

# Ocular findings and retinal involvement in COVID-19 pneumonia patients: A cross-sectional study in an Italian referral centre

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## Research Article

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## Abstract

**Background:** changes in immune and coagulation systems and possible viral spread through blood-brain barrier have been described in SARS-CoV-2 infection. In this study, we evaluate the possible retinal involvement and ocular findings in severe COVID-19 pneumonia patients.

**Methods:** a cross sectional study was conducted on 46 patients affected by severe COVID-19 who were hospitalized in one Intensive Care Unit (ICU) and in two Infectious Diseases wards, including a bedside eye screening, corneal sensitivity assessment and retinography.

**Results:** a total of 43 SARS-CoV-2 positive pneumonia patients affected with COVID-19 pneumonia were included, 25 males and 18 females, with a median age of 70 [IQR 59-78]. Except for one patient with unilateral posterior chorioretinitis of opportunistic origin, of whom aqueous tap was negative for SARS-CoV-2, no further retinal manifestation related to COVID-19 infection was found in our cohort. We found 3 patients (7%) with bilateral conjunctivitis in whom PCR analysis on conjunctival swab provided negative results for SARS-CoV-2. No alterations of corneal sensitivity were found.

**Conclusion:** we demonstrated the absence of retinal involvement in SARS-CoV-2 pneumonia patients. Ophthalmologic evaluation in COVID-19, particularly in patients hospitalized in an ICU setting, may be useful to reveal systemic co-infections by opportunistic pathogens.

## Introduction

As a result of its pandemic spread and the very limited therapeutic options, COronaVIrus Disease 19 (COVID-19) is considered an unprecedented global health challenge. Italy was the first European country affected by a severe outbreak of the SARS-CoV-2 epidemic that emerged from Wuhan region (China), and currently has 241.611 total cases and 34.861 deaths.<sup>1-3</sup> As a life-threatening condition, most of the research has been primarily focused on respiratory system for a survival rate improvement, leaving the effects on other systems or districts still unclear or unknown.<sup>4-7</sup> Regarding eye involvement in COVID-19, only few data are currently available.<sup>8</sup> The subfamily of *Orthocoronavirinae* - in which SARS-CoVs belong to the *Betacoronavirus* genus - is already known to occasionally affect ocular structures.<sup>9-12</sup> Several manifestations like uveitis, retinitis and optic neuritis have been described in animal models of murine and feline species, however these findings have never been confirmed in humans.<sup>13</sup> First evidence on humans came from a few studies conducted during the early 2000s Severe Acute Respiratory Syndrome (SARS) outbreak caused by SARS-CoV-1. The SARS RNA was detected in the tears of little cohorts of patients, suggesting the eye as an entrance window for infection and/or as a hypothetical source of viral

spread.<sup>14-16</sup> Eventually, the fast contention of the disease had rapidly turned off the scientific interest about the ocular involvement. In more recent times, the SARS-CoV-2 epidemic has revived the interest in ocular manifestations especially since an associated conjunctivitis has been described and colonization of ocular surface has been reported, arising the same unsolved questions emerged in 2000s and suggesting the implementation of quick precautionary strategies to protect ophthalmologists and their patients.<sup>17-21</sup> Nevertheless, although recent data suggests that COVID-19 infection may be associated to changes in immune and coagulation systems and possible viral spread through blood-brain barrier, with clinical and anatomopathological findings of disseminated intravascular coagulopathy (DIC), the effects of these alterations on the eye, specifically regarding the posterior segment involvement, have never been studied.<sup>13,22-24</sup>

The main objective of the present cross-sectional study was to explore the possible retinal involvement in COVID-19 and to provide real-world data on ocular findings from SARS-CoV-2 positive pneumonia patients.

## Methods

### Setting

We conducted a cross-sectional study at the *Policlinico Umberto I*, a large teaching hospital in Rome (Italy), that included a cohort of patients affected by COVID-19 who were hospitalized in one Intensive Care Units (ICU) and in two Infectious Diseases wards, from April 24 to May 24, 2020. The study was approved by the ethical board of the Sapienza University of Rome (Rif. 5965, Prot. 109/2020) and was conducted in accordance with the tenets of the Declaration of Helsinki. All patients gave written informed consent to the study.

During the study period, 68 patients were hospitalized at any stage of the disease in the above-mentioned units. Twenty-one patients were not able to be screened because in Continuous Positive Airway Pressure (CPAP) therapy and one patient denied the consent. Therefore, we finally screened a total of 92 eyes of 46 patients. Patients were treated with ad interim best available therapy (BAT), according to the Italian Society of Infectious and Tropical Diseases (SIMIT): Hydroxychloroquine 200 mg bid and azithromycin 500mg daily, plus Tocilizumab 8 mg/kg (up to a maximum of 800 mg per dose) twice with an interval of 12 hours. All patients were on weight-based low-molecular-weight heparin (LMWH) and systemic steroids treatment 0.5-1 mg/Kg.<sup>25</sup> Inclusion criteria were: (1) age between 18 to 90 years, (2) confirmed positive results for SARS-CoV-2 from nasopharyngeal or oropharyngeal swab testing at the time of the ophthalmological assessment, and (3) lung involvement related to COVID-19. We excluded patients who had: (1) active neoplasia; (2) history of any ocular diseases such as glaucoma, uveitis, retinal vascular occlusion or major eye surgery performed within the previous six months. Based on the clinical conditions, patients were stratified following the COVID-19 phenotypic classification proposed by the Italian Society of Anesthesiology, Analgesia, Resuscitation and Intensive Care (SIAARTI): paucisymptomatic disease (Stage I), mild pneumonia (Stage II), moderate to severe pneumonia (Stage

III), acute respiratory distress syndrome (ARDS, Stage IV), sepsis (Stage V), septic shock (Stage VI).<sup>26</sup> In order to classify anamnestic and prognostic comorbidity at baseline, we used the Charlson Comorbidity Index (CCI).<sup>27</sup> Finally, at time of ophthalmological screening, in order to assess the patient inflammatory status and thrombotic risk, we recorded the laboratory tests of the day. Erythrocyte sedimentation rate (ESR), C-reactive Protein (CRP), white blood cell (WBC) count and Lymphocytes (LYM) values were collected to evaluate the subject's inflammatory status, while the thrombotic risk was scored using the International Society on Thrombosis and Haemostasis (ISTH) criteria for DIC.<sup>28</sup>

### Ophthalmological evaluation

Bedside ophthalmologic evaluation was performed in both eyes and included: ocular annexes and anterior segment examination using a direct lighting and a 20-dioptral lens for magnification. In those cases, presenting mono or bilateral conjunctival hyperaemia, a conjunctival swab was performed in both eyes for RNA SARS-CoV-2 detection. Quantitative corneal sensitivity, scored from 0 to 6 (0 corresponding to the absence of sensitivity and 6 to the highest sensitivity), was further assessed following a previously described protocol, only in awake patients, using the Cochet-Bonnet aesthesiometer (COBO).<sup>29</sup> Ocular fundus examination was performed after pharmacological pupil dilation with 1% Tropicamide, using binocular indirect ophthalmoscopy and a 20-dioptral lens. Images of the posterior pole have been acquired by the same investigator (MPP), using a handheld fundus camera with a 40-degree field of view, 9 internal fixation targets for peripheral imaging and 5-megapixel resolution (Optomed Smartscope®).

### Data source and collection

For every patient included in the study we collected demographic data, systemic and ocular history, laboratory test results, medical administration data, and ocular findings. All data was recorded using an Electronic Case Report Form (eCRF) by one investigator (GV). Data is then securely transferred to a central database, where missing data or every discrepancy was corrected by a double-check analysis or after a collegial evaluation.

### Statistical analysis

Normal distribution of data was analysed by the Shapiro-Wilk test. Continuous variables were reported as mean, median, maximum and minimum values, and interquartile ranges (IQR 25% and 75%). Categorical variables were reported as counts and percentages. All analyses were performed using SPSS v. 25.0 (SPSS, Inc., Chicago, IL).

## **Results**

Starting from 46 screened patients, based on the inclusion and exclusion criteria, we excluded two patients with active neoplasia and one with chronic glaucoma. Finally, a total of 43 subjects (25 males and 18 females) with a median age of 70 [IQR 59-78] was included in the present study. The patients have been hospitalized after a median of 4 days (range, 0 to 11 days) from COVID-19 symptoms onset

and the ophthalmological screening was performed after a median of 21.5 days (range, 1 to 47 days) from hospitalization. Comorbidity index was calculated at admission and ranged from 0 to 7, with a median of 1. Ten out of 43 patients (9 male and 1 female) were screened in an ICU setting. Baseline anamnestic and clinical characteristics of the study cohort are shown in *Table 1*. Patients' clinical status, as assessed by the SIAARTI COVID-19 classification, varied from stage II to stage V, with men globally in worse conditions than women. COVID-19 stages' distributions are shown in *Table 2*. Laboratory tests showed signs of systemic inflammation with general high CRP and low lymphocytes count. Overall, d-dimer values were significantly elevated, however only one patient (2.3%) had suggestive criteria for DIC according to ISTH and 4 patients had a prior diagnosis of COVID-19 related pulmonary thromboembolism. *Table 3* shows the principal laboratory tests results in our cohort.

Regarding ocular anterior segment findings, we observed 3 cases (7%) of bilateral conjunctivitis: two patients were in stage II and one in stage III of SIAARTI COVID-19 classification. In all three patients the PCR assay from conjunctival swab for the detection of SARS-CoV-2 provided negative results. Corneal sensitivity score, in screened eyes, as assessed by esthesiometry, ranged from 4 to 6 with a median of 5. Regarding the ocular posterior segment findings, apart from one patient with unilateral posterior chorioretinitis that is discussed below, no further retinal manifestation related to COVID-19 infection was found in our cohort. The patient with chorioretinitis, was a 67-year-old male, hospitalized in ICU in stage V disease, presented grade 1 vitreous haze, a wide area of deep choriotelial whitening involving the posterior pole, associated with deep retinal haemorrhages (Figure 1a). According to standard protocol, an aqueous tap to rule out possible pathogens including SARS-CoV-2 was performed. A diagnosis of probable fungal retinitis was done, and the systemic antifungal therapy was changed accordingly, by replacing IV caspofungin with amphotericin B. Microbiological tests excluded the presence of SARS-CoV-2 in humour aqueous and blood culture subsequently confirmed the diagnosis of *Candida parapsilosis* infection. Chorioretinitis gradually improved (Figure 1b) and blood culture became sterile, however the patient died for SARS-CoV-2 related pneumonia 4 weeks later. *Table 4* shows the ocular findings observed in our cohort.

## Discussion

The primary outcome of the study was to evaluate the presence of posterior segment alterations through a cross-sectional sample at different stages of the COVID-19, and to the best of our knowledge this is the first study to address this issue in a cohort of hospitalized people positive for SARS-CoV-2. All available evidence in humans is focused on the ocular surface - where almost only conjunctivitis has been described - and most data comes from case reports or findings from human conjunctival samples.<sup>17,30,31</sup> In our patients, of whom we carefully considered baseline anamnestic, results of fundus examination seem to demonstrate that neither the retina nor retinal vessels are involved in the active phase of COVID-19 infection.

The rationale in focusing on potential ocular fundus alterations, relies on previous studies conducted in animals infected by viruses belonging to the large sub-family of *Orthocoronavirinae*. The occasional

onset of uveitis or retinitis in feline and murine models has been described and linked to an underlying autoimmune process inducing vasculitis or to a viral-mediated inflammation.<sup>9–13</sup> Recent clinical and anatopathological reports have described the endothelial damage as one of the most prominent causes of the systemic vascular thromboembolic and/or inflammatory manifestations of COVID-19.<sup>32–34</sup> In this setting, the retina as a privileged district for non-invasive and *in vivo* evaluation of systemic diseases, may reveal alterations such as vascular occlusion related to the thrombotic susceptibility and chorioretinitis or vasculitis directly mediated by the virus. Hence, as reported in the brain, we considered the possibility of a direct ocular spread of SARS-CoV-2 through the two blood-retinal barriers (BRBs). In the recent literature on COVID-19 there are only anecdotal reports of virus spread through the blood-brain barrier.<sup>35–37</sup> Although two proven cases of positive CSF testing for SARS-CoV-2 have been described and one post-mortem, there is no certain data proving that the virus is able to directly affect central nervous system.<sup>38,39</sup> Our findings, on a cohort of subjects in different stages of the disease, including ICU patients, seem to demonstrate that the SARS-CoV-2 may not be able to cross the ocular BRBs. Furthermore, to the best of our knowledge, here we report the first attempt to isolate SARS CoV-2 in human aqueous humour.

With respect to the known thrombotic susceptibility described in COVID-19, we did not find any sign of retinal vascular involvement, such as venous or arterial occlusion. However, it should be considered that all patients in our cohort were treated with LMWH to prevent systemic vascular complications and only one patient addressed the criteria for DIC.

At the present time, there is only one report that described retinal lesions in a little cohort of asymptomatic SARS-CoV-2 positive patients. The authors found cotton-wool-like lesions and microhaemorrhages in 4 out of 12 patients and inner retinal OCT hyperreflective spots in the whole sample. However, apart from “normal blood parameters”, the authors did not provide any specific information enabling the clinical characterization of their patients. Indeed, no data regarding the presence of systemic comorbidities as well as no details regarding the patients’ ongoing therapy were given. Hence, it cannot be excluded that their findings may be ascribed to pre-existing non COVID-19-related systemic diseases affecting the retina, such as hypertensive or diabetic retinopathy or other infectious diseases.<sup>40–42</sup> In our cohort, largely composed of subjects with severe COVID-19, we merged retinal findings with baseline anamnestic. Nevertheless, our negative results should also be attributed to the ongoing immune modulating treatment, including steroids or Tocilizumab, that could have concealed ophthalmoscopic findings. Finally, with regard to the patient with chorioretinitis from fungal sepsis, it should be considered that severe COVID-19 patients, especially when hospitalized in an ICU setting, may be affected by super-infection due to several opportunistic pathogens with possible eye localization.<sup>43</sup>

Regarding the anterior segment findings, literature describes conjunctivitis as a part of the clinical manifestation of COVID-19 with a variable rate of presentation, going from 0 to 32%. Only in 4-7% of cases PCR revealed the presence of SARS-CoV-2 from conjunctival swab.<sup>17,19,31,44</sup> In all three patients presenting bilateral conjunctivitis that were observed in our study, the conjunctival swab was negative for

SARS-CoV-2. Nevertheless, since other viruses (e.g. herpes and adenovirus) are known to induce and have been detected in conjunctivitis<sup>45</sup>, we cannot exclude a transient presence of SARS-CoV-2 on the ocular surface at any time before or after our swab. Alternatively, conjunctivitis may represent an epiphomenon in hospitalized patients. Since it has been definitely demonstrated that COVID-19 affects the peripheral nervous system, as shown by the reported 85-88% rate of olfactory and gustatory dysfunction<sup>46</sup>, we investigated the possible involvement of trigeminal sensory pathways by exploring the corneal sensitivity. However, results of aesthesiometry seem to demonstrate that, unlike herpes viruses, SARS-CoV-2 does not affect corneal sensitivity.<sup>47</sup>

One strength of this cross-sectional study is to have explored posterior segment involvement in COVID-19 pneumonia patients at different stages of disease and in patients who had different comorbidities at the time of their hospitalization. Furthermore, considering our brief study period and the actual feasibility of an ophthalmological evaluation in an emergency setting, we obtained data from a relevant sample size even if a larger study population is probably necessary to confirm our findings. Among the shortcomings of our research it should be disclosed potential bias resulting from systemic therapies put in place before the ophthalmological evaluation, and those deriving from the exclusion of patients in CPAP therapy.

## Conclusion

In conclusion our study demonstrated the absence of retinal manifestations in SARS-CoV-2 pneumonia patients. Given the frequent drug-induced immunological dysfunction, ophthalmological evaluation may be useful to reveal systemic co-infections by opportunistic pathogens, especially in ICU patients.

## Declarations

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**Author contributions:** Conceptualization & Methodology MPP, MG; Investigation MPP, MG, AC, GV; Supervision GC, MG; Data curation GV, AC, GC; Validation CMM, FP, AL; Writing - original draft MG, GV, AC; Writing - review & editing MG, MPP, GC, GdE, AL.

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## Tables

**Table 1:** Baseline anamnestic and clinical characteristics of the 43 patients enrolled.

<b>Patients</b>	<b>n. 43 (%)</b>	<b>Median [IQR]</b>
Sex (Male)	25 (58.1%)	
Age		70 [59-78]
Male age		67 [60-76]
Female age		74 [57-85]
Days before hospitalization*		4.0 [3-6.5]
Days before screening**		21.5 [10-34]
CCI		1 [0-2]
Hypertension	22 (51.2%)	
Diabetes mellitus	8 (18.6%)	
CAD	7 (16.3%)	
COPD	7 (16.3%)	
CVA or TIA	6 (14.0%)	
PAD	5 (11.6%)	
CHF	4 (9.3%)	
AF	4 (9.3%)	
Dementia	4 (9.3%)	
Hemiplegia	2 (4.7%)	
Liver disease	2 (4.7%)	

**Table 2:** Cohort stratification using SIAARTI COVID-19 classification: paucisymptomatic disease (Stage I), mild pneumonia (Stage II), moderate to severe pneumonia (Stage III), acute respiratory distress syndrome (ARDS, Stage IV), sepsis (Stage V), septic shock (Stage VI).

<b>COVID-19 stage</b>	<b>Total n. 43 (%)</b>	<b>Male n. 25 (%)</b>	<b>Female n. 18 (%)</b>
I	0 (0%)	0 (0%)	0 (0%)
II	19 (44.2%)	9 (36%)	10 (55.6%)
III	9 (20.9%)	5 (20%)	4 (22.2%)
IV	11 (25.6%)	7 (28%)	4 (22.2%)
V	4 (9.3%)	4 (16%)	0 (0%)
VI	0 (0%)	0 (0%)	0 (0%)

**Table 3:** Overall inflammatory and coagulation status at the moment of ocular screening. Only one patient had suggestive criteria for Disseminated Intravascular Coagulation.

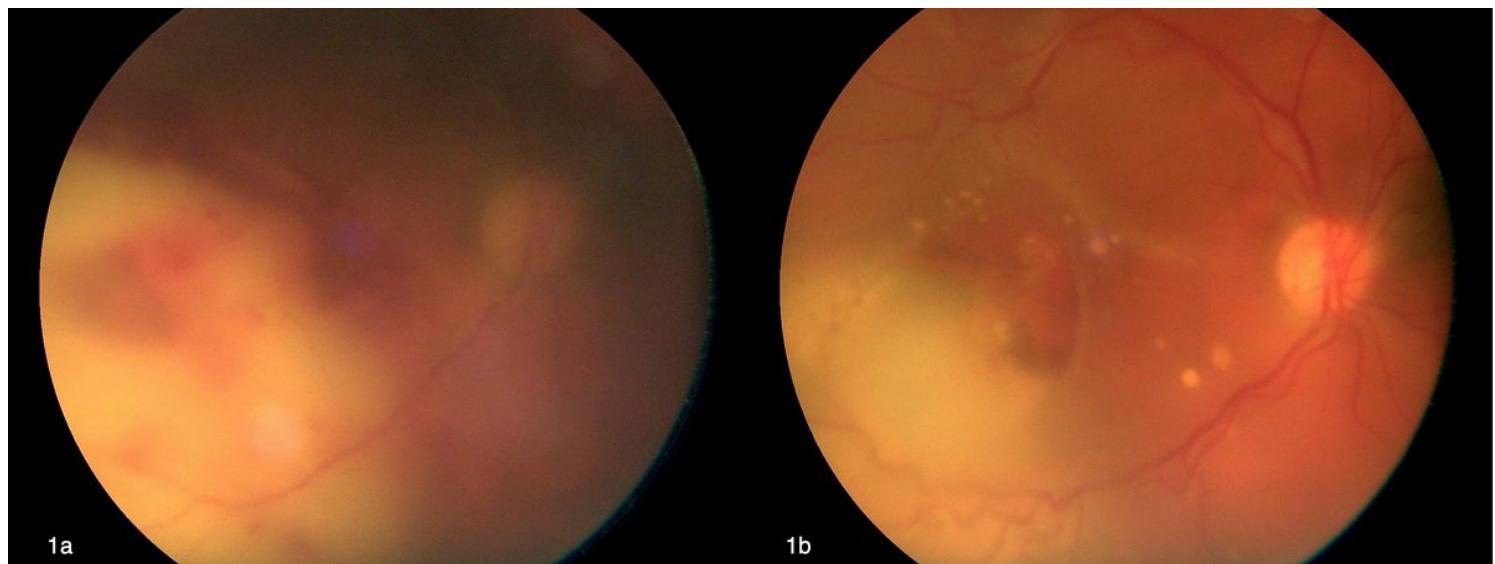
<b>Lab Tests</b>	<b>Median [IQR]</b>
WBC ( $\times 10^3/\mu\text{L}$ )	5.7 [4.1-6.8]
LYM ( $\times 10^3/\mu\text{L}$ )	0.720 [0.51-1.06]
PLT ( $\times 10^3/\mu\text{L}$ )	228 [172.5-270]
INR	1.0 [1.0-1.1]
PTT (sec)	28.6 [26.8-34.4]
Fibrinogen (mg/dL)	3.6 [2.7-5.6]
D-dimer ( $\mu\text{g/L}$ )	820.0 [389-1570]
PCR (mg/L)	4440 [550-22150]
ESR (mm/h)	33.0 [13-51.5]

WBC = White Blood Cells; LYM = Lymphocytes; PLTs = Platelets; INR = International Normalized Ratio; PTT = Partial Thromboplastin Time; CRP = C-Reactive Protein; ESR = Erythrocyte sedimentation rate.

**Table 4:** Anterior and posterior segments findings in the 43 enrolled patients.

Ocular findings	n (%)
Hypertensive retinopathy	4 (9.3%)
Conjunctival hyperemia	3 (7%)
Age-related Macular degeneration	2 (4.6%)
Diabetic retinopathy	1 (2.3%)
Chorioretinitis	1 (2.3%)

## Figures



**Figure 1**

Fundus image of the patient with unilateral chorioretinitis at time of first eye examination (a) showing an area of deep chorioretinal exudation involving the posterior pole, associated with deep retinal haemorrhages. Fundus image of the same eye 3 weeks after IV amphotericin B, the extent of the chorioretinal lesion is reduced, with sharper margins and pigment mottling at both the subretinal and sub-RPE level (b).