



Investigation of the Clinical Laboratory Indexes in COVID-19 Patients with Ocular Symptoms in Iran: A Single-Center Experience

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Received 2021 June 18; Revised 2021 December 26; Accepted 2022 January 17.

Abstract

Objectives: Ocular symptoms are prevalent in coronavirus infectious disease 2019 (COVID-19) patients, which may be related to clinical/paraclinical conditions. This study investigated the association between laboratory indexes and ocular symptoms in COVID-19 patients.

Methods: In this cross-sectional study, 108 polymerase chain reaction (PCR)-confirmed COVID-19 patients admitted to the Rouhani Hospital, Babol, Iran, were enrolled. Ocular symptoms were investigated using standard ophthalmologic examinations. Routine laboratory investigation was done according to the standard management in patients with COVID-19 infection.

Results: The erythrocyte sedimentation rate (ESR) and the serum levels of the blood urea nitrogen (BUN) and creatinine (Cr) were significantly higher in COVID-19 patients with ocular discharge and exudate ($P = 0.002, 0.045, 0.046,$ and $0.027,$ respectively), while the red blood cell (RBC) and albumin were lower in COVID-19 patients with ocular discharge and exudate ($P = 0.029$ and $0.027,$ respectively). The serum levels of creatine kinase (CPK) and iron (Fe) were significantly higher in non-photophobic COVID-19 patients than in photophobic patients ($P = 0.033$ and $0.050,$ respectively). In contrast, the serum level of procalcitonin was lower than photophobic COVID-19 patients ($P = 0.024$). The serum level of phosphorus (P) was significantly higher in COVID-19 patients with itchy eyes compared to COVID-19 patients without itchy eyes ($P = 0.026$).

Conclusions: The footprint of laboratory indexes was demonstrated in ocular symptoms of COVID-19 patients. The kidney biomarkers were correlated with ocular discharge and exudate, and electrolytes were associated with tear-related symptoms.

Keywords: COVID-19, SARS-CoV-2, Eye Manifestations, Laboratory Diagnosis, Inflammation

1. Background

Coronaviridae is the most prominent positive-strand RNA virus family corresponding to ocular pathogenesis (1). There are various contradictory reports about the ocular symptoms and other clinical conditions in coronavirus-infected patients (2). The clinical symptoms in different organs are related to secondary damage of the severe acute respiratory syndrome-related Coronavirus 2 (SARS-CoV-2). Other eye parts have a different impact on coronavirus-related infectious diseases (3). Also, due to the connection between the eye mucosa and the upper respiratory tract through the nasolacrimal duct, the eye can be a pathway for the entry and replication of respiratory viruses, e.g., SARS-CoV-2 (4).

The inflammation in the eye is related to inflammatory cytokines or active viral/bacterial infection (5, 6). Therefore, the cytokine storm, which appears in SARS-CoV-2-infected patients, can lead to ocular symptoms, i.e., blurred vision, epiphora, discharge and exudate, redness,

eye pain, photophobia, and itchy eye. These clinical symptoms are prevalent in SARS-CoV-2-infected patients (7, 8). The possible associations of clinical laboratory indexes and ocular manifestations may lead to a rapid estimation of prognosis in hospital-referred COVID-19 patients. Also, it can be critical in the management of ocular manifestation in COVID-19 patients (9-12).

2. Objectives

This study investigated the correlation of laboratory indexes and the presence of ocular symptoms (i.e., blurred vision, epiphora, discharge and exudate, redness, eye pain, photophobia, and itchy eye) in COVID-19 patients.

3. Methods

3.1. Sampling

This cross-sectional study was performed on 108 COVID-19 patients admitted to the Rouhani Hospi-

tal, Babol, Iran, from January to February 2021. The ethics committee of the Babol University of Medical Sciences confirmed the study (approval code: IR.MUBABOL.REC.1399.391). Detailed clinical examinations regarding ophthalmological protocols were conducted on ocular symptoms on the first day of hospitalization. All ocular symptoms were registered for all the patients. The sample size was estimated to be at least 44 ($P = 2.9\%$, $d = 0.05$, $\alpha = 0.05$) (13), but 108 patients were enrolled to obtain more accurate results.

3.1.1. Inclusion and Exclusion Criteria

All patients over 18 years of age who had been hospitalized for three days and had a positive nasopharyngeal PCR specimen were enrolled. Also, patients with a history of chronic eye diseases (Symblepharon, uveitis, lacrimal duct obstruction) and those treated with ocular steroids and systemic and ocular antibiotics were excluded from the study.

3.2. Laboratory Examinations

Oxygen saturation (SpO_2), differential white blood cell (WBC) count, erythropoiesis-related indexes (red blood cell (RBC), hemoglobin (Hb), mean cell volume (MCV), iron (Fe), total iron-binding capacity (TIBC), and ferritin), coagulation profile [platelet count (Plt), prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), and D-dimer], inflammatory profile [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)], electrolytes [calcium (Ca), magnesium (Mg), phosphorus (P), sodium (Na), and potassium (K)], interleukin-6 (IL-6), bio-enzymes [creatinine phosphokinase (CPK), lactate dehydrogenase (LDH), alanine aminotransferase (ALT), and aspartate aminotransferase (AST)], fasting blood sugar (FBS), blood urea nitrogen (BUN), creatinine (Cr), serum albumin, procalcitonin, and pro-B-type natriuretic peptides (proBNP), and triglyceride (TG) were investigated using the standard laboratory protocols in the Rouhani Hospital's Laboratory Department, Babol, Iran.

3.3. Statistical Analysis

The association between laboratory indexes and ocular symptoms was investigated in COVID-19 patients using the Mann-Whitney U test. All analyses were performed using SPSS version 25. The significant level was considered 95% ($P < 0.05$).

4. Results

4.1. Ocular Manifestations

Among the 108 patients, 60 cases (55.6%) had at least one ocular manifestation. The mean age was 62.50 ± 14.46

years in patients with at least one ocular manifestation and 59.52 ± 16.51 years in patients without any ocular manifestation. Of all the participants, eight cases (7.4%) had blurred vision, 17 cases (15.7%) had epiphora, nine cases (8.3%) had discharge and exudate, 23 cases (21.3%) had eye redness, seven cases (6.5%) had eye pain, 14 cases (13.0%) had photophobia, and nine cases (8.3%) had itchy eyes.

4.2. Association of Ocular Symptoms and Laboratory Indexes

The mean RBC level was $3.64 \pm 0.79 \times 10^6$ cells/ μ L in COVID-19 patients with discharge and exudate, while it was $4.30 \pm 0.85 \times 10^6$ cells/ μ L in COVID-19 patients without discharge and exudate ($P = 0.029$). ESR was significantly higher in COVID-19 patients with discharge and exudate (81.44 ± 43.28 mm/hours) than in COVID-19 patients without discharge and exudate (40.12 ± 26.25) ($P = 0.002$). Also, BUN and Cr (33.00 ± 9.84 mg/dL, and 1.91 ± 1.77 mg/dL, respectively) were significantly higher in COVID-19 patients with discharge and exudate than in COVID-19 patients without discharge and exudate (28.88 ± 21.06 mg/dL, and 1.37 ± 1.58 mg/dL, respectively) ($P = 0.045$, and 0.046 , respectively). The mean serum albumin level in COVID-19 patients with discharge and exudate was 3.24 ± 0.57 mg/dL, while it was 3.69 ± 0.55 mg/dL in COVID-19 patients without discharge and exudate ($P = 0.027$).

CPK was significantly higher in non-photophobic COVID-19 patients (178.22 ± 143.54 IU/L) than in photophobic COVID-19 patients (35.50 ± 9.19 IU/L) ($P = 0.033$). However, the serum level of procalcitonin (0.08 ± 0.03 ng/mL) was significantly lower in non-photophobic COVID-19 patients than in photophobic COVID-19 patients (1.65 ± 6.62 ng/mL) ($P = 0.024$). Also, Fe was significantly higher in non-photophobic COVID-19 patients (81.33 ± 59.88 ng/mL) than in photophobic COVID-19 patients (15.00 ± 2.00 ng/mL) ($P = 0.050$). The mean level of RBC count in COVID-19 patients with itchy eyes was $3.81 \pm 0.44 \times 10^6$ cell/ μ L, while it was $4.29 \pm 0.87 \times 10^6$ cell/ μ L in COVID-19 patients without itchy eyes ($P = 0.041$).

In COVID-19 patients with epiphora, the serum level of Ca was 9.01 ± 0.51 (mg/dL), while it was 8.60 ± 0.61 (mg/dL) in non-epiphoric COVID-19 ($P = 0.015$). There were no associations between other laboratory indexes and epiphora in COVID-19 patients.

5. Discussion

During the COVID-19 pandemic, various symptoms associated with COVID-19 are seen in patients. Ocular symptoms are usual in COVID-19 patients and may be accompanied by a change in laboratory indexes, which was investigated in the current study. Our results established the footprint of abnormal change of laboratory indexes in various ocular symptoms of COVID-19 patients. We found that the

kidney biomarkers were correlated with ocular discharge and exudate, and electrolytes were associated with tear-related symptoms.

Our results also showed that discharge and exudate were prevalent ocular symptoms in COVID-19 patients. In a 2017 study by Čolak et al., CRP and IL-6 were associated with exudate in age-related macular disease (AMD) (14). Unlike Čolak et al.'s study, our results did not show any correlation between CRP and IL-6 with ocular discharge and exudate. However, ESR was associated with ocular discharge and exudate.

Renal and ocular diseases are closely related. Various studies have investigated the association chronic kidney failure and retinal diseases (15). Also, various pieces of evidence established the footprint of renal involvement in COVID-19 (16). Our results demonstrated the association of laboratory indexes of renal damage with ocular discharge and exudate. BUN and Cr were significantly higher in COVID-19 patients with discharge and exudate than in others. In line with our results, Čolak et al. found an association between the reduction of uric acid and the exudative form of AMD (14). Also, we observed a reduced serum albumin level in ocular exudative COVID-19 patients, confirming the association of renal damage with discharge and exudate.

CPK increases in COVID-19 patients compared to other individuals (17). Our findings showed a reduced level of CPK in photophobic COVID-19 patients compared to non-photophobic COVID-19 patients. Procalcitonin is a protein involved in determining the severity of infectious disease (18). Procalcitonin is significantly higher in severe COVID-19 patients than in moderate and mild COVID-19 patients (19). Our results showed that the serum level of procalcitonin was about 20-fold higher in photophobic COVID-19 patients than in non-photophobic COVID-19 patients.

Itching is a common ocular symptom in COVID-19 patients (20). Combs et al. showed that a high level of serum P was related to ocular itching (21). According to our results, a high level of blood P was associated with itching in COVID-19. This finding establishes that the control of the serum level of P is critical in managing ocular itching in COVID-19 patients.

The Ca-related signaling pathway is involved in the exocrine secretion of lacrimal glands (22). Our results showed that the serum level of Ca was significantly higher in COVID-19 patients with epiphora than in patients without epiphora. Therefore, Ca level management should be a vital step in controlling epiphora in COVID-19 patients. Overall, our results established the role of cations in tear-related ocular symptoms.

Ocular redness is a symptom of ocular inflammation (23). The evidence shows that SARS-CoV-2 can affect the eyes. Therefore, ocular redness is an uncommon symp-

tom in COVID-19 patients (24). On the other hand, our results showed that the percentile count of lymphocytes was higher in COVID-19 patients with ocular redness than in COVID-19 patients without redness. Higher lymphocyte count is associated with more inflammation. Therefore, ocular redness and higher lymphocyte level probably have a confocal point: more severe infection of SARS-CoV-2.

In a study by Huang et al., LDH and D-dimer were introduced as biochemical screening tests for COVID-19 (25). However, our results showed that LDH and D-dimer were not correlated with any ocular symptoms.

In a review study, Fang et al. reported a change in laboratory indexes of COVID-19 patients. RBC, WBC, PT, PTT, INR, fibrinogen, blood gas, d-dimer, cations, ALT, AST, albumin, BUN, Cr, ESR, CRP, procalcitonin, CPK, and LDH were introduced to be involved in COVID-19 (26). Our study established the association of RBC, ESR, BUN, Cr, and serum albumin with discharge and exudate, the association of CPK, procalcitonin, and Fe with photophobia, the association of RBC, P, and Ca with itchy eyes and epiphora, and the association of lymphocyte count and ALT with ocular redness.

Finally, our results demonstrated the footprint of laboratory indexes in ocular symptoms of COVID-19 patients. The presence of ocular symptoms can alert clinicians to pay more attention to laboratory tests. These associations can be observed in the clinic. Also, ocular symptoms associated with COVID-19 can complicate medications for treating ocular diseases. Therefore, managing the serum level of specific biochemical and hematological indexes is critical to reducing ocular symptoms and preventing future problems. For further studies, it is suggested to investigate the association between ocular symptoms and the positivity status of conjunctiva PCR.

5.1. Limitations

The incompleteness of laboratory tests for all the patients, exclusion of cases with secondary complications, lack of awareness of some patients for conscious cooperation, and request to leave the study were the limitations of this study. We suggest a retrospective cohort study regarding our experiment for the involvement of more samples and higher probability of significant findings.

5.2. Conclusions

Our results demonstrated the footprint of laboratory indexes in ocular symptoms of COVID-19 patients. The kidney biomarkers were correlated with ocular discharge and exudate, and electrolytes were associated with tear-related symptoms.

Acknowledgments

We acknowledge that the Babol University of Medical Sciences, Babol, Iran, supported this study as part of a general medicine graduating thesis.

Footnotes

Authors' Contribution: S. A. R. supervised the study. M. F. provided technical support to the study. M. B., M. S., H. Z., and A. F. provided advice to the study team.

Conflict of Interests: There are no conflicts of interest in this manuscript.

Ethical Approval: The ethics committee of the Babol University of Medical Sciences approved the study (approval code: IR.MUBABOL.REC.1399.391).

Funding/Support: The study was not financially supported by any institution.

Informed Consent: No informed consent was obtained in the manuscript because clinical and laboratory data were used.

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