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Effect of COVID-19 pandemic on glaucoma

Neslihan Sevimli[1], Işılay Ozsoy Saygin[2], Efe Saygin[3]

[1]*Department of Ophthalmology, Fatih Sultan Mehmet Training and Research Hospital, Ataşehir, İstanbul, Türkiye*

[2]*Department of Ophthalmology, Ümraniye Training and Research Hospital, Ümraniye, İstanbul, Türkiye*

[3]*Department of Ophthalmology, Istanbul Medipol University, Istanbul, Türkiye*

ABSTRACT

Aim: To observe the course of glaucoma progression after coronavirus disease 2019 (COVID-19) treatment of patients with glaucoma.

Methods: This observational case-control study included a total of 74 patients with COVID-19 infection who were diagnosed with glaucoma previously. The study focused on the left eye of 37 patients each was treated as an inpatient (group 1) or outpatient (group 2). Age, gender, existence of systemic and ocular diseases, symptoms, laboratory results, drugs used for COVID-19 and glaucoma, length of hospital stay, intraocular pressure (IOP), and central corneal thickness (CCT) values were recorded. Peripapillary retinal nerve fiber layer thickness (*pp*RNFLT), ganglion cell–inner plexiform layer complex thickness (GCIPLT), and vertical cup-disc (C-D) ratio results were compared before and after COVID-19 treatment in both groups.

Results: A significant increase was observed in IOP and a significant decrease was observed in GCIPLT in both groups (groups 1 and 2 for both values $p<0.01$ and $p=0.02$, respectively) after COVID-19 infection. In both groups, the mean difference (MD) for IOP and GCIPLT values were higher in group 1. Although *pp*RNFLT values decreased in both groups, a significant decrease was observed in group 1 after COVID-19 infection ($p=0.03$). The mean C-D ratio was higher after COVID-19 infection in groups 1 and 2. ($p=0.04$ and $p=0.051$, respectively). CCT did not show a significant difference in either group ($p>0.05$).

Conclusion: *Pp*RNFLT and GCIPLT values were reduced and IOP and C-D ratio values were increased in glaucoma patients after COVID-19 infection. Infection progression was observed to be worse in the inpatient group.

Key words: Coronavirus, COVID-19, glaucoma, intraocular pressure, optical coherence tomography.

✉ *Dr. Neslihan Sevimli,*
Department of Ophthalmology, Fatih Sultan Mehmet Training and Research Hospital, Ataşehir, İstanbul Türkiye
E-mail: neslihandumanli@gmail.com
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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is the causative agent of the coronavirus disease (COVID-19), which affects the whole world, attaches to the angiotensin-converting enzyme 2 (ACE-2) receptors, which are common in the whole body, especially in the respiratory system [1]. The pandemic coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has several ocular findings [2-5].

Ocular complications associated with COVID-19 are mild and self-limiting [5]. Subtle retinal changes like hyperreflective

lesions at the level of the ganglion cell-inner plexiform layers (GCIPL) on optical coherence tomography (OCT), cotton-wool spots, and microhemorrhages have also been reported [2,3,6].

Glaucoma is defined as structural damage to the optic nerve (ON) which is associated with functional damage to be indicated by visual dysfunction. In clinical trials of glaucoma, peripapillary retinal nerve fiber layer thickness (*pp*RNFLT), macular ganglion cell–inner plexiform layer complex thickness (GCIPLT), and vertical cup-disc (C-D) ratio are a reliable clinical index of glaucomatous damage to the neuro-retinal rim. These factors help clinicians to investigate glaucoma progression by using OCT [7].

The primary objective of this study is to evaluate the effect of COVID-19 on glaucoma disease and detect any progression using trend analysis of *pp*RNFLT, GCIPLT, and C-D ratio measured by OCT. The secondary objective is to study the relationship between macular and ON findings and the severity of COVID-19 or medications for COVID-19.

Materials and methods

This multicentric observational case-control study was conducted by the Declaration of Helsinki and was approved by the Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital Research Ethics Committee (IRB number is 116.2017.R-220). Informed written consent was obtained from all patients before their enrollment in this study.

Between 01.01.2020 and 15.04.2021, 74 patients who were treated with COVID-19 (both inpatient and outpatient) and who were also followed up for primary open-angle glaucoma were screened from the hospitals' patient databases. Thirty-seven (n=37, 50%- group 1) patients were hospitalized as an inpatient for treatment of COVID-19 infection and 37 patients (n=37, %50- group 2) were treated as outpatients in the emergency room. COVID-19 infection was confirmed by nasopharyngeal and oropharyngeal swabs positive for the reverse transcriptase polymerase chain reaction (PCR). In the case of negative PCR, the decision was made according to the computerized tomography (CT) results and the patient's clinic. Patients younger than 18 years of age, who have a glaucoma follow-up for less than 2 years, patients with unstable, seconder or advanced stage glaucoma, without peripapillary and macular OCT before or after COVID-19, and with other ocular or neurological disease that may affect the macula and ON were excluded from the study.

All patients continued to use their glaucoma medications at the same time as long as they were hospitalized or at home.

All clinical data concerning the COVID-19 infection, diagnosis, and clinical course of glaucoma were obtained by consulting patients' records. Age, gender, systemic and ocular diseases, symptoms, laboratory results, drugs used for COVID-19 and glaucoma, length of hospital stay, IOP values, and central corneal thickness (CCT) were recorded. The IOP and CCT measurements were taken with a Cannon TX-20 tonometer (Canon Inc., Tokyo, Japan) at a fixed time from 8:00 a.m. to 9:00 a.m. to minimize the effect of diurnal variations. Structural OCT analysis was performed by two different expert physicians who used the same device, Spectral Domain Cirrus 5000-HD-OCT (Carl Zeiss, Meditec, Inc., Dublin, CA, USA), and an average of 3 measurements were taken. All global *pp*RNFLT measurements were made using a circular scan pattern with a diameter of 3.4 mm positioned in the middle of the optic disc center. Macular OCT was performed using a dense macular cube protocol, where an area

of 512x128 mm on the retina was scanned. The values of *pp*RNFLT, GCIPLT, and C-D ratio were assessed on OCT scans before and after COVID-19 infection.

The primary endpoint was a difference in the OCT variables before and after treatment of COVID-19 infection. We performed an additional analysis after the COVID-19 infection correlating the primary outcome measures with the other variables examined to detect potential risk factors for OCT variables impairment in glaucoma and COVID-19 patients.

Statistical analyses were performed using SPSS Statistics for Mac version 26 (IBM Corp., Armonk, NY). Continuous variables are presented as mean and standard deviation (SD) for normal distribution and those which are not normally distributed are typically presented in terms of median and interquartile range. Numbers and percentages are used to define categorical variables. Differences in age and sex between groups were compared using the Chi^2 test and t-student test. The normal distribution of the data was evaluated by performing the Shapiro-Wilk test.

For the primary objective, analysis of the data with a normal distribution was evaluated via Student's t-test, and data without a normal distribution were evaluated by using the Mann-Whitney U test. Repetitive measures were compared with a paired-sample t-test for data with a normal distribution and a Wilcoxon test for data without a normal distribution. A *P*-value below 0.05 was accepted as statistically significant.

Results

In our study, out of 37 glaucoma patients who were hospitalized for COVID-19 (group 1), 20 (54%) were male, 17 (46%) were female, and the mean age was 58.43 ±10.41 years. Of 37 glaucoma patients treated in the emergency department (group 2), 14 (38%) were male, 23 (62%) were female, and the mean age was 57.43 ±10.64 years. There was no significant difference between the groups regarding age and gender (p=0.684 and 0.160, respectively). The medical history showed that the prevalence of systemic arterial hypertension (HT), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), and coronary artery

Table 1. Analysis of descriptive data of the patients.

Variables	**Inpatients (Group 1)**	**Outpatients (Group 2)**	***p* value**
Age (years, mean ± SD)	58.43 (±10.41)	57.43 (±10.647)	0.684*
Sex	M= 20/37 (54%)	M=14/37 (38%)	0,16**
	F= 17/37 (46%)	F=23/37 (62%)	
Medical History			
DM	15/37 (40,5%)	14/37 (37,8%)	0,81**
HT	10/37 (27%)	10/37 (27%)	1**
COPD	3/74 (8,1%)	0/37 (0%)	0,24**
CAD	1/37 (2,7%)	7/37 (18,9%)	0,56**
PCR	32/37 (86,5%)	33/37 (89,2%)	1*

*DM, diabetes mellitus; HT, hypertension; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; PCR, polymerase chain reaction; *Independent samples t test; ** Chi-square test.*

disease (CAD) was 27%, 37.8%, 0%, and 18.9%, respectively in the outpatient group while it was 27%, %40.5, 8.1% and 2.7%, respectively in the inpatient group. There was no difference between the groups in terms of the prevalence of systemic diseases (p>0.05). The PCR result of 65 patients (87.8%) was positive. Nine patients (12.2%) were diagnosed with COVID-19 based on CT results and clinical findings. There was no significant difference between groups regarding PCR results (p=1) (Table 1).

There was no difference between the groups in terms of IOP, CCT, *pp*RNFLT, GCIPLT, and vertical c-d ratio before COVID-19 infection (p>0.05). While there was a significant increase in IOP values after COVID-19 infection in both groups compared to before COVID-19 (p<0.01 for group 1, p=0.02 for group 2), there was a significant decrease in GCIPLT values (p<0.01 for group 1 and p=0.02 for group 2). The mean difference (MD) was greater in group 1 for IOP (-1.76 and -0.81 for groups 1 and 2, respectively) and GCIPLT values (2.72 and 1.21 for groups 1 and 2, respectively).

While the *pp*RNFLT value decreased in both groups after COVID-19 infection, the increase in group 1 was statistically significant (p=0.03). While the vertical C-D ratio increased in both groups after COVID-19, a statistically significant increase was observed in group 2 (p=0.04). CCT did not differ significantly in both groups before and after COVID-19 (p>0.05) (Table 2).

The mean time between the end of COVID-19 treatment and the eye examination was 6.20 ± 3.63 months. The average hospitalization period was 10.77 ± 12.01 days. Three patients in the inpatient group (8.10%) were required to be taken into the intensive care unit.

All patients were treated with favipiravir and outpatients received only favipiravir therapy (200 mg tablet 2×8 loading dose, 2×3 tablets/day maintenance dose for the following 4 days, a total of 5 days of treatment). All patients in the inpatient group were treated with anticoagulant therapy (Enoxaparin sodium 4000 IU 1x1 subcutaneous). In the inpatient group; 26 patients (70.3%) were treated with hydroxychloroquine (200 mg 2×1 tablets/day),

Table 2. Analysis of the OCT parameters of study groups according to COVID-19 period.

Variables	Before COVID-19	After COVID-19	*p* value	MD
Inpatients (group 1)				
IOP (mmHg)	16,69 ± 0,34	18.50 ± 3.55	**<0,01***	-1,76
CCT (µm)	533.45 ± 65.86	525.71 ± 36.90	1*	
*pp*RNFLT (µm)	111.32 ± 19.31	105.86 ± 16.52	**0,03****	4,94
GCIPLT (µm)	82.05± 9.62	79.05 ± 9.6	**<0,01****	2,72
C-D ratio	0.56 ± 0.19	0.59 ± 0.19	**0,051****	-0,34
Outpatients (group 2)				
IOP (mmHg)	16.05 ± 3.14	16.86 ± 3.07	**0,02***	-0,81
CCT (µm)	544.59 ± 58.8	547.41 ± 41.87	0,31*	
*pp*RNFLT (µm)	107.62 ± 16.86	106.59 ± 16.52	0,23**	1,02
GCIPLT (µm)	85.43 ± 7.73	84.21 ± 11.86	**0,02***	1,21
C-D ratio	0.58 ± 0.18	0.62 ± 0.18	**0,04****	-0,41

OCT, optical coherence tomography; IOP, intraocular pressure; CCT, central corneal thickness; ppRNFLT, peripapillary retinal nerve fiber layer thickness; GCIPLT, ganglion cell layer internal plexiform layer thickness; -D, cup disc. MD: mean difference
**Wilcoxon test. **Paired samples t test. Significant differences are shown in bold.*

17 patients (45.9) were treated with colchicine (0.5 mg 2x1 tablet/day), 17 patients (45.9%) were treated with low dose corticosteroids (1 mg/kg/day) 4 patients (10.8%) were treated with pulse steroid (1 gr) and 2 patients (5.4%) were treated with interleukin-6 inhibitor (Tocilizumab).

All patients had primary open-angle glaucoma and were treated with a maximum of 3 drugs. All patients were in a stable stage of the disease and there were no patients with severe or advanced glaucoma. Thirty-three patients (44.6%) were treated with only selective alpha (2)-adrenoceptor agonist (Brimonidine); 4 patients (5.4%) were treated with only a prostaglandin analog and other patients were treated with combination therapy with beta-blocker and carbonic anhydrase inhibitors. Age distribution showed an inverse linear correlation with *pp*RNFLT and GCIPLT values after COVID-19 (p=0.03, $p < 0.001$, respectively). There was no significant difference between systemic medical history and drugs in COVID-19 treatment and OCT parameters (p>0.05).

Discussion

According to our results, *pp*RNFLT and GCIPLT values decreased after COVID-19 treatment in both groups, whereas IOP and C-D ratio values increased. When the two groups were compared, the change was more in the inpatient group. Although there are studies investigating the eye findings of COVID-19 in the literature [6,8-11], to our knowledge, it is the first study investigating the impact of COVID-19 on glaucoma patients.

COVID-19 systemic inflammatory reaction is characterized by a life-threatening hyper-inflammation sustained by a cytokine storm, eventually leading to thrombotic microangiopathy, vascular endothelial injury, and ischemic processes triggered by hypercoagulability. In addition to the thrombotic and inflammatory process, direct viral toxicity also plays a role in the pathogenesis [4,5,12].

Since SARS-Cov-2 can be detected in the retina, retinal findings of COVID-19 infection are deemed to be valuable [6,8-11]. Marinho et al. had found lesions at the ganglion cell-inner plexiform layers of patients with COVID-19 [6]. Studies suggest that retinal lesions could include optic neuritis [6], an increase in the incidence of ischemic or inflammatory optic neuropathies[12,13], retinal vasculitis, retinal degeneration, and blood–retinal barrier breakdown and ischemia [14]. We have not found any retinopathy in fundoscopy, this could be because of routine anticoagulant treatment in all hospitalized patients.

OCT is a noninvasive imaging technique that measures the *pp*RNFLT, macular GCIPLT, and C-D ratio, providing a comprehensive analysis of the ON for assessing glaucoma progression [11]. The retinal nerve fiber layer (RNFL) of the retina contains the non-myelinated axons of retinal ganglion cells that form the optic nerve. While the visual field is affected at a later stage of glaucoma, the macula is often involved early in the glaucomatous process. The study showed that both *pp*RNFLT and macular GCIPLT measures show faster loss rates in glaucomatous eyes [15].

Similar to our study, Oren et al. found that mean GCIPLT and *pp*RNFLT values were significantly lower in the COVID-19 patients. In the same study, they found the mean central macular thickness value was significantly higher in the COVID-19 patients. But unlike us, their study was not done only in glaucoma patients [8].

Ornek et al. found a significant thinning in the inferonasal sector of *pp*RNFLT in patients

with COVID-19. They suggested that it may be localized pathology rather than being a diffuse axonal injury [9]. In another study, superonasal and inferotemporal sectors of *pp*RNFLT were lower in patients with COVID-19 who suffer ocular pain compared to patients without ocular pain [10]. In our study, we did not check segmental defects, rather, we evaluated the global *pp*RNFLT, and all patients were also glaucoma patients.

Pappazoglu et al. reported no relevant changes in IOP values, best-corrected visual acuity (BCVA), and OCT variables in patients with COVID-19. They assessed the aggravation of pre-existing hyperglycemia and found that HT led to retinal alterations rather than direct viral cytotoxic effects or inflammatory responses. They suggested close monitoring for retinopathy underlying cardiovascular diseases in patients with COVID-19 [4]. We did not find a significant correlation between systemic diseases and OCT parameters. Although there was a decrease in both groups, impairment in OCT parameters is more evident in the inpatient group. The condition may depend on the severity of hypoxia and ischemia of the disease. Contrary to our study, some studies show an increase in *pp*RNFLT and macular GCIPLT in COVID-19 patients compared to the control group. They suggested that the increases observed in their study could be due to acute damage of inflammation, which could turn into atrophy in the long-term [11].

We found higher IOP values after COVID-19 in both groups. As COVID-19 is a systemic inflammatory syndrome, damage to trabecular meshwork function or anterior uveitis may lead to an increase in the IOP [5,16]. In addition, systemic corticosteroid (CS) treatment, regardless of route, used to manage COVID-19 or topical CS for uveitis may raise IOP. Risk is lower with systemic CS compared to that of topical, intraocular, and periocular routes [16]. What's more, the CS effect persisted until the first month, with a gradual decrease in the second and third month [17]. In our study, no correlation was observed between steroid and glaucoma progression. Systemic CS was used for a short time only in the inpatient group, and the patients were followed up at least 2 months after they were discharged.

In our study, all patients diagnosed with COVID-19 were treated with favipiravir, an RNA polymerase inhibitor that inhibits the proliferation of SARS-CoV-2, to accelerate the improvement of lung infection findings and reduce the clinical recovery period [18].
Hydroxychloroquine (HCQ) was used to shorten the time to clinical recovery and promote the resolution of pneumonia [9] in our inpatient group. It is known that HCQ leads to bilateral maculopathy characterized by a ring of parafoveal RPE depigmentation that initially spares the fovea [2]. Various studies, including ours, showed that HCQ use does not produce a toxic effect on GCIPL or RNFL during COVID-19 infection [11,19]. Since HCQ increases the risk of QT prolongation and ventricular arrhythmia, it should be used with caution when accompanied by topical anti-glaucomatous beta-blocker (e.g., Timolol), another drug that causes bradycardia, hypotension, and atrioventricular block. It would be advisable to consider discontinuing topical treatment with these eye drops in COVID-19 patients and replace them with other anti-glaucoma therapy options such as eye drops with prostaglandin analogs or carbonic anhydrase inhibitors, as well as considering laser trabeculoplasty, if the patient's general condition allows it [20].

Due to risk factors like invasive mechanical ventilation, prone position, and multiresistant bacterial exposure, Intensive care unit (ICU)

patients may develop IOP elevation [2]. In ICU patients, acute angle-closure glaucoma can be observed by the prone position and use of drugs such as anticholinergics and sympathomimetics [21]. In our study, only 2 patients were followed up in ICU. The IOP levels were stable and angle closure did not occur.

During the COVID-19 pandemic, protecting public health and preventing the spread of the virus is as important as preventing glaucoma progression [22]. Reports suggest that the ocular surface could serve as a reservoir for viral transmission and an access point via exposure to aerosolized droplets or hand-eye contact [2].

During glaucoma examination, disposable tonometers with single-use protective tips (i.e., Tonopen, Perkins tonometer) or noncontact instruments (i.e., Ocular response analyzer) should be used. Pneumotonometers can presumably aerosolize the tear film and viral particles may need to be avoided [23]. Telemedicine has been increasingly implemented in glaucoma practices to reduce in-patient volume. New data regarding the efficacy and feasibility of tools for home monitoring of IOP, virtual visual field (VF) testing, and remote disc photography are reviewed. Innovative modifications to reduce viral transmission and optimize patient and staff safety in the office and operating room are under development [24].

This study had certain limitations. Patients had no visual field assessment after COVID-19 treatment. Visual field test is not recommended in some studies because it takes a long time and increases the risk of transmission [25].

The lack of instant effect of COVID-19 due to the long period between COVID-19 recovery and ophthalmic evaluation, small sample size, and non-normal age distribution between groups were other limitations of this study.

In conclusion, this study demonstrated convincing evidence that COVID-19 infection can affect glaucoma patients both anatomically and functionally. Previous studies included COVID-19 patients without glaucoma. COVID-19 may be exacerbating the damage already present with glaucoma. The severity of hypoxia, ischemia of the COVID-19 disease, and age may have a worsening effect on the progression of glaucoma. Retinal imaging by OCT is a non-invasive technique that shows retinal layers and ON for glaucoma progression that might be detected during the COVID-19 period. In our study, while *pp*RNFLT and GCIPLT decreased, the IOP and C-D ratio increased in patients. Management of glaucoma patients with COVID-19 should include retinal assessment, with a close follow-up; especially in elderly patients and in patients with severe symptoms of the disease. Glaucoma patients should be warned that glaucoma may be affected by COVID-19 and the drugs used during treatment. Further studies are required to evaluate the permanent and long-term effects of COVID-19 on glaucoma patients.

Abbreviations

COVID-19: coronavirus disease 2019
IOP: intraocular pressure
CCT: central corneal thickness
ppRNFLT: peripapillary retinal nerve fiber layer thickness
RNFL: retinal nerve fiber layer
GCIPLT: ganglion cell–inner plexiform layer complex thickness
GCIP:, ganglion cell–inner plexiform layer
C-D ratio: cup-disc ratio
MD: mean difference
OCT: optical coherence tomography
ON: optic nerve
CS: corticosteroid

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