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ORIGINAL ARTICLE

Evaluation of the relationship between ocular surface symptoms and platelet-to-lymphocyte ratio in COVID-19 patients

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ABSTRACT

Objective: This study aims to evaluate ocular surface symptoms and their association with platelet-to-lymphocyte ratio (PLR) in patients who were clinically confirmed with coronavirus disease 2019 (COVID-19) using Ocular Surface Disease Index (OSDI) questionnaire.

Material and Methods: Thirty-five COVID-19 hospitalized patients were included in the study. All patients had positive severe acute respiratory syndrome coronavirus 2 reverse-transcription polymerase chain reaction test results of nasopharyngeal and throat swab specimens as well as positive findings on computed tomography consistent with COVID-19. Ocular and medical histories were obtained from patients. Laboratory findings were noted. OSDI questionnaire was used to evaluate ocular surface symptoms.

Results: There were 20 females (57.1%) and 15 males (42.9%) with a mean age 40.5 (95% CI: 35.8–45.2) years in the study. The mean OSDI scores were 12.6 (95% CI: 7.8–17.5). OSDI scores were significantly correlated with PLR (r=–0.516, p=0.028).

Conclusion: Ocular surface problem is likely to occur in COVID-19 patients even in the absence of apparent ocular surface findings. PLR may have a relevance to ocular surface symptoms in COVID-19 patients.

Keywords: COVID-19, dry eye; ocular surface disease index, ocular surface, symptoms.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) which can result in serious pneumonia and respiratory failure was first reported in Wuhan, the capital of Hubei, China.[1] Analysis of respiratory samples demonstrated a novel coronavirus responsible for COVID-19 which is now known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2] Within a few months following initiation of the outbreak in China, COVID-19 has begun to spread worldwide rapidly, therefore, the World Health Organization announced COVID-19 as a pandemic in March 2020. Patients with COVID-19 characteristically show fever, cough, fatigue, and less frequently gastrointestinal infection symptoms.[3] Classically, human-to-human transmission of the disease occurs through droplets. Alternative routes of transmission have also been proposed through ocular tissue and/or fluid.[4]

A study has evaluated a total of 64 tear samples from 19 patients from the 1st, 2nd, and 3rd week of initial symptoms of COVID-19. The authors have found a lower risk of SARS-CoV-2 transmission through tears.[5] Another study has revealed a 5.2% prevalence of SARS-CoV-2 nucleotides in conjunctival specimens of COVID-19 patients indicating a possible transmission of SARS-CoV-2 through the eye.[6] Hong et al.[7] have assessed ocular symptoms in COVID-19 patients using the Ocular Surface Disease Index (OSDI) and Salisbury Eye Evaluation Questionnaire. They documented significant differences of OSDI scores between before and after disease onset implying disturbance of the ocular surface condition. Gambini et al.[8] demonstrated ocular surface impairment in post-COVID-19 patients.

Platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) are accessible biomarkers that are associated with inflammation in various diseases.[9] Changes in PLR and NLR have also been demonstrated in COVID-19 infection.[9,10]

In the present study, we aimed to evaluate the relationship between changes in OSDI score and laboratory values in COVID-19 cases.

MATERIAL AND METHODS

This prospective observational study was approved by the institutional review board (ref. no. 2020/16) and conducted according to the tenets laid out in Declaration of Helsinki. The study was done in the isolation ward of a referral tertiary hospital which is one of the specified centers for hospitalization of COVID-19 patients across the region.

All patients in the study were diagnosed with COVID-19. Disease diagnosis has been made based on clinical symptoms and positive SARS-CoV-2 reverse-transcription polymerase chain reaction test results of nasopharyngeal and throat swab specimens along with positive computed tomography findings indicating COVID-19.

Recruitment was done during hospitalization. All procedures were explained in details to patients and both oral and written informed consents were obtained. Systemic and ocular history was taken. Pertinent laboratory test results were noted for each patient, including blood urea nitrogen, creatinine, total protein, albumin, lactate dehydrogenase and transaminase levels, procalcitonin and C-reactive protein levels, white blood cell, neutrophil, lymphocyte, monocyte, basophil, eosinophil, red blood cell counts, hemoglobin and hematocrit levels, platelet counts, PLR, and NLR.

Systemic and Ocular History

Systemic and ocular history query was done before administration of OSDI questionnaire in all patients. Systemic query includes presence of hypertension, diabetes mellitus, chronic lung disease, thyroid disease, other chronic conditions such as allergy and/or rheumatic diseases, use of any systemic drug, and smoking history. Ocular history query includes presence of any refractive error, contact lens use, previous intraocular and/or extraocular surgery, ocular trauma, any ocular pathology and use of any ophthalmic drug.

Exclusion criteria for the study were, patients with a history of any systemic and/or ocular pathology that may cause ocular surface disease, previous ocular surgery, higher refractive error, contact lens use, ocular trauma, ocular medication, and unable to filling the OSDI questionnaire.

Patients with a history of uncomplicated essential hypertension were included in the study.

Evaluation of Ocular Symptoms

Ocular assessment was performed at bedside macroscopically.

The OSDI questionnaire is used in each patient to evaluate any existing subjective complaint to quantitatively assess ocular surface condition. The OSDI was a 12-item questionnaire including five different levels of symptoms those were scored as, 0 (none of the time), 1 (some of the time), 2 (half of the time), 3 (most of the time), and 4 (all of the time). The total OSDI score was calculated based on the formula as, OSDI = ([sum of scores for all questions answered] × 100)/([total number of questions answered] × 4).[11]

Patients were evaluated on a scale of 0–100 with higher scores indicating the degree of disability. OSDI scores in the study were then classified into four categories, including a normal OSDI score (0–12 points), a mild symptom severity OSDI score (13–22 points), a moderate symptom severity OSDI score (23–32 points), and a high symptom severity OSDI score (33–100 points).[12,13]

Statistical Analysis

The statistical analysis was performed using Statistical Package for the Social Sciences for Windows (SPSS version 22.0). Descriptive statistics were presented using mean and 95% confidence interval, upper and lower bounds. Distribution of the data was determined with Shapiro–Wilk test. Mann–Whitney U-test was used for non-normally distributed data to detect any difference between the groups. Spearman's rho correlation was performed to assess any relationship between OSDI scores, age, and laboratory findings. Influence of age, gender, and PLR on OSDI score was evaluated using multivariate linear regression analysis. P-value level under 0.05 was considered as statistically significant.

RESULTS

Fifty COVID-19 patients were recruited in the study. Six patients have systemic diseases which may affect results (e.g., diabetes mellitus, allergy, rheumatoid arthritis, Parkinson's disease, etc.), three patients have high refractive error and/or contact lens use, two patients have previous ocular surgery, two patients use ocular medication, and two

Table 1: Comparison of laboratory test results between patients with OSDI scores of <12 and with OSDI scores of >12

	OSDI scores <12 n=21	OSDI scores >12 n=14	p
Blood urea nitrogen (mg/dL)	11.8 (9.8–13.8)	11.4 (8.9–14.0)	0.78
Creatinine (mg/dL)	0.7 (0.6–0.8)	0.7 (0.6–0.9)	0.58
Total protein (g/L)	65.9 (62.7–69.2)	66.6 (47.7–85.5)	0.73
Albumin (g/L)	37.9 (35.4–40.4)	39.5 (33.8–45.2)	0.25
Aspartate aminotransferase (u/L)	26.4 (18.4–34.4)	20.1 (15.0–25.3)	0.26
Alanine aminotransferase (u/L)	25.0 (11.2–38.7)	25.0 (9.4–40.5)	0.89
Lactate dehydrogenase (IU/L)	188.7 (156.7–220.6)	218.5 (102.0–335.0)	0.45
C-Reactive protein (mg/L)	30.5 (–3.8–64.8)	5.8 (–3.7–15.4)	0.77
Procalcitonin	0.05 (0.02–0.08)	0.03 (0–0.07)	0.20
White blood cell (K/uL)	6.2 (4.4–8.15)	5.5 (4.4–6.7)	0.85
Neutrophil# (K/uL)	3.9 (2.1–5.6)	3.1 (2.0–4.2)	0.78
Lymphocyte# (K/uL)	1.5 (0.9–2.0)	1.8 (1.5–2.2)	0.25
Monocyte# (K/uL)	0.7 (0.3–1.1)	0.4 (0.3–0.5)	0.08
Basophil# (K/uL)	0.02 (0–0.05)	0.02 (0–0.07)	0.61
Eosinophil# (K/uL)	0.1 (0–0.18)	0.08 (0.05–0.12)	0.79
Red blood cell (M/uL)	4.5 (4.3–4.8)	4.4 (3.9–4.9)	0.77
Hemoglobin (g/dl)	13.2 (12.5–13.9)	13.5 (11.8–15.1)	0.89
Hematocrit (%)	38.8 (36.7–40.8)	39.7 (35.0–44.4)	0.92
Platelet (K/uL)	295.0 (227.2–362.7)	237.2 (167.9–306.6)	0.25
Neutrophil-to-lymphocyte ratio	3.08 (1.1–5.0)	1.78 (0.8–2.6)	0.22
Platelet-to-lymphocyte ratio	242.6 (159.3–325.9)	131.2 (82.8–179.6)	**0.02**

Mann–Whitney U-test, P<0.05; OSDI: Ocular Surface Disease Index; *: Results are expressed as mean (95% confidence interval lower bound-upper bound).

patients failed to fill OSDI questionnaire. Thirty-five subjects were included in the study. There were 20 females (57.1%) and 15 males (42.9%) mean age 40.5 (95% CI: 35.8–45.2) years in the study. The mean OSDI scores were 12.6(95% CI: 7.8–17.5).

There were 14(40%) patients whose OSDI score was over 12 (abnormal). Six of them (17.1%) had mild symptom severity OSDI score, 2(5.7%) moderate symptom severity OSDI score, and 6 (17.1%) severe symptom severity OSDI score.

No comorbidity exists in the study with exception of three COVID-19 patients who had hypertension. No conjunctival hyperemia, conjunctival chemosis, epiphora, photophobia, and presence of secretions were noted in patients during hospitalization based on ocular surface inspection.

Table 1 shows comparison of laboratory test results between patients with OSDI scores of <12 and with OSDI scores of >12. Mean PLR was found to be significantly lower in patients who had an OSDI score of >12 (131.2, 95% CI: 82.8–179.6) than in patients with an OSDI score of <12 (242.6, 95% CI: 159.3–325.9) (p=0.02). No other significant differences were observed in terms of laboratory analyses.

Further correlation analysis showed that OSDI scores did not show significant correlation with age (r=–0.058, p=0.79). OSDI scores were significantly correlated with PLR (r=–0.516, p=0.028). In a multivariate regression model, as OSDI score a dependent variable; age, gender, and PLR were an independent variables, only PLR had a significant association with OSDI score (p=0.02).

DISCUSSION

In the current study, the mean OSDI score was 12.6 in all patients. Ocular symptom severity was above 12 in 40% of the patients. While a negative correlation was found between the PLR and the OSDI score, no relationship was observed between the other laboratory data and the OSDI score.

In the literature, there are few papers about OSDI questionnaire in COVID-19 patients.[7,8] In most publications, the OSDI score was found to be higher in patients with COVID-19.[7,8] In this study, in accordance with the literature, we found the mean OSDI score above the normal value in individuals who had COVID-19 infection. To the best of our knowledge, this is the first study showing a relationship between OSDI score and PLR.

The OSDI questionnaire has been widely used as a reliable tool to detect ocular surface problems as well as severity of dry eye. The OSDI questionnaire is also a valuable instrument to identify the influence of dry eye associated ocular symptoms on vision-related func-

tion.[11] It easily evaluates ocular irritation symptoms related to ocular surface disturbance.[14] As for further analysis to assess different ocular surface disease severity, self-stated OSDI scores have been stratified as normal, mild, moderate, and severe. It has been reported that OSDI scores >12 highly estimate clinically important difference in terms of severity of ocular surface problem.[15,16]

Hong et al.[7] have administered OSDI questionnaire to discharged patients who had well recovered from COVID-19 using telephone call. They have observed significant differences of OSDI scores between before (mean, 6.25) and following (mean, 6.81) onset of COVID-19. Based on their findings, they have suggested that ocular surface disturbance may occur in COVID-19 patients. The authors have also postulated that systemic immune system reaction, secondary infection by other ocular pathogens, and ocular tissue infection by SARS-CoV-2 are probable factors for ocular surface alteration in these patients.[7] Gambini et al.[8] have demonstrated both qualitative and quantitative ocular surface impairments in their study on post-COVID-19 patients. Ocular surface symptoms may begin with the disease and may persist after the disease has healed.

From the beginning of the outbreak, several reports tried to elucidate association between COVID-19 and its possible ophthalmic manifestations. It was reported that transmission of SARS-CoV-2 may occur through conjunctival epithelium through infectious droplets and body fluids.[4] Another study found ocular abnormalities compatible with conjunctivitis, including conjunctival hyperemia, chemosis, epiphora, or increased secretions. The authors indicated a possible transmission of the virus through the eyes.[6] Another study suggested a low risk of SARS-CoV-2 transmission through tears.[5] Like other coronaviruses, SARS-CoV-2 invades host cells through binding angiotensin-converting enzyme 2 (ACE2) receptor. This process allows virus to be mainly spread through the respiratory tract, thereby facilitating infection.[3] A lower degree of ACE2 gene expression has also been demonstrated in human corneal and conjunctival epithelial cells compared to that in lung and heart cells.[17] This arises the possibility of virus inoculation through ocular surface epithelium.[7]

Several reports demonstrated ocular surface manifestations in hospitalized COVID-19 patients. Chen et al.[18] showed bilateral acute follicular conjunctivitis in a patient with confirmed COVID-19. They were able to demonstrate presence of viral RNA in conjunctival specimen 13 days after disease onset. Cheema et al.[19] presented a COVID-19 case with an initial presentation of keratoconjunctivitis. Conjunctival swab of the affected eye was also positive for the SARS-CoV-2 virus. Xie et al.[20] have studied ocular surface swabs from 33 patients. They have detected viral RNA in specimens from two eyes of two patients. Zhang et al.[21] have observed a 2.78% incidence of conjunctivitis in 72 patients with a laboratory confirmed COVID-19. In the present study, we did not collect conjunctival swab specimens from patients, hence, we were not able to detect the presence of viral RNA in ocular surface. We also did not observe any evidence of ocular surface problem at least based on our ocular surface inspection. Interestingly, OSDI score severity remained higher despite lack of any ocular surface findings. This may suggest that ocular surface problem may be an issue in COVID-19 patients even in the absence of apparent ocular surface findings.

Significant changes in complete blood counts have been documented during the course of COVID-19.[22] It has been concluded that PLR can be a predictor for disease severity.[10] In the current study, we generated a novel finding that OSDI scores have an association with PLR. Patients with higher OSDI scores tend to have lower PLR. This finding deserves further investigation.

There are several limitations of the present study. First, ocular surface assessment requires multiple tools to obtain accurate results, but we were not able to perform slit-lamp examination to better assess ocular surface condition of the subjects due to isolation and restriction criteria during the pandemic. Thus, we could not carry out routine objective basic test panels such as Schirmer test, ocular staining, tear film break-up time test, and tear film osmolarity assessment. Without objective measures of dry eye, reliance solely on OSDI questionnaire might be associated with high risk of performance bias. Second, patients with COVID-19 may be more inclined to report more symptoms compared to healthy participants. Third, environmental factors such as hospital stay, sleep duration, and ambience humidity may be present, which can affect the ocular surface symptoms in the patient group. Fourth, the present study includes relatively lower number of patients, thus our results should be interpreted carefully. We also put strict inclusion and exclusion criteria during recruitment of the patients to avoid the possible impact of several systemic conditions on ocular surface changes. On the other hand, as there is a growing evidence toward an association between COVID-19 and ophthalmologic findings, the present study can yield important results for clinicians.

CONCLUSION

COVID-19 patients were prone to have higher OSDI scores. This may arise possibility of ocular surface alterations in COVID-19 patients. Severity of ocular surface-related symptoms may be correlated with the severity of COVID-19. Significant clinical correlation between OSDI scores and PLR ratio needs to be supported with further evidence. We think that further studies are necessitated to validate the results of the present work and to better ascertain relationship between COVID-19 and ocular surface.

Statement

Ethics Committee Approval: The Trabzon Kanuni Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 20.05.2020, number: 2020/16).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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Conflict of Interest: The authors have no conflict of interest to declare.

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