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The Course of Glaucoma in Recovered COVID-19 Patients

Neslihan Sevimli (neslihandumanli@gmail.com)
Fatih Sultan Mehmet Eğitim Ve Araştırma Hastanesi
Işılay Özsoy Saygın
Ümraniye Eğitim ve Araşıtırma Hastanesi
Efe Saygın
Istanbul Medipol University

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Abstract

Purpose

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

Design

Multicentric observational case-control study

Materials and Methods

This observational case-control study included total 74 patients with COVID-19 infection who were diagnosed with glaucoma previously. The study focused on the left eye of 37 patients each were treated as inpatient or outpatient. 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 (pre-COVID-19) and after (post-COVID-19) COVID-19 treatment in both groups.

Results

A significant increase was observed in IOP values in both inpatient and outpatient groups ($p = 0,02$, $p < 0,01$ respectively) after COVID-19 infection. However, mean difference (MD) was higher in inpatient group for IOP levels (-1,76). Inpatient and outpatient groups showed statistically significant decrease in GCIPLT values post-COVID-19 ($p < 0,01$ and $p = 0,02$, respectively). In addition, MD value was higher in inpatient group (2,72). A significant decrease was observed in *pp*RNFLT values in inpatient group after COVID-19 infection ($p = 0,03$). In both groups, the mean C-D ratio was higher post-COVID-19.

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 observed to be worse in inpatient group.

Introduction

The pandemic coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has several ocular findings [1, 2, 3].

Ocular complications associated with COVID-19 are mild and self-limiting [4]. 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 [1, 2]..

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 reliable clinical index of glaucomatous damage to the neuro-retinal rim. These factors help clinicians to investigate glaucoma progression by using OCT [5].

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 relation between macular and ON findings and severity of COVID-19 or medications for COVID-19.

Methods

This multicentric observational case-control study was approved by Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital Research Ethics Committee (116.2017.R-220) and was conducted in accordance with the Helsinki Declaration. All patients have been provided with information and their written consent was obtained.

Between 01.01.2020 and 15.04.2021, 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. COVID-19 infection was confirmed by nasopharyngeal and oropharyngeal swabs positive for the reverse transcriptase polymerase chain reaction (PCR). In 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 has a glaucoma follow-up for less than 2 years, patients with unstable or advance 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 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) values for left eye were recorded. Structural OCT analysis was performed by an expert physician who used Spectral Domain Cirrus 5000-HD-OCT (Carl Zeiss, Meditec, Inc., Dublin, CA, USA) and Revo 80 (Optopol, Poland). All global *pp*RNFLT measurements were made using a circular scan pattern with a diameter of 3.4 mm positioning on 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 value 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 within the post-COVID-19 period 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 by 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 Chi2 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 were 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. *P*-value below 0.05 was accepted as statistically significant.

Results

In our study, we screened 74 eyes of 74 glaucoma patients; 37 (50%) of whom were treated as outpatient in the emergency room while 37 (50%) of whom were admitted for a treatment of COVID-19 infection.

Among the 37 outpatient subjects included, 14 patients (38%) were male and 23 patients (62%) were female, with a mean age of 57.43 (± 10.647). Twenty patients (54%) were male, and 17 patients (%46) were female with mean age of 63.65 (± 10.605) in the inpatient group. There was significant difference between the outpatient and inpatient groups for age (p = 0,014) and there was no significant difference between groups for gender distribution (p = 0,16). The medical history showed that the prevalence of systemic arterial hypertension (HT), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD) and coronary artery disease (CAD) was 27%, 37,8%, 0% and 18,9%, respectively in outpatient group while it was 27%, %40,5, 8,1% and 2,7%, respectively in inpatient group. When we examined the ocular history, the prevalence of diabetic retinopathy (DR) and cataract was 18,9% and 8,1%, respectively in outpatient group and %18,9% and 37,8%, respectively in inpatient group. There was no significant difference between groups for systemic medical history while the number of patients with cataracts in inpatient group was significantly higher than the outpatient group (p = 0,02). The PCR result of 65 patients (87,8%) was positive. Nine patients (12,2%) were diagnosed as COVID-19 based on CT results and clinical findings. There was no significant difference between groups in terms of PCR results (p = 1) (Table 1).

Table 2 shows the distribution and analysis of the OCT parameters in the outpatient and inpatient group (Table 2). The median (interquartile range) IOP value pre-COVID-19 (17 (3,75)) and post-COVID-19 (18,5 (7)) showed a statistically significant increase in inpatient group (p=0,04)). Post-COVID-19, GCIPLT value was 84 µm (10,5) in outpatient group and 79,05 ± 9,6 µm in inpatient group. Inpatient group showed statistically significant decrease in GCIPLT values post-COVID-19 (p<0,01).

Table 3 shows the distribution and analysis of the OCT parameters of study groups before or after COVID-19 treatment (Table 3). There was a significant decrease in the post-COVID-19 GCIPLT values in outpatient and inpatient groups compared to pre-COVID-19 (p=0,02 and p<0,01, respectively). Mean difference was higher in inpatient group for GCIPLT values (2,72). In the outpatient group, IOP and C-D ratio values were higher post-COVID-19 (p=0,02 and p=0,04, respectively). Meanwhile, IOP values measured post-COVID-19 were higher in inpatient group (p<0,01). The mean difference between pre- and post-COVID-19 IOP values (-1,76) was higher in inpatient group. In the outpatient and inpatient groups, mean C-D ratio values were higher post-COVID-19, the difference was significant only in outpatient group (p=0,04) although the value of mean difference was still close in both groups.

Representative images of ppRNFL and GCIPL of the patients shown in Figs. 1 and 2, respectively.

The mean time between the end of COVID-19 treatment and the eye examination was 6,20 ± 3,63 months. Average hospitalization period was 10,77 ± 12,01 days. Three patients in inpatient group (8,10%) required to be taken into intensive care unit.

All patients were treated with favipiravir and outpatients received only favipiravir therapy. All patients in the inpatient group were treated with anticoagulant therapy. In inpatient group; 26 patients (70,3%) were treated with hydroxychloroquine, 17 patients (45,9) were treated with colchicine, 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 treated with 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 post-COVID-19 (p = 0,01, p = 0,01, p < 0.001, p < 0.001, respectively) and positive correlation with cataract (p = 0,02). There was no significant difference between systemic medical history and drugs and OCT parameters.

Discussion

According to our results, while RNFLT and GCIPLT values decreased after COVID-19 treatment in both outpatient and inpatient groups, whereas IOP and C-D ratio values increased. When the two groups were

compared, the change was more in the inpatient group. 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 cytokines 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 pathogenesis [3],[6].

Since SARS-Cov-2 can be detected in the retina, retinal findings of COVID-19 infection are deemed to be valuable. Marinho et al. had found lesions at the ganglion cell-inner plexiform layers of patients with COVID-19 [7]. Studies suggest that retinal lesions could include optic neuritis [2], an increase in the incidence of ischemic or inflammatory optic neuropathies [8], retinal vasculitis, retinal degeneration and blood–retinal barrier breakdown and ischemia [9]. 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 [10]. The retinal nerve fiber layer (RNFL) of the retina contains the non-myelinated axons of retinal ganglion cells that form the optic nerve. While visual field is affected at a later stage of glaucoma, macula is often involved early in the glaucomatous process. The study showed that both *pp*RNFLT and macular GCIPLT measures show faster rates of loss in glaucomatous eyes [11, 12].

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 [13].

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 [14]. 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 [15]. In our study, we did not check segmental defects, rather, we evaluated the global *pp*RNFLT.

Decreases in RNFLT have been described with age in healthy individuals [16]. In our study, although there was a decrease in both groups, impairment in OCT parameters is more evident in inpatient group. The condition may depend on the severity of hypoxia and ischemia of the disease as well as being age-related since the age of the patients in the inpatient group was significantly higher.

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 that aggravation of pre-existing hyperglycemia and found that HT led to the 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 [3]. We did not find a significant correlation between systemic diseases and OCT parameters.

Contrary to our study, there are studies that show an increase in *pp*RNFLT and macular GCIPLT of COVID-19 patients compared to control group [10],[17]. The only results that showed a decrease in *pp*RNFL and GCIPLT was the one with glaucoma. 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 [10].

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 [4],[18]. 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 [18]. What's more, CS effect persisted until the first month, with a gradual decrease in the second and third month [19]. In our study no correlation was observed between steroid and glaucoma progression. Systemic CS were used for a short time for only in inpatient group, and the patients were followed up at least for 2 months after they were discharged.

Hydroxychloroquine (HCQ) was used to shorten the time to clinical recovery and promote the resolution of pneumonia 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 [1]. Various studies, including ours, showed that HCQ use does not produce a toxic effect on GCIPL or RNFL during COVID-19 infection [10][20]. 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 analogues or carbonic anhydrase inhibitors, as well as considering laser trabeculoplasty, if the patient's general condition allows it [21].

Due to risk factors like invasive mechanical ventilation, prone position, and multiresistant bacterial exposure, Intensive care unit (ICU) patients may develop IOP elevation [1]. In ICU patients, acute angle-closure glaucoma can be observed by the prone position and use of drugs such as anticholinergics and sympathomimetics [1], [22, 23]. In our study, only 2 patients were followed up in ICU. The IOP levels were stable and angle closure did not occur.

During COVID-19 pandemic, protecting public health and preventing the spread of the virus are as important as preventing glaucoma progression [24]. 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 [1].

During glaucoma examination, disposable tonometers with single-use protective tips (ie, Tonopen, Perkins tonometer) or noncontact instruments (ie, Ocular response analyzer) should be used. Pneumotonometers can presumably aerosolize the tear film and viral particles may need to be avoided.

Some institutions may require the use of single-use gonioscopy [25, 26]. 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 [27].

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 [28].

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 the 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. 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 COVID-19 period. In our study, while RNFLT and GCIPLT decreased, 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 effect of COVID-19 on glaucoma patients.

Declarations

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Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital Research Ethics Committee (116.2017.R-220)

Competing Interests: The authors have no relevant financial or non-financial interests to disclose

Author Contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Işılay Özsoy Saygın. All figures and tables were prepared by Efe Saygın. The first draft of the manuscript was written by Neslihan Sevimli and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Consent to participate: Informed consent was obtained from all individual participants included in the study

Consent to publish: The authors affirm that human research participants provided informed consent for publication of the images in Figures.

Conflicting Interest:

Neslihan Sevimli declares that she has no conflict of interest.

Işılay Özsoy Saygın declares that he has no conflict of interest.

Efe Saygın declares that he has no conflict of interest.

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Tables

Tables 1 to 3 are available in the Supplementary Files section.

Figures

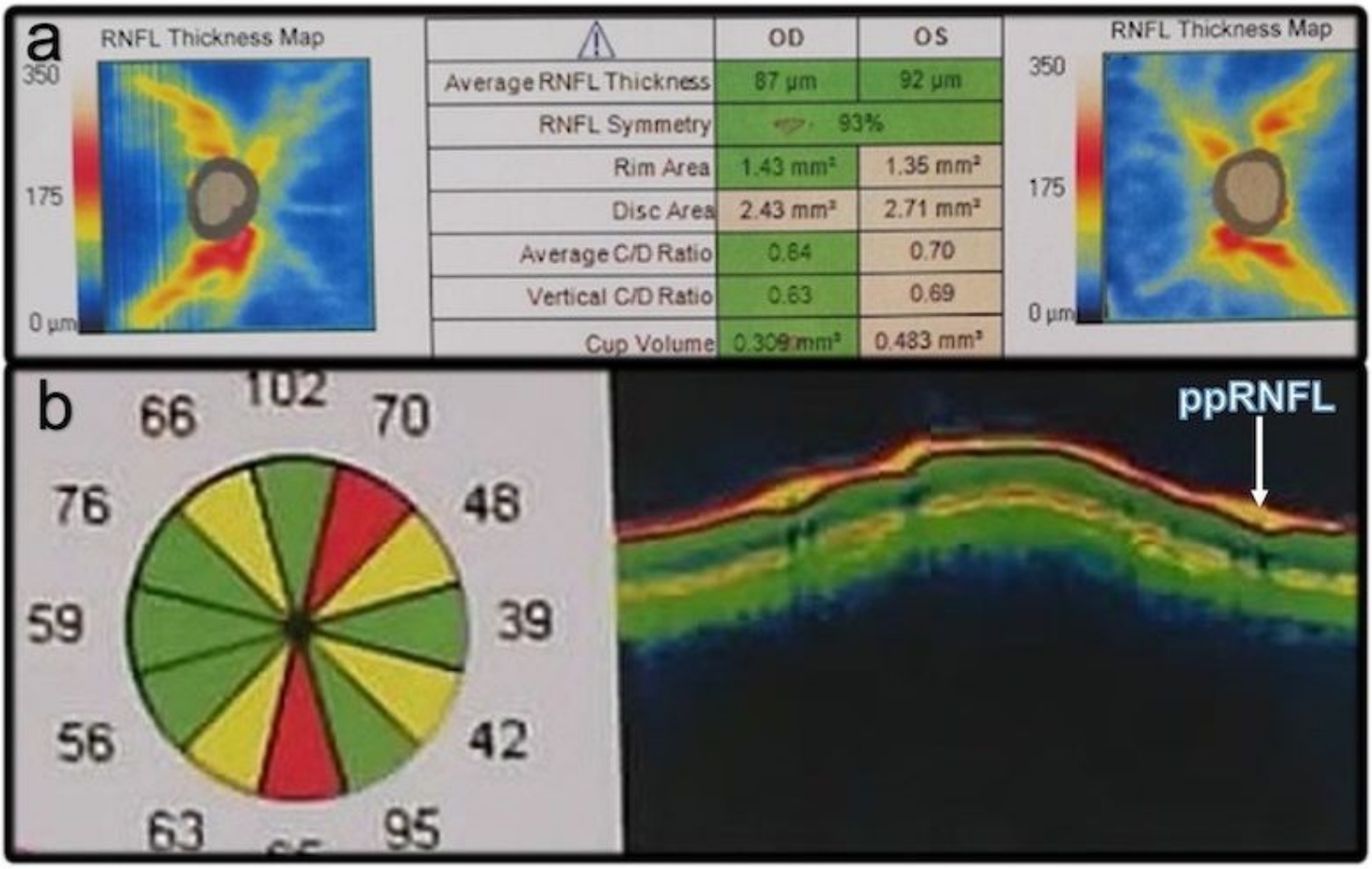


Figure 1

a- Analysis of *pp*RNFL*, including vertical C-D** ratio. **b-** PpRNFL thickness of all quadrants was included in the study, *pp*RNFL indicated by arrow.

*peripapillary retina nerve fiber layer

**Cup-disc

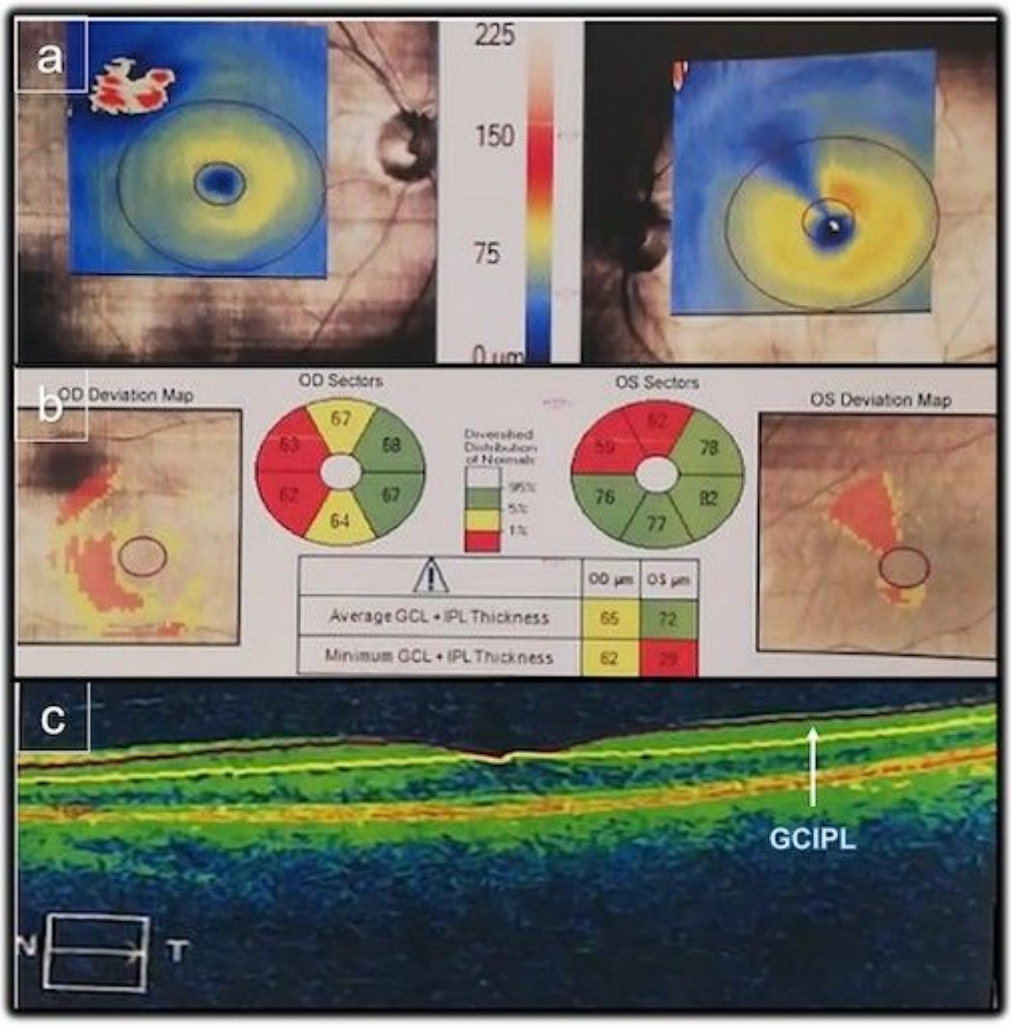


Figure 2

a- GCIPL* thickness map. **b-** GCIPL deviation map. **c-** A view of macula OCT**scan included in the study, GCIPL indicated by arrow.

*Ganglion cell-inner plexiform layers

**Optical coherence tomography

Supplementary Files

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- Tables.docx