the eyeball but with complete loss of vision [47].

Jain et al. [48] reported a case of fulminant endogenous endophthalmitis that required evisceration. Subsequent culture and gene-sequenced analysis confirmed Aspergillus fumigatus to be the causative organism [47]. In our series, panophthalmitis in Patient 7 progressed despite management, necessitating left eye evisceration due to scleral abscess formation. Histopathological examination revealed extensive intraocular tissue disorganization with marked acute inflammatory infiltrates,

neovascularization, and necrosis, without evidence of fungal infection, granulomatous inflammation, or malignancy, indicating a severe non-fungal inflammatory process.

Deepa et al. [49] reported a patient who was a known diabetic with a history of COVID-19 pneumonia, treated with steroids and remdesivir. He had pyelonephritis and urinary culture had grown *Klebsiella.* The patient had been diagnosed with left-eye endogenous endophthalmitis. He underwent pars plana vitrectomy and vitreous biopsy with intraocular antibiotics (imipenem) for suspected endogenous bacterial endophthalmitis. The biopsy did not yield organisms on the smear/culture. A repeat vitreous biopsy was done along with intravitreal injection of voriconazole (suspecting fungal etiology), and the organism was identified as *Cryptococcus laurentii* [49].

The Sahu et al. [50] series included five cases who had all received systemic corticosteroids for a mean duration of seven days during severe COVID-19 treatment, presenting 1–31 days after recovering. All patients had presumed fungal endogenous endophthalmitis based on clinical profile. Four out of five patients were subjected to pars plana vitrectomy and had microbiologically proven aspergillus species on vitreous fluid assessment. Four eyes underwent pars plana vitrectomy with silicone oil injection with reasonable anatomical outcome and controlled infection, but did not gain vision [50].

We would like to make a special mention of neutrophil lymphocyte ratio (NLR) in our series. We are the first to report NLR values in sight-threatening manifestations post-COVID-19. The mean value was significantly raised compared to normal values [20, 21]. NLR, calculated as a simple ratio between neutrophil and lymphocyte counts measured in peripheral blood, is a biomarker that reflects the balance between two aspects of the immune system: acute and chronic inflammation (as indicated by neutrophil count) and adaptive immunity (lymphocyte count) [51].

NLR is normally in the 0.78–3.53 range in adult nongeriatric populations [20]. In a study of elderly patients, NLR was significantly higher in unmedicated patients with depression compared with healthy controls (2.10 ± 2.13 vs. 2.01 ± 0.75) [21]. NLR is an easily performed, reproducible, cheap, and reliable laboratory biomarker to test inflammatory response in ocular inflammatory diseases [21, 51]. The predictive value of NLR has been reported in ocular vascular and inflammatory diseases such as diabetic retinopathy, age-related macular degeneration, retinal vein occlusion, glaucoma, ischemic optic neuropathy, and dry eye disease [52–57]. Inflammation induces neutrophilia while physiological stress induces lymphopenia. The release of endogenous glucocorticoids in response to local/systemic disorders, including ocular disorders, may play a significant role in the production of lymphopenia [52, 53]. The mean NLR in our case series was 4.79, with markedly elevated values observed in Patient 2 (6.69) and Patient 7 (10.50), suggesting a heightened systemic inflammatory response in patients with more severe ocular involvement.

The other interesting feature of this study was the role of D-Dimer, lactate dehydrogenase, serum ferritin, procalcitonin, and serum fibrinogen [58, 59]. All these could entail the risk of developing ocular complications post-COVID-19, as they were all elevated in our study.

Endogenous ocular infections are seen in patients who have been hospitalized. COVID-19 can cause hypercoagulable state, which may lead to vasculitis and occlusions. Sight-threatening manifestations are a distinct possibility post-COVID-19. Early recognition and management improves chances of functional visual outcome. Hypercoagulable and hyper-inflammatory systemic status are common and need systemic management along with rheumatologists and infectious disease specialists. This study has a diverse group of patients with no control group available of patients who had COVID-19 but no ophthalmic symptoms. The diagnosis of COVID-19 to ocular presentation is a different time frame that could not be generalized. Patients in this group had both vascular occlusions and infection as a cause of sight-threatening visual loss. Larger prospective studies with controls are required to clarify pathogenesis, optimal screening, and management strategies for post-COVID-19 ocular complications.

CONCLUSIONS

Steroids and diabetes are potential risk factors for developing endogenous endophthalmitis/panophthalmitis. Intraocular sampling may not yield SARS-CoV-2 virus or any organisms. Polymerase chain reaction may help identify eubacterial or fungal genome. As seen in this diverse group of patients, post-COVID-19 ophthalmic manifestations can be sight-threatening and functional visual outcome may not always be achieved.

ETHICAL DECLARATIONS

Ethical approval: The Ethics Committee of our hospital approved the study (approval number C/2020/09/09). The study was conducted under the tenets of the 1964 Declaration of Helsinki and its later amendments. Patients' written informed consent for participation and publication of the study data was obtained. All patients gave consent for their images to be published.
Conflict of interests: None.

FUNDING

ACKNOWLEDGMENTS

REFERENCES

1. Wu P, Duan F, Luo C, Liu Q, Qu X, Liang L, Wu K. Characteristics of Ocular Findings of Patients With Coronavirus Disease 2019 (COVID-19) in Hubei Province, China. JAMA Ophthalmol. 2020 May 1;138(5):575-578. doi: 10.1001/jamaophthalmol.2020.1291. PMID: 32232433; PMCID: PMC7110919.

2. Acharya S, Diamond M, Anwar S, Glaser A, Tyagi P. Unique case of central retinal artery occlusion secondary to COVID-19 disease. IDCases. 2020;21:e00867. doi: 10.1016/j.idcr.2020.e00867. Epub 2020 Jun 18. PMID: 32572363; PMCID: PMC7301806.

3. Insausti-García A, Reche-Sainz JA, Ruiz-Arranz C, López Vázquez Á, Ferro-Osuna M. Papillophlebitis in a COVID-19 patient: Inflammation and hypercoagulable state. Eur J Ophthalmol. 2022 Jan;32(1):NP168-NP172. doi: 10.1177/1120672120947591. Epub 2020 Jul 30. PMID: 32735134; PMCID: PMC7399568.

4. Landecho MF, Yuste JR, Gándara E, Sunsundegui P, Quiroga J, Alcaide AB, García-Layana A. COVID-19 retinal microangiopathy as an in vivo biomarker of systemic vascular disease? J Intern Med. 2021 Jan;289(1):116-120. doi: 10.1111/joim.13156. Epub 2020 Jul 30. PMID: 32729633.

5. Dumitrascu OM, Volod O, Bose S, Wang Y, Biousse V, Lyden PD. Acute ophthalmic artery occlusion in a COVID-19 patient on apixaban. J Stroke Cerebrovasc Dis. 2020 Aug;29(8):104982. doi: 10.1016/j.jstrokecerebrovasdis.2020.104982. Epub 2020 May 23. PMID: 32689586; PMCID: PMC7245224.

6. Ortiz-Seller A, Martínez Costa L, Hernández-Pons A, Valls Pascual E, Solves Alemany A, Albert-Fort M. Ophthalmic and Neuro-ophthalmic Manifestations of Coronavirus Disease 2019 (COVID-19). Ocul Immunol Inflamm. 2020 Nov 16;28(8):1285-1289. doi: 10.1080/09273948.2020.1817497. Epub 2020 Oct 6. PMID: 33021422.

7. Sanjay S, Srinivasan P, Jayadev C, Mahendradas P, Gupta A, Kawali A, Shetty R. Post COVID-19 Ophthalmic Manifestations in an Asian Indian Male. Ocul Immunol Inflamm. 2021 May 19;29(4):656-661. doi: 10.1080/09273948.2020.1870147. Epub 2021 Mar 18. PMID: 33733987.

8. Sanjay S, Gowda PB, Rao B, Mutalik D, Mahendradas P, Kawali A, Shetty R. "Old wine in a new bottle" - post COVID-19 infection, central serous chorioretinopathy and the steroids. J Ophthalmic Inflamm Infect. 2021 May 14;11(1):14. doi: 10.1186/s12348-021-00244-4. PMID: 33987731; PMCID: PMC8118683.

9. Sanjay S, Mutalik D, Gowda S, Mahendradas P, Kawali A, Shetty R. "Post Coronavirus Disease (COVID-19) Reactivation of a Quiescent Unilateral Anterior Uveitis". SN Compr Clin Med. 2021;3(9):1843-1847. doi: 10.1007/s42399-021-00985-2. Epub 2021 Jun 7. PMID: 34124585; PMCID: PMC8184259.

10. Sanjay S, Kawali A, Mahendradas P, Shetty B. Post Coronavirus Disease (COVID)-19 Disease and Unilateral Visual Impairment. Curr Eye Res. 2021 Dec;46(12):1938. doi: 10.1080/02713683.2021.1905001. Epub 2021 Mar 25. PMID: 33729900.

11. Mahendradas P, Hande P, Patil A, Kawali A, Sanjay S, Ahmed SA, Thomas S, Shetty R. Bilateral Post Fever Retinitis With Retinal Vascular Occlusions Following Severe Acute Respiratory Syndrome Corona Virus (SARS-CoV2) Infection. Ocul Immunol Inflamm. 2022 Oct-Nov;30(7-8):1715-1720. doi: 10.1080/09273948.2021.1936564. Epub 2021 Jul 6. PMID: 34228600.

12. Sanjay S, Agrawal S, Jayadev C, Kawali A, Gowda PB, Shetty R, Mahendradas P. Posterior segment manifestations and imaging features post-COVID-19. Med Hypothesis Discov Innov Ophthalmol. 2021 Nov 17;10(3):95-106. doi: 10.51329/mehdiophthal1427. PMID: 37641707; PMCID: PMC10460223.

13. Sanjay S, Rao VK, Mutalik D, Mahendradas P, Kawali A, Shetty R. Post corona virus Disease-19 (COVID-19): Hyper inflammatory syndrome-associated bilateral anterior uveitis and multifocal serous retinopathy secondary to steroids. Indian Journal of Rheumatology. 2021 Oct 1;16(4):451-5. doi: 10.4103/injr.injr_330_20.

14. Sanjay S, Singh YP, Roy D, Mahendradas P, Kawali A, Shetty R. Recurrent bilateral idiopathic anterior uveitis with vitritis post Coronavirus Disease 2019 infection. Indian Journal of Rheumatology. 2021 Dec;16(4):460-3. doi: 10.4103/injr.injr_114_21.

15. Sanjay S, Kawali A, Agrawal S, Mahendradas P. Unilateral acute anterior sclero-uveitis preceding Corona virus disease (COVID-19). The Pan-American Journal of Ophthalmology. 2022 Jan 1;4(1):26. doi: 10.4103/pajo.pajo_14_22.

16. Sanjay S, Bhakti Mistra S, Patro SK, Kawali A, Shetty R, Mahendradas P. Systemic Markers in Ophthalmic Manifestations of Post Corona Virus Disease-19 (COVID-19). Ocul Immunol Inflamm. 2023 Feb;31(2):410-415. doi: 10.1080/09273948.2021.2025253. Epub 2022 Feb 9. PMID: 35138993.

17. Sanjay S, Poornachandra B, Kawali A, Shetty R, Narayana VC, Agrawal S, Mahendradas P. Unilateral Endogenous Bacterial Endophthalmitis Post-Coronavirus Disease-19 in an Healthy Asian Indian Male. Beyoglu Eye J. 2022 Aug 5;7(3):240-246. doi: 10.14744/bej.2022.94546. PMID: 36185987; PMCID: PMC9522998.

18. Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005 Sep;140(3):509-16. doi: 10.1016/j.ajo.2005.03.057. PMID: 16196117; PMCID: PMC8935739.

19. Nussenblatt RB, Palestine AG, Chan CC, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. Ophthalmology. 1985 Apr;92(4):467-71. doi: 10.1016/s0161-6420(85)34001-0. PMID: 4000641.

20. Forget P, Khalifa C, Defour JP, Latinne D, Van Pel MC, De Kock M. What is the normal value of the neutrophil-to-lymphocyte ratio? BMC Res Notes. 2017 Jan 3;10(1):12. doi: 10.1186/s13104-016-2335-5. PMID: 28057051; PMCID: PMC5217256.

21. Arabska J, Łucka A, Magierski R, Sobów T, Wysokiński A. Neutrophil-lymphocyte ratio is increased in elderly patients with first episode depression, but not in recurrent depression. Psychiatry Res. 2018 May;263:35-40. doi: 10.1016/j.psychres.2018.02.043. Epub 2018 Feb 21. PMID: 29490259.

22. Prokop M, van Everdingen W, van Rees Vellinga T, Quarles van Ufford H, Stöger L, Beenen L, Geurts B, Gietema H, Krdzalic J, Schaefer-Prokop C, van Ginneken B, Brink M; COVID-19 Standardized Reporting Working Group of the Dutch Radiological Society.

CO-RADS: A Categorical CT Assessment Scheme for Patients Suspected of Having COVID-19-Definition and Evaluation. Radiology. 2020 Aug;296(2):E97-E104. doi: 10.1148/radiol.2020201473. Epub 2020 Apr 27. PMID: 32339082; PMCID: PMC7233402.

23. Elmokadem AH, Mounir AM, Ramadan ZA, Elsedeiq M, Saleh GA. Comparison of chest CT severity scoring systems for COVID-19. Eur Radiol. 2022 May;32(5):3501-3512. doi: 10.1007/s00330-021-08432-5. Epub 2022 Jan 15. PMID: 35031841; PMCID: PMC8760133.

24. Merli G, Spiro TE, Olsson CG, Abildgaard U, Davidson BL, Eldor A, Elias D, Grigg A, Musset D, Rodgers GM, Trowbridge AA, Yusen RD, Zawilska K; Enoxaparin Clinical Trial Group. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. Ann Intern Med. 2001 Feb 6;134(3):191-202. doi: 10.7326/0003-4819-134-3-200102060-00009. PMID: 11177331.

25. Cerfolio RJ, Bryant AS, Thurber JS, Bass CS, Lell WA, Bartolucci AA. Intraoperative solumedrol helps prevent postpneumonectomy pulmonary edema. Ann Thorac Surg. 2003 Oct;76(4):1029-33; discussion 1033-5. doi: 10.1016/s0003-4975(03)00879-8. PMID: 14529979.

26. Billett HH, Reyes-Gil M, Szymanski J, Ikemura K, Stahl LR, Lo Y, Rahman S, Gonzalez-Lugo JD, Kushnir M, Barouqa M, Golestaneh L, Bellin E. Anticoagulation in COVID-19: Effect of Enoxaparin, Heparin, and Apixaban on Mortality. Thromb Haemost. 2020 Dec;120(12):1691-1699. doi: 10.1055/s-0040-1720978. Epub 2020 Nov 13. PMID: 33186991; PMCID: PMC7869055.

27. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, Nigoghossian C, Ageno W, Madjid M, Guo Y, Tang LV, Hu Y, Giri J, Cushman M, Quéré I, Dimakakos EP, Gibson CM, Lippi G, Favaloro EJ, Fareed J, Caprini JA, Tafur AJ, Burton JR, Francese DP, Wang EY, Falanga A, McLintock C, Hunt BJ, Spyropoulos AC, Barnes GD, Eikelboom JW, Weinberg I, Schulman S, Carrier M, Piazza G, Beckman JA, Steg PG, Stone GW, Rosenkranz S, Goldhaber SZ, Parikh SA, Monreal M, Krumholz HM, Konstantinides SV, Weitz JI, Lip GYH; Global COVID-19 Thrombosis Collaborative Group, Endorsed by the ISTH, NATF, ESVM, and the IUA, Supported by the ESC Working Group on Pulmonary Circulation and Right Ventricular Function. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020 Jun 16;75(23):2950-2973. doi: 10.1016/j.jacc.2020.04.031. Epub 2020 Apr 17. PMID: 32311448; PMCID: PMC7164881.

28. Bapaye MM, Nair AG, Bapaye CM, Bapaye MM, Shukla JJ. Simultaneous Bilateral Central Retinal Artery Occlusion following COVID-19 Infection. Ocul Immunol Inflamm. 2021 May 19;29(4):671-674. doi: 10.1080/09273948.2021.1891262. Epub 2021 Apr 15. PMID: 33856275.

29. Erdem S, Karahan M, Dursun ME, Ava S, Hazar L, Katran I, Keklikci U. Retinal Vasculitis Case Developing in the Early Period after COVID-19. Klin Monbl Augenheilkd. 2022 Sep;239(9):1132-1133. English. doi: 10.1055/a-1363-1326. Epub 2021 Apr 14. PMID: 33853180.

30. Seah I, Agrawal R. Can the Coronavirus Disease 2019 (COVID-19) Affect the Eyes? A Review of Coronaviruses and Ocular Implications in Humans and Animals. Ocul Immunol Inflamm. 2020 Apr 2;28(3):391-395. doi: 10.1080/09273948.2020.1738501. Epub 2020 Mar 16. PMID: 32175797; PMCID: PMC7103678.

31. Hooks JJ, Percopo C, Wang Y, Detrick B. Retina and retinal pigment epithelial cell autoantibodies are produced during murine coronavirus retinopathy. J Immunol. 1993 Sep 15;151(6):3381-9. PMID: 8397257.

32. Becker RC. COVID-19 update: Covid-19-associated coagulopathy. J Thromb Thrombolysis. 2020 Jul;50(1):54-67. doi: 10.1007/s11239-020-02134-3. PMID: 32415579; PMCID: PMC7225095.

33. Sen S, Kannan NB, Kumar J, Rajan RP, Kumar K, Baliga G, Reddy H, Upadhyay A, Ramasamy K. Retinal manifestations in patients with SARS-CoV-2 infection and pathogenetic implications: a systematic review. Int Ophthalmol. 2022 Jan;42(1):323-336. doi: 10.1007/s10792-021-01996-7. Epub 2021 Aug 11. PMID: 34379290; PMCID: PMC8356207.

34. Tao DL, Bien JY, DeLoughery TG, Shatzel JJ. Extended thromboprophylaxis with direct oral anticoagulants for medical patients: a systematic review and meta-analysis. Blood. 2017 Feb 2;129(5):653-655. doi: 10.1182/blood-2016-10-747931. Epub 2016 Dec 20. PMID: 27998890.

35. Pinto AA, Carroll LS, Nar V, Varatharaj A, Galea I. CNS inflammatory vasculopathy with antimyelin oligodendrocyte glycoprotein antibodies in COVID-19. Neurol Neuroimmunol Neuroinflamm. 2020 Jun 10;7(5):e813. doi: 10.1212/NXI.0000000000000813. PMID: 32522768; PMCID: PMC7309522.

36. Roncati L, Ligabue G, Fabbiani L, Malagoli C, Gallo G, Lusenti B, Nasillo V, Manenti A, Maiorana A. Type 3 hypersensitivity in COVID-19 vasculitis. Clin Immunol. 2020 Aug;217:108487. doi: 10.1016/j.clim.2020.108487. Epub 2020 May 29. PMID: 32479986; PMCID: PMC7256503.

37. Xie CA, Singh J, Tyagi M, Androudi S, Dave VP, Arora A, Gupta V, Agrawal R, Mi H, Sen A. Endogenous Endophthalmitis - A Major Review. Ocul Immunol Inflamm. 2023 Sep;31(7):1362-1385. doi: 10.1080/09273948.2022.2126863. Epub 2022 Oct 28. PMID: 36306406.

38. Cunningham ET, Flynn HW, Relhan N, Zierhut M. Endogenous Endophthalmitis. Ocul Immunol Inflamm. 2018;26(4):491-495. doi: 10.1080/09273948.2018.1466561. PMID: 29768116; PMCID: PMC6448583.

39. Ren C, Li Z, Meng F, Du Y, Sun H, Guo B. Endogenous endophthalmitis caused by urinary tract infection: A case report. Medicine (Baltimore). 2023 Nov 17;102(46):e36139. doi: 10.1097/MD.0000000000036139. PMID: 37986372; PMCID: PsMC10659675.

40. Shroff D, Narula R, Atri N, Chakravarti A, Gandhi A, Sapra N, Bhatia G, Pawar SR, Narain S. Endogenous fungal endophthalmitis following intensive corticosteroid therapy in severe COVID-19 disease. Indian J Ophthalmol. 2021 Jul;69(7):1909-1914. doi: 10.4103/ijo.IJO_592_21. PMID: 34146056; PMCID: PMC8374784.

41. Obata R, Maeda T, Rizk D, Kuno T. Increased Secondary Infection in COVID-19 Patients Treated with Steroids in New York City. Jpn J Infect Dis. 2021 Jul 21;74(4):307-315. doi: 10.7883/yoken.JJID.2020.884. Epub 2020 Dec 25. PMID: 33390434.

42. Agarwal M, Sachdeva M, Pal S, Shah H, Kumar R M, Banker A. Endogenous Endophthalmitis A Complication of COVID-19 Pandemic: A Case Series. Ocul Immunol Inflamm. 2021 May 19;29(4):726-729. doi: 10.1080/09273948.2021.1945111. Epub 2021 Jul 13. PMID: 34255587.

43. Bilgic A, Sudhalkar A, Gonzalez-Cortes JH, March de Ribot F, Yogi R, Kodjikian L, Mathis T. ENDOGENOUS ENDOPHTHALMITIS IN THE SETTING OF COVID-19 INFECTION: A Case Series. Retina. 2021 Aug 1;41(8):1709-1714. doi: 10.1097/IAE.0000000000003168. PMID: 33734193.

44. Verma S, Walinjkar JA. A case of endogenous endophthalmitis in COVID-19 pandemic. Apollo Medicine. 2020 Sep;17(3):229-32. doi: https://journals.sagepub.com/doi/abs/10.4103/am.am_71_20.

45. Shah KK, Venkatramani D, Majumder PD. A case series of presumed fungal endogenous endophthalmitis in post COVID-19 patients. Indian J Ophthalmol. 2021 May;69(5):1322-1325. doi: 10.4103/ijo.IJO_3755_20. PMID: 33913891; PMCID: PMC8186646.

46. Khatwani PR, Goel NP, Trivedi KY, Aggarwal SV. Unveiling endophthalmitis post COVID-19 - A case series. Indian J Ophthalmol. 2021 Oct;69(10):2869-2871. doi: 10.4103/ijo.IJO_1616_21. PMID: 34571655; PMCID: PMC8597453.

47. Abdelkader MFSO, Elshafei AMK, Nassar MM, Abu Elela MA, Abdallah RMA. Combined endophthalmitis and orbital cellulitis in patients with corona virus disease (COVID-19). J Ophthalmic Inflamm Infect. 2021 Sep 15;11(1):27. doi: 10.1186/s12348-021-00258-y. PMID: 34523045; PMCID: PMC8440116.

48. Jain M, Brar AS, Rath S, Kelgaokar A, Behera HS. Fulminant fungal endogenous endophthalmitis following SARS-CoV-2 infection: A case report. Indian J Ophthalmol. 2022 May;70(5):1819-1821. doi: 10.4103/ijo.IJO_1951_21. PMID: 35502083; PMCID: PMC9333037.

49. Deepa MJ, Megharaj C, Patil S, Rani PK. Cryptococcus laurentii endogenous endophthalmitis post COVID-19 infection. BMJ Case Rep. 2022 May 11;15(5):e246637. doi: 10.1136/bcr-2021-246637. PMID: 35545307; PMCID: PMC9096502.

50. Sahu ES, Lahoti K, Bhargava A, Subhedar V, Sahu A. Subretinal Aspergillus Abscess in Post COVID-19 Recovered Patients - An Emerging Problem. Ocul Immunol Inflamm. 2023 Jan;31(1):127-133. doi: 10.1080/09273948.2021.1993271. PMID: 34784260.

51. Song M, Graubard BI, Rabkin CS, Engels EA. Neutrophil-to-lymphocyte ratio and mortality in the United States general population. Sci Rep. 2021 Jan 11;11(1):464. doi: 10.1038/s41598-020-79431-7. PMID: 33431958; PMCID: PMC7801737.

52. Kurtul BE, Ozer PA. Neutrophil-to-lymphocyte ratio in ocular diseases: a systematic review. Int J Ophthalmol. 2019 Dec 18;12(12):1951-1958. doi: 10.18240/ijo.2019.12.18. PMID: 31850181; PMCID: PMC6901879.

53. Ozgonul C, Sertoglu E, Mumcuoglu T, Kucukevcilioglu M. Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio as Novel Biomarkers of Primary Open-Angle Glaucoma. J Glaucoma. 2016 Oct;25(10):e815-e820. doi: 10.1097/IJG.0000000000000392. PMID: 26918914.

54. Chittawar S, Dutta D, Qureshi Z, Surana V, Khandare S, Dubey TN. Neutrophil-lymphocyte Ratio is a Novel Reliable Predictor of Nephropathy, Retinopathy, and Coronary Artery Disease in Indians with Type-2 Diabetes. Indian J Endocrinol Metab. 2017 Nov-Dec;21(6):864-870. doi: 10.4103/ijem.IJEM_197_17. PMID: 29285450; PMCID: PMC5729675.

55. Ulu SM, Dogan M, Ahsen A, Altug A, Demir K, Acartürk G, Inan S. Neutrophil-to-lymphocyte ratio as a quick and reliable predictive marker to diagnose the severity of diabetic retinopathy. Diabetes Technol Ther. 2013 Nov;15(11):942-7. doi: 10.1089/dia.2013.0097. Epub 2013 Aug 6. PMID: 23919588.

56. Dursun A, Ozturk S, Yucel H, Ozec AV, Dursun FG, Toker MI, Erdogan H, Arici MK, Topalkara A. Association of neutrophil/lymphocyte ratio and retinal vein occlusion. Eur J Ophthalmol. 2015 Jul-Aug;25(4):343-6. doi: 10.5301/ejo.5000570. Epub 2015 Jan 27. PMID: 25633622.

57. Celik T. Assessment of Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio in Patients with Dry Eye Disease. Ocul Immunol Inflamm. 2018;26(8):1219-1222. doi: 10.1080/09273948.2017.1340486. Epub 2017 Sep 14. PMID: 28910561.

58. Hanafi FD, Esa T, Nurulita A, Mumang AA. D-Dimer, ferritin, and lactate dehydrogenase (LDH) as predictors of mortality in hospitalized COVID-19 patients. J Infect Dev Ctries. 2024 Sep 30;18(9.1):S27-S32. doi: 10.3855/jidc.18833. PMID: 39499744.

59. Shama, Mahmood A, Mehmood S, Zhang W. Pathological Effects of SARS-CoV-2 Associated with Hematological Abnormalities. Curr Issues Mol Biol. 2023 Aug 28;45(9):7161-7182. doi: 10.3390/cimb45090453. PMID: 37754237; PMCID: PMC10528388.