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Original Article

Prospective Study: Frequency of Ophthalmic Findings, Relationship with Inflammation Markers, and Effect on Prognosis in Patients Treated in the COVID-19 Intensive Care Unit

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Abstract

Objectives: To prospectively evaluate the frequency of ocular findings and inflammation markers levels in patients treated in the intensive care unit due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection to determine the relationship between these parameters and mortality.

Materials and Methods: We prospectively evaluated 53 patients who were treated in the intensive care unit of a pandemic hospital between January 1 and June 30, 2021 and whose SARS-CoV-2 diagnosis was confirmed by reverse transcriptase polymerase chain reaction test from nasopharyngeal swab samples. Ocular findings were evaluated together with white blood cell, neutrophil, lymphocyte count, C-reactive protein, lactate dehydrogenase and ferritin levels, and mortality rate.

Results: There was no statistically significant correlation between lactate dehydrogenase, white blood cell, neutrophil, and lymphocyte count elevation and the frequency of inflammatory eye signs (p=0.308, p=0.694, p=0.535, p=0.374). In multivariate analyses, no statistically significant correlation was observed between ferritin level and the frequency of inflammatory eye findings (p=0.087). In addition, for each 1 mg/dL increase in C-reactive protein level, the detection of inflammatory eye findings decreased by 1.9% (95% confidence interval: 3.3%-0.4%; p=0.015). It was determined that 7 of 13 patients with inflammatory eye findings died and this was not statistically significant (p=0.810).

Conclusion: Inflammatory examination findings of the ocular surface were detected in 13 (24.5%) of 53 patients treated in the intensive care unit for SARS-CoV-2 infection. Ocular surface examination of patients treated in the intensive care unit due to the SARS-CoV-2 epidemic is important.

Keywords: SARS-CoV-2, chemosis, congestion, intensive care unit

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Introduction

In December 2019, an enveloped RNA virus of unknown origin was reported to be the cause of pneumonia-related deaths in Wuhan, China.[1] Because of its structural similarity to SARS-CoV (severe acute respiratory syndrome coronavirus), the novel virus was named SARS-CoV-2. Within a short time, the World Health Organization announced that coronavirus disease 2019 (COVID-19) was a pandemic.[2,3] Later, there were reports of ocular findings associated with SARS-CoV-2, especially conjunctivitis, and it was shown that the virus could be transmitted through tears.[4,5,6,7]

In this study, we prospectively evaluated the ocular surface examination findings and laboratory data of 53 patients who had a positive SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) test result and were treated in the COVID-19 intensive care unit. The results were compared with mortality data.

Materials and Methods

Patients who were hospitalized in the COVID-19 intensive care unit of a pandemic hospital in accordance with predetermined treatment criteria and had a positive RT-PCR test between January 1 and June 30, 2021 were included in the study (Table 1). We prospectively recorded the patients' age, sex, presence of systemic disease, mechanical ventilation support, white blood cell, neutrophil, and lymphocyte counts, and C-reactive protein (CRP), lactate dehydrogenase (LDH), and ferritin levels. Other than the routine follow-up tests recommended in the Turkish Ministry of Health COVID-19 guideline (https://covid19.saglik.gov.tr/TR-66301/covid-19-rehberi.html), no additional tests were ordered for the study. Necessary measures were taken to prevent SARS-CoV-2 transmission, especially the use of N95 masks. Each patient underwent daily ocular surface examination using a handheld biomicroscope (Portable Slit Lamp, Reichert Inc, NY, USA). In addition, the optic nerve, macula, and vascular arcades of all patients were evaluated using a 90 D Lens (V 90C, Volk Optical Inc, OH, USA) lens due to the risk of developing Valsalva retinopathy and intraretinal hemorrhage or optic neuropathy associated with impaired perfusion. Ethics committee approval was obtained for the study. Written informed consent was obtained from conscious patients and from the first-degree relatives of unconscious patients. The study was conducted in accordance with the Declaration of Helsinki.

The diagnosis of SARS-CoV-2 infection was made by detection of viral RNA using the nucleic acid amplification method by RT-PCR. The SARS-CoV-2 RNA test kit developed in the Microbiology Reference Laboratories-Virology Laboratory of the Turkish Ministry of Health General Directorate of Public Health was used.[8] Diagnostic nasopharyngeal/oropharyngeal swabs and sputum specimens were tested using marked oligonucleotides specific to SARS-CoV-2 target gene regions. The single-step RT-PCR test was evaluated by sending it to an authorized microbiology laboratory.

Statistical Analysis

The data were tested for normal distribution using visual (histogram and probability charts) and analytical methods (Shapiro-Wilk test). Categorical variables were presented as number and percentage, and continuous variables were presented as mean ± standard deviation (SD) or median (25^{th}-75^{th} percentile). Pearson's chi-square test was used to compare categorical variables between independent groups. Fisher's Exact test was performed if the requirements for Pearson's chi-square test were not met (if the expected value in more than 20% eyes was less than 5 or the observed value was less than 2). In comparisons between two independent groups, Student's t-test was used for normally distributed variables and Mann-Whitney U test was used for non-normally distributed variables. In order to evaluate variables associated with inflammatory eye findings and survival, multiple logistic regression analysis was performed with variables that had results with $p<0.05$ and $p<0.200$ in pairwise comparisons. The multiple logistic regression model was established using the backward LR method. Results were evaluated within a 95% confidence interval with an alpha error of 0.05. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) software.

Results

Of the 53 patients included in the study, 26 (49.1%) were men and 27 (50.9%) were women. The mean age was 69.9±16.0 (19-94) years. Twenty-six patients (49.1%) received noninvasive ventilation via face mask with reservoir bag, 19 patients (35.8%) received invasive ventilation via high-flow oxygen therapy (HFOT), and 8 patients (15.1%) received invasive ventilation support after endotracheal intubation. Thirty-seven patients (69.8%) had hypertension (HT), 7 (13.2%) had diabetes mellitus (DM), and 21 (39.6%) had chronic obstructive pulmonary

Table 1. Criteria for admission to the COVID-19 intensive care unit
Respiratory rate ≥30/min
PaO_2/FiO_2 <300
SpO_2 <90% or PaO_2 <70 mmHg despite receiving 5 L/min oxygen therapy
Hypotension (SBP <90 mmHg and decrease of >40 mmHg from normal SBP and mean arterial pressure <65 mmHg)
Tachycardia >100/min
Acute kidney injury
Acute liver function test abnormality
Confusion
Acute bleeding diathesis
Immunosuppression
Troponin elevation and arrhythmia
Lactate >2 mmol
Skin findings associated with delayed capillary refill
PaO_2: Partial pressure of oxygen, FiO_2: Fraction of inspired oxygen, SpO_2: Peripheral oxygen saturation, SBP: Systolic blood pressure

disease (COPD). Twenty-six patients (49.1%) survived and 27 (50.9%) died (Table 2). Congestion was detected in 13 patients (24.5%) cases, serous secretion in 6 patients (11.3%), and chemosis in 3 patients (5.7%) (Table 3; Figure 1). On fundus examination, none of the patients exhibited intraretinal hemorrhage, optic neuritis, or Valsalva retinopathy, which are the main findings reported to increase in frequency in COVID-19. The prevalence of inflammatory eye signs was significantly higher among women than men (p=0.031). There was no statistically significant difference in the frequency of inflammatory eye signs between patients who received invasive and noninvasive ventilation (p=0.691). The frequency of inflammatory eye signs did not differ significantly according to survival (p=0.810). The prevalence of inflammatory eye signs increased significantly with age (p=0.011).

No significant relationship was observed between inflammatory eye findings and LDH, white blood cell, neutrophil, or lymphocyte levels (p=0.308, p=0.694, p=0.535, and p=0.374, respectively). In univariate analyses, higher CRP level was associated with a lower prevalence of inflammatory eye signs (p=0.01). In addition, inflammatory eye signs were more frequent among patients with low ferritin levels (p=0.006) (Table 4). However, in multivariate analyses, there was no statistically significant association between ferritin level and the frequency of inflammatory eye signs (p=0.087). In contrast, each 1 mg/dL increase in CRP level was associated with 1.9% lower odds of detecting inflammatory eye signs (95% confidence interval [CI]: 3.3%-0.4%; p=0.015). Each additional year of age increased the risk of inflammatory eye signs by 1.083 times (95% CI: 1.008-1.163; p=0.030) (Table 5).

There was no statistically significant relationship between survival and patient sex or presence of HT, DM, or COPD (p=0.335, p=0.928, p=0.250, and p=0.695, respectively). Older age was associated with significantly higher risk of death (p=0.004). Survival was significantly better among patients for whom respiratory support with noninvasive ventilation via face mask with reservoir bag was sufficient for treatment (p<0.001). No significant difference in survival was observed in patients who received invasive ventilation support with HFOT (p=0.749). All eight patients who received invasive ventilation support after intubation died, which was statistically significant (p=0.004). Seven of the 13 cases with inflammatory eye signs died, which was not statistically significant (p=0.810).

The mortality rate was higher among patients with higher white blood cell and neutrophil counts (p=0.011 and p=0.024, respectively). There was no significant relationship between

Figure 1. Congestion in a patient being treated in the COVID-19 intensive care unit

Table 2. Sociodemographic and clinical characteristics of the patients

Variable	n (%)
Sex	
Male	26 (49.1)
Female	27 (50.9)
Age (years)	
Mean ± standard deviation	69.9±16.0
Median (min-max)	72.0 (19-94)
Noninvasive ventilation with reservoir mask	
No	27 (50.9)
Yes	26 (49.1)
Invasive ventilation with high-flow oxygen therapy	
No	34 (64.2)
Yes	19 (35.8)
Invasive ventilation by endotracheal tube	
No	45 (84.9)
Yes	8 (15.1)
Hypertension	
No	16 (30.2)
Yes	37 (69.8)
Diabetes mellitus	
No	46 (86.8)
Yes	7 (13.2)
Chronic obstructive pulmonary disease	
No	32 (60.4)
Yes	21 (39.6)
Congestion	
No	40 (75.5)
Yes	13 (24.5)
Chemosis	
No	50 (94.3)
Yes	3 (5.7)
Secretion	
No	47 (88.7)
Yes	6 (11.3)
Survival	
Survived	26 (49.1)
Died	27 (50.9)

min: Minimum, max: Maximum

Table 3. Distribution of inflammatory eye findings

Eye findings	n
Congestion	13
Secretion	6
Chemosis	3
Subconjunctival hemorrhage	2

Table 4. Factors associated with the frequency of inflammatory eye findings			
	Inflammatory eye findings (n=13)	**No inflammatory eye findings (n=40)**	**P**
Sex, n (%) Male Female	 3 (11.5) 10 (37.0)	 23 (88.5) 17 (63.0)	**0.031**[1]
Ventilation type, n (%) Invasive ventilation Noninvasive ventilation	 6 (22.2) 7 (26.9)	 21 (77.8) 19 (73.1)	0.691[1]
Survival, n (%) Survived Died	 6 (23.1) 7 (25.9)	 20 (76.9) 20 (74.1)	0.810[1]
Age (years) Mean ± SD	77.2±8.8	67.5±17.2	**0.011**[2]
Lactate dehydrogenase, U/L Mean ± SD	384.9±91.1	432.0±156.0	0.308[2]
C-reactive protein, mg/dL Mean ± SD	86.5±51.2	154.2±86.8	**0.010**[2]
White blood cells, x10^3/µL Median (25^{th}-75^{th} percentile)	**8.2 (10.7-14.8)**	**8.6 (11.2-13.7)**	0.694[3]
Neutrophils, x10^3/µL Median (25^{th}-75^{th} percentile)	3.8 (5.9-7.9)	3.2 (4.9-8.1)	0.535[4]
Lymphocytes, x10^3/µL Median (25^{th}-75^{th} percentile)	0.5 (0.6-0.8)	0.5 (0.7-0.9)	0.374[3]
Ferritin, ng/mL Median (25^{th}-75^{th} percentile)	138.5 (237-603.5)	411 (695-1544.8)	**0.006**[3]
[1]Pearson chi-square test, [2]Student's t test, [3]Mann-Whitney U test, SD: Standard deviation			

survival and LDH, CRP, ferritin, or lymphocyte level (p=0.600, p=0.877, p=0.493, and p=0.239, respectively) (Table 6). Logistic regression analysis showed that the risk of death was 40.9 times (95% CI: 6.2-269.9) higher in the group that received invasive ventilation via HFOT or intubation (p<0.001). With each 1000/mm^3 increase in neutrophil count, the risk of death was increased by 1.6 times (95% CI: 1.1-2.3; p=0.015) (Table 7).

Discussion

In the SARS-CoV outbreak of 2003, researchers proved that the coronavirus was transmitted through tears.[9] After the SARS-CoV-2 outbreak that started in 2019, the novel coronavirus was found to have similar infectious properties.[10,11,12,13,14] Wu et al.[15] observed findings such as conjunctival hyperemia, conjunctivitis, chemosis, epiphora, and increased secretion in 12 (31.6%) of 38 patients with positive nasopharyngeal RT-PCR test results. In our study, ocular findings were detected in 13 (24.5%) of 53 patients. Wu et al.[15] reported that two-thirds of the patients in their study were treated with mechanical ventilation in the intensive care unit. In our study, 27 (50.9%) of the 53 patients received mechanical ventilation, and the prevalence of ocular surface findings we detected is similar to that observed by Wu et al.[15]

Zhou et al.[16] reported that they prospectively observed conjunctivitis as an ocular surface examination finding in 8 (6.6%) of 121 patients with positive RT-PCR. However, their study did not include patients treated in the COVID-19 intensive care unit. The rate of inflammatory findings of the ocular surface was higher in our study than that reported by Zhou et al.[16] Inflammatory eye signs may be more common in patients receiving treatment in the intensive care unit.

In another study, conjunctivitis findings were reported in 35 (11.6%) of 301 patients. Of these, 28 patients (9.3%) had conjunctival hyperemia, 15 (5%) had epiphora, and 12 (3.9%) had foreign body sensation. When evaluated together with inflammation markers such as white blood cell, neutrophil, and lymphocyte counts, CRP, and ferritin level, no significant relationship was found between ocular surface examination findings and inflammation markers.[17] In our study, we also observed no link between higher levels of inflammation markers and the frequency of inflammatory signs of the ocular surface.

Xia et al.[6] detected no correlation between illness severity and the frequency of conjunctivitis. However, the results reported by Wu et al.[15] and Guan et al.[18] indicated that the frequency of conjunctivitis increased in severe illness. According to their meta-analysis of a limited number of patients, Liu et al. found no link between the frequency of conjunctivitis and disease severity.[19] In our study, the incidence of inflammatory ocular surface findings was not statistically associated with LDH level, white blood cell count, neutrophil count, or lymphocyte count (p=0.308, p=0.694, p=0.535, and p=0.374, respectively). In addition, multivariate analyses indicated no statistically significant correlation between ferritin level and the frequency of

Table 5. Univariate and multiple logistic regression models of variables associated with the frequency of inflammatory eye findings

	Univariate analysis							Multivariate analysis						
	B	S.E.	Wald	p	OR	95% CI for OR		B	S.E.	Wald	p	OR	95% CI for OR	
						Lower	Upper						Lower	Upper
Female (ref: Male)	1.506	0.732	4.236	0.040	4.51	1.074	18.929	1.586	0.917	2.992	0.084	4.884	0.81	29.46
Age	0.048	0.026	3.438	0.064	1.05	0.997	1.105	0.08	0.037	4.733	**0.030**	1.083	1.008	1.163
C-reactive protein, mg/dL	-0.013	0.005	5.709	**0.017**	0.987	0.976	0.998	-0.019	0.008	5.921	**0.015**	0.981	0.967	0.996
Ferritin, ng/mL	-0.002	0.001	4.689	**0.030**	0.998	0.997	0.999	-0.001	0.001	2.938	0.087	0.999	0.997	1
Constant	-1.506	0.732	4.236	0.040	0.222	0.053	0.931	-4.842	2.557	3.586	0.058	0.008		

CI: Confidence interval, OR: Odds ratio

inflammatory signs on ocular surface examination (p=0.087). In fact, with each 1 mg/dL increase in CRP level, the odds of detecting inflammatory signs on ocular surface examination decreased by 1.9% (95% CI: 3.3%-0.4%; p=0.015) (Table 5). We found no other study in the literature in which the risk of detecting signs of ocular surface inflammation decreased with higher CRP level. This suggests that the increase in ocular surface inflammation may have been related to dry eye occurring in the intensive care setting, not due to increased inflammation associated with COVID-19. Studies evaluating patients treated in COVID-19 intensive care units using Schirmer test and fluorescein staining and including larger case series are needed.

In another study of 400 cases, ocular findings were detected in 38 patients (9.5%). Conjunctival injection was reported to be the most common ocular finding. Age, sex, fever, mechanical ventilation, and elevated inflammation markers were not significantly associated with the frequency of ocular findings. Although the prevalence of inflammatory ocular surface findings was lower than in our study, the results were similar in terms of the lack of a relationship between eye signs and elevated inflammation markers or mechanical ventilation.[20] The higher frequency of inflammatory findings on ocular surface examination in our study may be because only patients treated in the COVID-19 intensive care unit were included.

Öncül et al.[21] detected inflammatory eye findings in 28 (7.7%) of the 359 patients in their study. Of these, 294 patients were treated in the ward and 65 were treated in the COVID-19 intensive care unit. Among the 65 intensive care patients, inflammatory eye findings were detected in 4 patients (6.2%). Whereas we included only patients with positive RT-PCR results in our study, Öncül et al.[21] considered it sufficient for patients to be diagnosed based on lung tomography and clinical evaluation as well as by RT-PCR test for SARS-CoV-2. In our study, the prevalence of inflammatory findings on ocular surface examination was 24.5%, which is a higher rate than reported by Öncül et al.[21] Unlike Öncül et al.[21], we defined RT-PCR positivity as a required criterion for the diagnosis of SARS-CoV-2 infection. This may explain the difference in results between the two studies.

In another study conducted prospectively in the intensive care unit before the SARS-CoV-2 pandemic, Öncül and Yektaş[22] observed inflammatory signs such as conjunctivitis and increased secretion that required an ophthalmology consultation in 29 (31.2%) of 93 patients. Johnson and Rolls[23] reported that ocular surface problems were seen in 23-60% of intensive care patients. The higher frequency of ocular surface inflammation findings in the COVID-19 intensive care unit may also be related to the conditions in the intensive care unit. Some of the inflammatory signs observed on ocular surface examination in our study may have been a result of problems such as bacterial conjunctivitis. This prospective study was conducted exclusively with patients in the COVID-19 intensive care unit. Therefore, it differs from many other studies, which may explain why our results are different from previous studies in the literature. Further research with larger case series is needed on this subject.

Table 6. Factors associated with survival			
	Survived (n=26)	**Died (n=27)**	**P**
Sex, n (%) Male Female	 11 (42.3) 15 (55.6)	 15 (57.7) 12 (44.4)	0.335[1]
Noninvasive ventilation via mask with reservoir bag, n (%) No Yes	 5 (18.5) 21 (80.8)	 22 (81.5) 5 (19.2)	<0.001[1]
Invasive ventilation via high-flow oxygen therapy, n (%) No Yes	 25 (73.5) 15 (78.9)	 9 (26.5) 4 (21.1)	0.749[2]
Invasive ventilation via endotracheal tube, n (%) No Yes	 26 (57.8) 0 (0)	 19 (42.2) 8 (100)	0.004[2]
Hypertension, n (%) No Yes	 8 (50) 18 (48.6)	 8 (50) 19 (51.4)	0.928[1]
Diabetes mellitus, n (%) No Yes	 21 (45.7) 5 (71.4)	 25 (54.3) 2 (28.6)	0.250[2]
COPD, n (%) No Yes	 15 (46.9) 11 (52.4)	 17 (53.1) 10 (47.6)	0.695[1]
Inflammatory eye findings, n (%) No Yes	 20 (76.9) 6 (23.1)	 20 (74.1) 7 (25.9)	0.810[1]
Age Mean ± SD	 63.5±17.5	 76±11.8	**0.004**[3]
LDH, U/L Mean ± SD	 409.8±142.3	 430.7±146.5	0.600[3]
Neutrophils, x10^3/µL Mean ± SD	 4.9±2.5	 6.7±3.1	**0.024**[3]
Lymphocytes, x10^3/µL Mean ± SD	 0.7±0.3	 0.7±0.3	0.239[3]
CRP, mg/dL Mean ± SD	 139.4±96.8	 135.8±72.2	0.877[3]
White blood cells, x10^3/µL Median (25th-75th percentile)	 7.5 (9.8-12.4)	 9.3 (12.2-17.7)	0.011[4]
Ferritin, ng/mL Median (25th-75th percentile)	 232.8 (497.5-1137.8)	 287 (573-1577)	0.493[4]

[1]Pearson chi-square test, [2]Fisher's exact test, [3]Student's t test, [4] Mann-Whitney U test, COPD: Chronic obstructive pulmonary disease, SD: Standard deviation, LDH: Lactate dehydrogenase, CRP: C-reactive protein

Table 7. Multiple logistic regression model of variables associated with survival							
	B	**S.E.**	**Wald**	**p**	**OR**	**95% CI for OR**	
						Lower	**Upper**
Mask with reservoir bag (ref: Yes)	3.713	0.962	14.906	<0.001	40.9	6.2	269.9
Neutrophils, x103/µL	0.453	0.186	5.91	0.015	1.6	1.1	2.3
Constant	-0.796	0.978	0.662	0.416	0.451		

CI: Confidence interval, OR: Odds ratio

Study Limitations

During the COVID-19 pandemic, many hospitals have dedicated intensive care units to patients with COVID-19. A similar study with a control group of individuals being treated in a different intensive care unit for reasons other than COVID-19 may yield more accurate results. In our study, patients treated in the COVID-19 intensive care unit were not evaluated for pulmonary involvement by computed tomography, and a positive RT-PCR test was the only criterion considered for COVID-19 diagnosis. A link may be detected between increased inflammation in the lungs on computed tomography and inflammatory eye signs. A study including patients who have negative RT-PCR results but a history of COVID-19 contact and consistent computed tomography findings could yield different results. In addition, conjunctival RT-PCR samples were not obtained from patients with ocular surface findings because the RT-PCR kit available in Turkey can only detect virus in oropharyngeal/nasopharyngeal swab samples. In the future, new studies should be conducted using conjunctival RT-PCR kits. Another limitation of the study is that in the retinopathy screening, patients were only evaluated for findings expected to increase in COVID-19, such as intraretinal hemorrhage, Valsalva retinopathy, and optic neuritis. For example, the frequency of hypertensive retinopathy could be found to be correlated with mortality and ocular findings in COVID-19 intensive care. New studies on this subject are needed. The patients were not evaluated with Schirmer and fluorescein staining tests. New studies can be planned taking into consideration the possible role of dry eye in ocular findings. The new drugs that have recently been introduced due to the SARS-CoV-2 pandemic may also cause inflammatory findings on the ocular surface, thus warranting further investigation.

Conclusion

The results of this prospective study showed that 24.5% of patients treated in a COVID-19 intensive care unit exhibited inflammatory signs such as congestion, secretion, and chemosis on ocular surface examination. Examination of the ocular surface is important in patients receiving intensive care for COVID-19, and ophthalmologists have an important duty in this field.

Ethics

Ethics Committee Approval: Afyonkarahisar Health University of Sciences, 4/12/20-2020/14.

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.E.A., Concept: İ.E.A., D.A., Design: İ.E.A., D.A., Data Collection or Processing: İ.E.A., D.A., Analysis or Interpretation: İ.E.A., D.A., Literature Search: İ.E.A., D.A., Writing İ.E.A., D.A.

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