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RELATIONSHIP BETWEEN OCULAR FINDINGS AND LABORATORY DATA IN PATIENTS WITH HOSPITALIZED COVID-19 PATIENTS

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Abstract

Purpose To investigate the relationship between laboratory blood parameters and ocular findings in hospitalized moderate or severe COVID-19 patients. Methods Ophthalmologic examination of 215 patients who were hospitalized with the diagnosis of COVID-19 was performed in their beds and their ocular findings were noted. Blood parameters were compared in patients with and without conjunctivitis like symptoms. Results Conjunctivitis like inflammatory findings were detected in 15 (7.44%) of 215 moderate or severe COVID-19 patients. There was no difference between the patients with and without ocular findings in terms of laboratory findings such as WBCs, neutrophil counts, lymphocyte counts, NLR, LDH, procalcitonin, D-dimer, CRP, and ferritin. Conclusion There was a significant relationship between COVID-19 and an acute conjunctival inflammatory response. Blood parameters that determined progression in patients with COVID-19 were not significant in terms of ocular findings.

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ABSTRACT

Purpose

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Methods

Ophthalmologic examination of 215 patients who were hospitalized with the diagnosis of COVID-19 was performed in their beds and their ocular findings were noted. Blood parameters were compared in patients with and without conjunctivitis like symptoms.

Results

Conjunctivitis like inflammatory findings were detected in 15 (7.44%) of 215 moderate or severe COVID-19 patients. There was no difference between the patients with and without ocular findings in terms of laboratory findings such as WBCs, neutrophil counts, lymphocyte counts, NLR, LDH, procalcitonin, D-dimer, CRP, and ferritin.

Conclusion

There was a significant relationship between COVID-19 and an acute conjunctival inflammatory response. Blood parameters that determined progression in patients with COVID-19 were not significant in terms of ocular findings.

Key Words: COVID-19, conjunctivitis, blood parameters, laboratory findings, SARS-CoV2

What is already known about this topic?

Inflammatory findings such as conjunctivitis and dry eye in covid-19 patients have been proven by studies. In addition, studies have shown that crp, procalcitonin, d-dimer and ferritin are associated with poor prognosis in covid-19 patients. Conflicting results have been reported in a small number of studies comparing ocular findings and laboratory findings in covid-19 patients.

What does this article add?

In this study, a conclusion was reached by comparing the laboratory findings and ocular findings of the patients who were hospitalized and had severe disease, taking into account the conflicting results presented in previous studies.

INTRODUCTION

The latest pandemic, which started on December 31st, 2019, when cases of pneumonia of unknown etiology in Wuhan, Hubei province of China, were reported to the World Health Organization (WHO), has continued with the identification of a new coronavirus (2019-nCoV), and this new virus has spread rapidly and become a global problem. The new virus was named (SARS-CoV-2) due to its close similarity to severe acute respiratory syndrome coronavirus (SARS-CoV), and the disease caused by the virus was named COVID-19. In limited studies for SARS-CoV-2, the average incubation period has been determined as 5-6 days. Symptoms may occur within 2-14 days after contact and contamination may begin 1-2 days earlier. In the clinical presentation of COVID-19, fever, dry cough, and respiratory distress are considered as major findings (1,2). Although patients mostly present with an asymptomatic or mild clinical picture, it may progress to pneumonia or acute respiratory distress syndrome in patients with additional disease and those aged over 65 years (3)(4). Infection is transmitted from person to person by inhalation of droplets or contact with the eyes, nose, and mouth after touching surfaces contaminated by the virus (5).

Some respiratory system viruses such as adenovirus and H7 influenza virus can strongly stimulate the immune system in the cornea and conjunctiva, causing the inflammatory pathway to be activated and to consequently form conjunctivitis or keratoconjunctivitis (6).

Coronaviruses that can cause conjunctivitis in humans have also been reported. Human coronavirus NL 63 (HCoV-NL63) was first identified with bronchiolitis and conjunctivitis in an infant. Then, conjunctivitis was defined in 17% of 29 In pediatric patients with HCoV-NL63. No ocular involvement was reported in Middle East respiratory syndrome-related coronavirus (MERS-CoV) or SARS-CoV infections (7). However, in animal studies, ocular infection was observed as a result of direct inoculation of SARS-COV in the mouth,

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nose or eye (8)(9)(10). A tear film mostly covers the eye surface and prevents bacteria and viruses from adhering to the cornea and conjunctiva with antimicrobial agents and the immunoglobulins it contains (11).

It has been shown that SARS-CoV-2 infects host cells via angiotensin-converting enzyme 2 (ACE2) just like SARS-CoV and has similar receptor binding sites (12). ACE-2 receptor has been detected in the retina (13), choroid (14) and conjunctival epithelium (15) in the human eye. In previous studies, findings such as acute follicular conjunctivitis, conjunctival hyperemia, chemosis, epiphora, and increased secretion have been described in patients with COVID-19 (16). As with other viral infections, it is assumed that the ocular symptoms of COVID-19 are self-limited and can be managed with symptomatic treatment.

It is known that SARS-COV-2 can be found in tears and adhere to the ocular surface. Conjunctivitis in patients with COVID-19 has been reported at different rates in various studies. It is not clear whether it causes different findings or subclinical conditions on the ocular surface.

The aim of this study was to evaluate the frequency of ocular involvement in hospitalized patients with COVID-19 and to compare the demographic findings and various blood parameters of patients with and without ocular findings.

MATERIALS AND METHODS

A total of 215 patients who were diagnosed as having COVID-19 with clinical findings or with polymerase chain reaction (PCR) test positivity and who were hospitalized between July 2020 and August 2020 were included in the study. The hospitalized patients were seen individually in their rooms, and the lower eyelid conjunctiva and ocular surface were macroscopically examined with penlight by inspection. The eyes of the patients were examined in terms of conjunctival follicle in the lower eyelid, congestion on the ocular surface, hyperemia or chemosis. The patients were questioned as to whether there was burning, foreign body sensation, itching, epiphora or blurred vision. Patients with any symptoms were asked when they started, whether their symptoms increased or not, and whether they had similar symptoms before the COVID-19 infection. Patients who had previously been diagnosed as having dry eye or allergic conjunctivitis or had symptoms and signs similar to dry eye, and patients who used regular eye drops for any reason were considered negative in terms of ocular findings.

Nasopharyngeal SARS-CoV-2 real-time (RT)-PCR results, lung computed tomography (CT) imaging findings, lactate dehydrogenase (LDH), white blood cells (WBC), neutrophil counts, lymphocyte counts, neutrophil/lymphocyte ratio (NLR), procalcitonin, C-reactive protein (CRP), and ferritin values were recorded.

Ethics approval was obtained from the Medeniyet University Göztepe Training and Research Hospital Ethics Board before the start of the study. The study followed the tenets of the Declaration of Helsinki.

Statistical analysis

Statistical analysis was performed using the SPSS 16.0 (SPSS Inc., Chicago, IL) software. The Shapiro-Wilk test was used to test the normality of data distribution. The independent sample t-test was used for data with normal distribution; data shown as mean $\pm$ standard deviation in the table. Numerical data without normal distribution were analyzed using the Mann-Witney U test and shown as median (maximum-minimum) values. Categorical data were analyzed using the Chi-square and Fischer's exact tests and shown as percentage (%). Statistical significance was assessed as p-values <0.05.

RESULTS

Of the 215 patients hospitalized with COVID-19, 113 (53%) were male (mean age: 54.27 years) and 102 (47%) were female (mean age: 58.71 years). One hundred forty-five (67%) patients were found to be positive due to nasopharyngeal SARS-CoV-2 RT-PCR tests and they were defined as laboratory-proven patients. In 176 (82%) patients, CT findings were found to be significant for COVID-19.

During the examination, there were 15 patients (7.44%) who had at least two findings of conjunctivitis-related findings such as conjunctival congestion, conjunctival hyperemia, conjunctival follicle, chemosis and

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epiphora, who were considered as having conjunctivitis. The ocular findings during the visit to the patients are given in Table 1.

Table 1: Ocular findigs of Covid-19 patients

Findings of patients	**n= 215**
Conjunctival congestion	% 1,86 n= 4
Epiphora	% 4,65 n= 10
Hyperemia	% 4,65 n= 10
Chemosis	% 2,79 n= 6
Conjunctival follicle	% 2,79 n=6

It was observed that the most common ocular findings in Covid-19 patients were epiphora and hyperemia. Patients with chronic dry eye or allergic conjunctivitis who had such symptoms before were not included in the study. When the patients with and without ocular findings were evaluated in terms of age, sex, CT findings, and nasopharyngeal PCR positivity, no significant difference was found (Table 2).

Table 2: Comparison of demographic and clinical features and laboratory findings of patients with COVID-19 with and without ocular findings

	Patients with ocular findings (n=16)	**Patients without ocular findings (n=199)**
Age	51.87±16.05	56.76±14.84
Male sex n (%)	8 (50)	105 (52.8)
PCR positivity n (%)	12 (75)	133 (66.8)
Presence of CT findings	11 (68.8)	165 (82.9)
WBC	5680 (3700-8150)	6100 (4540-7680)
Neutrophil	4020 (2245-6345)	3650 (2680-5170)
Lymphocyte	1470 (1018-1938)	1440 (1070-1960)
NLR	2.27 (1.47-4.89)	2.56 (1.63-3.88)
LDH	216.50 (190.50-267.0)	233 (196.0-272.0)
Procalcitonin	<0.05 (<0.05-0.55)	<0.05 (<0.05-0.08)
D-Dimer	0.64 (0.49-1.34)	0.66 (0.37-1.12)
CRP	2.85 (0.54-9.36)	2.90 (0.80-7.0)
Ferritin	242.96 (54.78-363.0)	221.29 (98.43-374.59)

WBC: White blood cell, NLR: Neutrophil/lymphocyte ratio, LDH: Lactate dehydrogenase, CRP: C-reactive Protein

In addition, there was no difference between the patients with and without ocular findings in terms of laboratory findings such as WBCs, neutrophil counts, lymphocyte counts, NLR, LDH, procalcitonin, D-dimer, CRP, and ferritin (Table 1).

DISCUSSION

There is suspicion and some evidence that SARS-COV2 invades ocular surfaces. Possible mechanisms such as direct conjunctival contact of infected droplets, hematogenous infection of the lacrimal gland or viral migration from the upper respiratory system have been described for the SARS-COV-2 virus to infect the ophthalmic surface (17). The incidence of conjunctivitis in patients with COVID-19 has been reported as 0.8 and 4.76 percent (18)(19)(20).

In the study conducted by Ping Wu et al., the ocular symptoms of 38 patients who were clinically diagnosed as having COVID-19 and treated as inpatients were questioned, and RT-PCR was performed by taking

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nasopharyngeal and conjunctival samples. Although SARS-CoV-2 was detected in nasopharyngeal samples in 28 (73.7%) patients, it was shown in conjunctival samples in only 2 (5.2%) patients. However, in 12 of 38 patients (31.6%), symptoms related to conjunctivitis such as conjunctival hyperemia, chemosis, and epiphora were observed. Ocular symptoms were mostly observed in patients with severe pneumonia and the middle stage of the disease (16).

In an epidemiologic study conducted in China on 534 patients who were SARS-CoV-2–positive, 25 (4.68%) patients had conjunctival congestion, and dry eye (112, 20.97%), blurred vision (68, 12.73%), and foreign body sensation (63, 11.80%) were reported as the most common symptoms associated with COVID-19 (21). In another epidemiologic study conducted in a total of 30 hospitals in China, conjunctivitis was found in 9 (0.8%) of 1099 patients who had a positive SARS-CoV-2 test and were hospitalized (22).

In a study from Wuhan, China, conducted by Deng et al., SARS-CoV-2 was detected using RT-PCR in nasopharyngeal samples in 90 (76%) of 114 patients followed up in hospital due to COVID-19 pneumonia, and the virus was not detected in any of the conjunctival samples. In addition, none of the 114 patients had ocular symptoms such as red eyes or pain (23). In another study, five patients with COVID-19 presenting only with symptoms and signs of conjunctivitis were described (24).

In our study, there were 15 (7.44%) patients showing conjunctival inflammatory response who had foreign body sensation, epiphora, and conjunctival congestion symptoms, which were not present prior to the COVID-19 infection. Although more comprehensive studies are needed, our study seems to be compatible with the existing literature. The rate of conjunctivitis or conjunctival inflammatory response has been shown in a wide spectrum in these studies. These spectra were explained by the fact that no biomicroscopy examination was performed on patients in any studies in the literature, and even that the data in most studies were based on patients' subjective symptoms obtained through teleconferences. During our study, the fact that the patients were seen by an ophthalmologist in person and evaluated with a penlight, although a biomicroscopic examination was not performed, was a positive situation for the safety of our data.

In a meta-analysis evaluating laboratory findings, 5350 patients from 25 studies were included and high levels of CRP, procalcitonin, D-dimer, and ferritin were associated with poor outcomes (25). In another study, it was shown that patients with COVID-19 with ocular symptoms had higher WNC counts, neutrophil counts, and CRP, LDH, and procalcitonin values compared with patients without ocular symptoms (16). In another study, no significant difference was found between patients with and without SARS-CoV 2 virus isolated from the conjunctiva in terms of laboratory findings (26). In our study, when the laboratory data of 234 patients were compared, no significant difference was found between patients with and without ocular symptoms. Our patients had moderate or severe symptoms and were hospitalized patients. Patients with very severe disease in the intensive care unit (ICU) or asymptomatic patients followed up at home were excluded from the study. As far as we know, no other comprehensive studies have investigated the relationship between conjunctivitis and laboratory data in patients with COVID-19.

It was suggested that the ocular surface might be an entry point for SARS-CoV-2, and ocular involvement was less common thanks to the antiviral defense system in the conjunctiva and cornea, as well as lactoferrin and secretory immunoglobulin (Ig)-A (27).

Viruses trigger the immune system, leading to an increase in immunoglobulin, chemokine and antibody production, and cause tissue damage, apoptosis, and inflammation (28).

Ocular findings associated with COVID-19 may be due to viral effects or to dry eye that develops in these patients. There may be several reasons why dry eye occurs in these patients. The first is the prolongation of the time of watching screens following restrictions of social activities in patients. Another reason is that with the use of a mask, the airflow from the mask to the ocular surface evaporates the tears earlier. Indeed, there are some viruses associated with dry eye disease (29). Considering the presence of viruses associated with dry eye disease, it can be thought that the SARS-CoV-2 virus will affect the conjunctival goblet cells or the lacrimal gland through blood, disrupting the tear structure and playing a role in the development of dry eye or conjunctival inflammatory response.

Our study had some limitations. The sample size was relatively small, patients with severe clinical findings in the ICU were not included, and SARS-CoV-2 RT-PCR examinations were not performed on conjunctival samples.

As a result, there was a significant relationship between COVID-19 and an acute conjunctival inflammatory response. Blood parameters that determined progression in patients with COVID-19 were not significant in terms of ocular findings.

Declarations of interest: none

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