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The Frequency of Ocular Surface Inflammation Findings and Relationship with Mortality in Patients Diagnosed with SARS-CoV-2 Infection: A Retrospective Study

SARS-CoV-2 Enfeksiyonu Tanısı Almış Olgularda Oküler Yüzey İnflamasyon Bulgularının Sıklığı ve Mortalite ile İlişkisi: Retrospektif Bir Çalışma

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ABSTRACT Objective: To investigate the frequency of inflammation-related examination findings of the ocular surface observed in patients with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), levels of inflammation markers and their relationship with mortality. **Material and Methods:** One hundred ninety-one patients with laboratory-confirmed SARS-CoV-2 infection who received inpatient treatment in the Afyonkarahisar/Sandıklı State Hospital between April 1 and September 30, 2020 were included in the study. The relationship was examined between ocular surface examination findings and white blood cell, neutrophil and leukocyte counts, C-reactive protein, lactate dehydrogenase and, ferritin levels.The relationship between duration of hospital and intensive care unit stay, mortality and ocular surface examination was also evaluated. **Results:** A statistically significant correlation was determined between an increase in white blood cells and neutrophil count (p=0.011, p=0.008) and C-reactive protein and ferritin levels (p=0.044, p=0.031) with ocular surface examination findings. However, the relationship between the level of lactate dehydrogenase, another inflammatory marker, and ocular surface examination findings was not statistically significant (p=0.338). The relationship between length of stay in hospital, intensive care unit, mortality and ocular surface examination findings was determined to be statistically significant (p=0.038, p=0,003, p<0.001). **Conclusion:** The study results showed that a relationship was frequently seen between the ocular surface examination findings and white blood cell and neutrophil counts and C-reactive protein and ferritin levels. Due to increased mortality associated with SARS-CoV-2 infection in cases with pathology observed in the ocular surface examination, it must be considered in the treatment process that there could be a worse prognosis of the clinical course.

Keywords: COVID-19; conjunctivitis; ferritins; lactate dehydrogenases; neutrophils

ÖZET Amaç: Şiddetli akut solunum sendromu-koronavirüs-2 [severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2)] tanısı almış olgularda izlenen oküler yüzeyin inflamasyonla ilişkili muayene bulgularının sıklığını, inflamasyon belirteçleri düzeyleri ve bunların mortalite ile ilişkisini araştırmaktır. **Gereç ve Yöntemler:** 1 Nisan 2020 ve 30 Eylül 2020 tarihleri arasında Afyonkarahisar/Sandıklı Devlet Hastanesi'nde laboratuvar olarak doğrulanmış SARS-CoV-2 enfeksiyonu nedeniyle yatışı yapılarak takip edilen 191 olgu çalışmaya alındı. Olguların beyaz küre, nötrofil, lenfosit sayısı ile C-reaktif protein, laktat dehidrojenaz ve ferritin düzeyleri ile oküler yüzey muayenesi bulguları arasındaki ilişki araştırıldı. Ayrıca hastanede ve yoğun bakımda kalış süresi, mortalite ile oküler yüzey muayenesi bulgularının varlığı arasındaki bağlantı değerlendirildi. **Bulgular:** Beyaz küre hücresinin ve nötrofil sayısının artışı (p=0,011 ve p=0,008) ile C-reaktif protein ve ferritin düzeylerinin (p=0,044 ve p=0,031) oküler yüzey muayenesi bulguları ile ilişkisi istatistiksel olarak anlamlıdır. Ancak bir diğer inflamasyon belirleyicisi olan laktat dehidrojenaz düzeyi ile oküler yüzey muayene bulguları arasındaki ilişki anlamsızdır (p=0,338). Hastanede ve yoğun bakımda kalış süresi ve mortalite ile oküler yüzey muayene bulguları arasındaki ilişki istatistiksel olarak anlamlı izlendi (p=0,038, p=0,003, p<0,001). **Sonuç:** Oküler yüzey muayene bulgularının artmış beyaz küre hücresi, nötrofil sayısı, C-reaktif protein ve ferritin düzeyi ile ilişkili olarak daha sık görüldüğü tespit edilmiştir. Oküler yüzey muayenesinde patoloji izlenen olgularda, SARS-CoV-2 enfeksiyonuna bağlı artmış mortalite gözlenmesi nedeniyle klinik seyrin daha kötü prognozlu olabileceği, tedavi sürecinde göz önünde bulundurulmalıdır.

Anahtar Kelimeler: COVID-19; konjonktivit; ferritinler; laktat dehidrogenaz; nötrofiller

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A membranous RNA virus of unknown origin, which leads to pneumonia, first emerged in the city of Hubei in Wuhan province, China, in December 2019, and was defined as an infectious agent. This agent had structural similarity to the severe acute respiratory syndrome-coronavirus (SARS-CoV) virus, which causes severe acute respiratory syndrome and so was named SARS-CoV-2.[1-3] The disease caused by SARS-CoV-2 was named coronavirus disease-2019 (COVID-19) and was declared a pandemic by the World Health Organisation in March 2020. To date, approximately 100 million cases of confirmed COVID-19 have been recorded worldwide, a significant proportion of which are healthcare personnel. With the spread of the disease, ocular findings of COVID-19, primarily conjunctivitis have started to be identified. It has been shown that the virus enters the cells through the angiotensin-converting- enzyme-2 molecule, which is expressed on the surface of the conjunctiva and cornea. Using reverse transcription-polymerase chain reaction (RT-PCR) tests on samples taken from conjunctival secretions, the virus has been determined on the ocular surface.[4-7]

Just as in other cases receiving intensive care support, in cases admitted to intensive care unit (ICU) as a result of systemic effects of COVID-19, complications may be observed such as exposure keratopathy, chemosis, and secondary bacterial conjunctivitis associated with mechanical ventilation, in addition to the direct effect on the ocular surface.[8]

The aim of this study was to evaluate the ocular surface examination findings and laboratory data of 191 cases confirmed as COVID-19 positive with the RT-PCR test.

MATERIAL AND METHODS

Patients with positive RT-PCR test results who received inpatient treatment in the pandemic clinic between April 1 and September 30, 2020 were evaluated. All samples had been obtained by nasopharyngeal and oropharyngeal swab before. The demographic information and clinical findings of all patients were obtained, including age, gender, onset of symptoms, admission time, hospital stay, and laboratory testing results such as; white blood cell (WBC), neutrophil and leukocyte counts, C-reactive protein (CRP), lactate dehydrogenase (LDH), and ferritin levels. These findings were compared with ocular surface inflammation findings, such as foreign body sensation, congestion, secretion, subconjunctival hemorrhage, and chemosis. Approval for the study was granted by the Afyonkarahisar University of Health Sciences Clinical Research Ethics Committee (06.11.2020 and 2020/489). All study procedures were applied in compliance with the Helsinki Declaration. Approval from the Ministry of Health was obtained for this study.

The diagnosis of COVID-19 was made from the determination of viral RNA using the nucleic acid amplification method with RT-PCR. The SARS-CoV-2 RNA test kit used was developed in the Turkish Ministry of Health, Public Health Directorate, Microbiology Reference Laboratories- Virology Laboratory.[9]

In the certified Microbiology Laboratory of Health Sciences University, the single-stage RT and real-time PCR test (qPCR) was applied using marked oligonucleotides specifically designed to target the SARS-CoV-2 gene regions in the nasopharyngeal/ oropharyngeal smears and sputum samples taken from the cases for diagnostic purposes.

Since the test kit used in Turkey was only validated for the detection of SARS-CoV-2 in respiratuar samples, detection of the virus from the conjunctival samples was not able to be performed.

The kit used at the start of the process targeted the SARS-CoV-2 RdRp gene, then the N and Orf1ab gene regions specific to SARS-CoV-2 were targeted. In both kit versions, the human ribonuclease P gene was used as the internal control, and thus inhibition control of sample origin and kit reactive control were applied (Bio-Speedy COVID-19 RT-qPCR Determination Kit and SARS-CoV-2 Double Gene RT-qPCR Kit, BIOEKSEN). The manual extraction procedure then real-time PCR analyses were applied with Roche Light Cycler 480, Biorad CFX96, and Qiagen Rotor-Gene 5 Plex devices according to the manufacturer's instructions. By evaluating amplification curves after the assays, the presence of SARS-CoV-2 RNA in the case sample was reported qualitatively.

STATISTICAL ANALYSIS

Statistical analyses were performed using Number Cruncher Statistical System, 2007 version software (Kaysville, Utah, USA). As the continuous variables did not show the normal distribution in the Shapiro-Wilk normality test, they were presented as median (minimum-maximum) values, and two groups were compared using the Mann-Whitney U test. Categorical variables were presented as frequency and percentage, and two groups were compared using the Pearson chi-square test with Yate's correction. A value of $p<0.05$ was considered statistically significant.

RESULTS

A total of 191 patients, 80 males and 111 females, with a mean age of 61 years were included in the study (range, 18-92 years). The WBC, neutrophil and leukocyte counts were retrieved from the files of all cases, and LDH was determined from the records of 180 cases and the ferritin level from the records of 164 cases. Ocular surface inflammation findings were seen statistically significantly more often in elderly patients ($p<0.001$). Gender was not a statistically significant variable in terms of the frequency of ocular surface inflammation findings ($p=0.138$). The frequency of ocular surface inflammation findings with increased WBC and neutrophil count was determined to be statistically significant ($p=0.011$, $p=0.008$).

No statistically significant relationship was determined between lymphocyte count and ocular surface examination findings ($p=0.924$).

A statistically significant correlation was determined between CRP and ferritin levels and ocular surface examination findings ($p=0.044$, $p=0.031$). No significant relationship was seen between the inflammation marker, LDH, and ocular surface examination findings ($p=0.338$).

The relationship between length of stay in hospital and ICU, and mortality and ocular surface examination findings was determined to be statistically significant ($p=0.038$, $p=0.003$; $p<0.001$) (Table 1).

A statistically significant result was observed between mortality and age, WBC, neutrophil, and lymphocyte count, CRP, and ferritin levels. A statistically significant result was observed between mortality and length of stay in hospital and ICU (Table 2).

As ocular surface examination findings, conjunctivitis was determined in 14 cases, foreign body sensation in 9, congestion and epiphora in 7, secretion in 5, chemosis in 4, and subconjunctival hemorrhage in 2 (Table 3). Treatment was applied to these cases in the ward in 6 cases, and in ICU in 8. All the cases who were followed up in ICU deceased because of COVID-19.

TABLE 1: The comparative results of patients with and without ophthalmological findings.

Variable	Ophthalmic findings (+) (n=14)	Ophthalmic findings (-) (n=177)	p value
Age, years	72 (50-92)	60 (18-89)	<0.001$^{\alpha}$
Male, n (%)	9 (64.3)	71 (40.1)	0.138$^{\beta}$
White blood cell count, µL	8,950 (3,700-25,500)	5,800 (900-19,400)	0.011$^{\alpha}$
Neutrophil count, µL	6,035 (2,500-22,200)	3,800 (593-14,100)	0.008$^{\alpha}$
Lymphocyte count, µL	1,205 (340-2,270)	1120 (290-3,040)	0.924$^{\alpha}$
C-reactive protein, mg/dL	125 (1-247)	41 (1-332)	0.044$^{\alpha}$
Lactate dehydrogenase‡, U/L	290 (165-1,412)	261 (129-1,837)	0.338$^{\alpha}$
Ferritin‡, mL/ng	540 (49-1,974)	259 (15-1,991)	0.031$^{\alpha}$
Duration of intensive care unit stay, days	0.5 (0-27)	0 (0-18)	0.003$^{\alpha}$
Duration of hospital stay, days	6 (1-17)	9 (0-23)	0.038$^{\alpha}$
Mortality	8 (57.1)	11 (6.2)	<0.001$^{\beta}$

‡There were missing values for the lactate dehydrogenase and ferritin values in 11 and 27 patients, respectively;
$^{\alpha}$Mann-Whitney U test; $^{\beta}$Pearson chi-square test with Yate's correction.

TABLE 2: The demographic and clinical characteristics of the study population.

Variable	Overall (n=191)	Mortality (+) (n=19)	Mortality (-) (n=172)	p value
Age, years	61 (18-92)	72 (50-92)	59 (18-88)	<0.001[α]
Male, n (%)	80 (41.9)	9 (47.4)	71 (41.3)	0.791[β]
White blood cell count, µL	5,900 (900-25,500)	11,200 (3,700-25,500)	5,700 (900-17,700)	<0.001[α]
Neutrophil count, µL	3,870 (593-22,200)	9,230 (1,540-22,200)	3,755 (14,100-593)	<0.001[α]
Lymphocyte count, µL	1,130 (290-3,040)	740 (390-2,040)	1,130 (290-3,040)	0.036[α]
C-reactive protein, mg/dL	44 (1.0-332)	195 (38-332)	35.5 (1-312)	<0.001[α]
Lactate dehydrogenase‡, U/L	265.5 (129-1,837)	493 (218-1,412)	261 (129-1,837)	0.004[α]
Ferritin‡, mL/ng	272 (15-1,991)	737 (73-1,974)	250 (15-1,991)	0.001[α]
Ophthalmicalogical findings, n (%)	14 (7.3)	8 (42.1)	6 (3.5)	<0.001[β]
Duration of intensive care unit stay, days	0 (0-27)	5 (0-27)	0 (0-18)	<0.001[α]
Duration of hospital stay, days	9.0 (0-23)	0 (0-10)	9 (0-23)	<0.001[α]

‡There were missing values for the lactate dehydrogenase and ferritin values in 11 and 27 patients, respectively;
[α]Mann-Whitney U test; [β]Pearson chi-square test with Yate's correction.

TABLE 3: Symptom distribution in cases with ocular surface examination findings.

	Total (n=14)
Foreign body sensation	9
Congestion	7
Epiphora	7
Secretion	5
Chemosis	4
Subconjunctival hemorrhage	2

DISCUSSION

In the 2003 SARS-CoV outbreak, it was shown by many researchers that coronavirus could spread through tears. At the onset of the COVID-19 pandemic, caused by the SARS-CoV-2 virus, this new CoV was determined to have similar transmission properties.[10-14]

Qing et al. claimed that after SARS-CoV-2 spread to the ocular surface via tears, it passed into the nasal cavity through the nasolacrimal canal system, and could pass into the systemic circulation, but could not find sufficient evidence to prove this.[15]

In a study of 38 nasopharyngeal samples tested positive with RT-PCR, findings such as hyperemia in the conjunctiva, conjunctivitis, chemosis, epiphora, and increased secretion were determined in 12 (31.6%) out of 38 cases. This rate is one of the highest published in the literature related to ocular findings of SARS-CoV-2. However, it must be taken into consideration that two-thirds of the cases in that study were receiving mechanical ventilator treatment in ICU and ocular surface examination findings can emerge like a complication of intensive care.[16] In the current study, this rate was 7.3%, and 18.2% of the patients were in ICU.

In a retrospective study by Guan et al. of RT-PCR-positive cases, 552 hospitals in 30 separate locations were included, and of 1,099 cases, congestion in the conjunctiva was determined as a symptom on the ocular surface in 9 (0.8%) patients.[17] This rate is extremely low compared to the findings of the current study. However, it must be taken into consideration that the current study only included hospitalized patients. Since the inflammatory response will be weak due to the milder disease in outpatients, less ocular surface examination findings can be expected.

In another study of 56 COVID-19-positive cases, ocular findings were reported in 15 (27%).[18] A retrospective study that included 214 COVID-19-positive cases from 3 separate hospitals reported conjunctivitis symptoms in 3 (1.4%) cases.[19]

There are publications stating that conjunctivitis could be the first finding of SARS-CoV-2 infection. Cheema et al. reported that keratoconjunctivitis could be the first finding of COVID-19. Similarly, Scalinci and Trovato Battagliola published a series of 5 cases in which conjunctivitis was the first symptom of COVID-19.[7,20]

In a prospective study by Seah et al., hyperemia in the conjunctiva and chemosis were determined in 1 (5.5%) of 18 cases, while Zhou et al. reported that conjunctivitis was seen as an ocular surface finding in 8 (6.6%) of 121 cases with a positive RT-PCR test.[5,6] Chen et al. evaluated 534 cases diagnosed with COVID-19 and reported conjunctivitis in 33 (6.1%).[21] The results reported by Seah, Zhou, and Chen are similar to the findings of the current study. It can be seen that the data in the literature vary, and there is, therefore, a need for studies of a more extensive patient group.

In the literature, it was reported that 127 cases diagnosed with COVID-19, 18 (14.17%) had spectacles and 50 (39.37) cases had a history of hand-eye contact. It was reported that 12 (9.45%) cases had ocular complaints and 11 (8.66%) cases had these complaints after diagnosis. And conjunctival congestion was detected in 8 (6.29%) of these 11 cases. In 5 (3.93%) cases, no other ocular symptom of congestion was observed.[22]

In a study involving 400 cases diagnosed with COVID-19, ocular signs and symptoms were observed in 38 (9.5%) cases, and the most common ocular abnormality was conjunctival injection, vision changes and ocular irritation. No correlation was found between age, gender, ocular history, fever, mechanical ventilation, and increased inflammation markers and ocular findings in the univariate analyzes performed. The results of this study contradict our study.[23]

In another study of 301 cases, findings of conjunctivitis were reported in 35 (11.6%). Of these cases, conjunctival hyperemia was observed in 28 (9.3%), epiphora in 15 (5%), and foreign body sensation in 12 (3.9%). WBC and neutrophil count were evaluated together with inflammation markers such as CRP and ferritin levels, and no significant relationship was determined between ocular surface examination findings and inflammation markers.[24] In the current study, the difference between WBC and neutrophil counts and inflammation markers such as CRP and ferritin levels in the cases with ocular involvement was seen to be statistically significant compared to the results of cases with no ocular involvement and normal values. However, the LDH level, which is another inflammation marker, was similar in cases both with and without ocular surface examination findings. In addition, the relationship between the length of stay in ICU and ocular surface ocular findings were found to be statistically significant ($p=0.003$).

In the current study, the mortality rate was determined to be 57.1% in cases with ocular involvement and 6.2% in those with no ocular involvement, and the difference was statistically significant ($p<0.001$). Of the total cases in the current study, the rate of ICU admission was 4.1% of those with ocular involvement and 5.75% of those with no ocular involvement. All of the cases with ocular involvement followed-up in ICU deceased, and 40.7% of the cases without ocular involvement followed-up in ICU were lost to mortality.

STUDY LIMITATIONS

There may be bias in the study results as it only included hospitalized patients. The viral load and inflammation level are expected to be greater in hospitalized cases than in those receiving outpatient treatment. Therefore, ocular surface examination findings may be determined more frequently in hospitalized cases. Furthermore, as the study included patients in ICU and ocular surface complications may be seen in intensive care, this could have increased the frequency of ocular surface examination findings determined in the study. A patient with viral pneumonia and fever-up may have conjunctival hyperemia associated with vasodilation of the head and neck. It is not easy for clinical ophthalmologists to distinguish by slit-lamp examination between viral conjunctivitis due to viral multiplication locally in the eye or just due to a head and neck finding of fever. The virus infecting the nasopharynx, which is connecting with the lacrimal duct, is possibly detected in tear. PCR was not applied with a conjunctival swab in this study. That the study was retrospective in design could also constitute a limitation.

CONCLUSION

When all these results are evaluated together, it can be seen that ocular involvement was more frequent in cases with increased WBC and neutrophil count,

CRP, and ferritin levels, and the mortality rate was greater in cases with ocular involvement. No previous study could be found in the literature that has evaluated the relationship between ocular surface examination findings and mortality. Therefore, despite the limitations of this study, if there is ocular involvement in COVID-19 cases, the clinical course should be followed more closely. Moreover, there is a need for further studies of more extensive series on this subject.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

***Idea/Concept:** İbrahim Ethem Ay; **Design:** İbrahim Ethem Ay, Melahat Gürbüz; **Control/Supervision:** İbrahim Ethem Ay; **Data Collection and/or Processing:** İbrahim Ethem Ay; **Analysis and/or Interpretation:** İbrahim Ethem Ay; **Literature Review:** İbrahim Ethem Ay; **Writing the Article:** İbrahim Ethem Ay; **Critical Review:** İbrahim Ethem Ay; **References and Fundings:** Melahat Gürbüz; **Materials:** Melahat Gürbüz.*

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