Journal of
Babol University of Medical Sciences
JBUMS
e-ISSN: 2251-7170 p-ISSN: 1561-4107

The Association between Laboratory Blood Parameters and Ocular Manifestations in COVID-19 Patients Admitted to the Intensive Care Unit

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Article Type
Research Paper

Received:
Jun 18th 2022
Revised:
Jul 25th 2022
Accepted:
Aug 13rd 2022

ABSTRACT

Background and Objective: With the spread of coronavirus disease 2019, secondary ocular manifestations were observed as common complications in COVID-19 patients, which can challenge the diagnosis and treatment of ocular diseases. The aim of this study is to investigate the association between laboratory parameters and ocular diseases and to determine their specificity and sensitivity in the diagnosis of ocular diseases in COVID-19 patients admitted to the intensive care unit.

Methods: In this cross-sectional study, 89 patients with COVID-19 admitted to the intensive care unit of Ayatollah Rouhani Hospital in Babol were examined from December 2020 to February 2021. Clinical examinations were performed according to the global standards for ophthalmology examinations for patients, and patients were examined in terms of intraocular pressure, cup-to-disc ratio, ocular manifestations, and ocular diseases. Routine hematology and biochemical laboratory tests were performed for all patients. Patients were compared in the group with an ocular disease (manifestation) and the group without that ocular disease (manifestation).

Findings: Out of 89 patients with COVID-19 hospitalized in the intensive care unit, 44 women and 45 men participated in the study and the mean age of the patients was 58.5±14.64 years. The number of white blood cells was significantly lower in COVID-19 patients with pinguecula compared to non-pinguecula patients (p=0.026). Furthermore, the relative percentage of lymphocytes was significantly lower (p=0.003) in COVID-19 patients with cataract (9.64±13.20%) compared to non-cataract patients (14.25±17.95%). The relative percentage of neutrophils was higher in COVID-19 patients with cataract compared to non-cataract patients (p=0.01). RBC is significantly reduced in COVID-19 patients with chemosis (p=0.024). For the relative percentage of neutrophils greater than or equal to 82.55%, cataract for COVID-19 patients admitted to the intensive care unit with 0.83% sensitivity and 66.7% specificity is positive.

Conclusion: The results of the study showed that blood cells and some biochemical parameters are associated with ocular diseases in COVID-19 patients admitted to the intensive care unit.

Keywords: *Rare Bleeding Disorders, Patients, Human T-Cell Leukemia Virus Type 1.*

Cite this article: Babaei M, Sadeghi Hadad Zavareh M, Amri Maleh P, Rasoulinejad SA. The Association between Laboratory Blood Parameters and Ocular Manifestations in COVID-19 Patients Admitted to the Intensive Care Unit. *Journal of Babol University of Medical Sciences*. 2022; 24(1): 355-62.

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[DOR: 20.1001.1.15614107.1401.24.1.43.9]
[DOI: 10.22088/jbums.24.1.355]

Introduction

The 2019 coronavirus disease (COVID-19) is a major challenge of the 21st century that has affected the whole world. COVID-19 is a kind of respiratory disease in which the virus enters the target cells through the angiotensin-converting enzyme receptor, and it leads to the spread of general inflammation and deterioration of the patient's condition through excessive induction of inflammatory cytokines by the immune system (1). This disease has infected more than 579 million people and killed more than 6 million 400 thousand people by August 2022 (2). The cause of COVID-19 is the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is from the coronaviridae family (3). Coronaviridae is the largest positive-strand RNA virus family, which is associated with some ocular manifestations (4).

The occurrence of various diseases during the COVID-19 pandemic is accompanied by numerous diagnostic and treatment challenges (5). For example, the diagnosis and treatment of ocular diseases face many challenges due to the delay in refereeing to medical centers, less access to related specialists, the presence of secondary diseases, etc. In addition, the presence of ocular manifestations such as redness, pain, inflammation, and eye irritation as secondary symptoms in patients with COVID-19 makes the treatment during the course of the disease more challenging (6-8). There are various reports about the occurrence of ocular diseases in patients with COVID-19. Moreover, due to the connection between the ocular mucosa and the upper respiratory tract through the nasolacrimal duct, the eye can be a way for respiratory viruses such as SARS-CoV-2 to enter and multiply (9). The serious physiological conditions of COVID-19 patients hospitalized in the intensive care unit increase the diagnostic challenges of ocular diseases (10, 11).

Cataract, pinguecula, pterygium, fixed pupil, chemosis, epiphora, secretion and exudation and redness of the eye are among the most common ocular diseases during the COVID-19 pandemic. Cataract disease is mainly related to the eye, the indicator of which is the presence of a cloudy area in the lens of the eye. A pinguecula is a small, raised, white or yellow raised lesion confined to the conjunctiva. Also known as surfer's eye, a pterygium is a raised conjunctival growth that extends over the cornea. Fixed pupil is also a state in which the pupil of the eye does not respond to external stimuli such as light. Chemosis is also a sign of eye irritation. In this condition, the outer surface of the eye (conjunctiva) may look like a big blister. Epiphora is an abnormal overflow of tears without a stimulus. Secretion and exudation are a combined liquid of cells, proteins and solid substances caused by infection or inflammation. Moreover, eye redness, which indicates increased blood supply to the ulcer, is one of the common eye manifestations in COVID-19. Laboratory parameters are the most important pillar of paraclinical diagnosis (9, 12, 13). Since the beginning of the COVID-19 pandemic, an attempt has been made to better understand the pathogenesis of the disease and make the treatment path smoother for patients by determining the role of routine laboratory parameters in the diagnosis and prognosis of COVID-19. Furthermore, the association between laboratory parameters and the occurrence of ocular manifestations in various diseases has been proven. For example, a study by Čolak et al. showed that CRP was associated with secretion and exudation in patients with age-related macular degeneration (14). Moreover, Combs et al. showed that high serum potassium level was associated with eye itching in COVID-19 patients. These studies confirm the importance of laboratory findings in the occurrence of ocular manifestations (7, 15).

Studies have been conducted about the relationship between laboratory parameters and the occurrence of clinical symptoms in patients with COVID-19 (16, 17). Possible correlation of clinical laboratory parameters and ocular manifestations may lead to rapid estimation of prognosis in hospitalized COVID-19 patients. Also, it can be critical in the management of ocular manifestations in COVID-19 patients. Finding the above-mentioned possible relationships in patients admitted to the intensive care unit is more important due to more complex clinical conditions compared to patients admitted to the general ward. In this study,

[DOR: 20.1001.1.15614107.1401.24.1.43.9]
[DOI: 10.22088/jbums.24.1.355]

the aim is to investigate the relationship between laboratory parameters and ocular diseases such as cataract, pinguecula, pterygium, fixed pupil, chemosis, dry eye, eye irritation, epiphora, secretion and exudation, blurred vision, eye redness and other manifestations in COVID-19 patients admitted to the intensive care unit. In addition, in case of finding a significant relationship, an attempt has been made to determine the specificity and sensitivity of the changes of relevant laboratory parameters in the diagnosis of some eye diseases.

Methods

After being approved by the ethics committee of Babol University of Medical Sciences with the code IR.MUBABOL.REC.1400.073, this cross-sectional study was conducted on 89 patients with COVID-19 admitted to the intensive care unit of Rouhani Babol Hospital from December 2020 to February 2021. The calculation of the sample size was based on the study of Samra et al. (18). Patients with the age of more than 18 years and less than 85 years, the positive result of nasopharyngeal PCR, admission in the intensive care unit, the possibility to see the retina in them, as well as the consent of the subjects to participate in the research were included in the study. In case of unavailability of complete patient information, inability to see the retina, blockage of tear ducts, history of ocular disease confirmed by an ophthalmologist before contracting COVID-19 and taking eye medications before contracting COVID-19, patient's dissatisfaction with entering the study or deciding to withdraw were excluded from the study.

Clinical examinations were performed according to the standard of ophthalmology examinations for patients admitted to the intensive care unit using Ophthalmoscope Keeler and Schiotz Tonometer, and the patients were evaluated in terms of intraocular pressure, cup-to-disc ratio, cataract, pinguecula, pterygium, fixed pupil, chemosis, eye dryness, eye irritation, epiphora, secretion and exudation, blurred vision, eye redness and other diseases. Routine hematology and biochemical laboratory tests such as hemoglobin, CRP, BUN, calcium, proBNP, total serum protein, relative percentage of neutrophils, relative percentage of lymphocytes, serum potassium, serum albumin, SPO2, serum lactate dehydrogenase, D-dimer, prothrombin time, the international normalized ratio (INR), alkaline phosphatase, white blood cell count, red blood cell count, serum albumin, ProBNP, relative thromboplastin time and ferritin were performed for all patients.

Statistical analyses were performed to compare the measured parameters in two groups suffering from an ocular disease (symptom) and the group not suffering from that ocular disease (symptom). Mann-Whitney U test was used to investigate the relationship between diseases and quantitative abnormal laboratory parameters. In addition, Pearson's test was used to evaluate abnormal quantitative variables and $p<0.05$ was considered significant.

Results

Out of 89 COVID-19 patients admitted to the intensive care unit, 44 women and 45 men participated in the study, and the mean age of the patients was 58.5±14.64 years. The white blood cell count in 19 COVID-19 patients with pinguecula (10375.45±4438.69 cells per microliter) was significantly lower ($p=0.026$) compared to non-pinguecula patients (12587.54±4335.25 cells per microliter). Moreover, the relative percentage of lymphocytes in 31 COVID-19 patients with cataract (9.64±13.20%) was significantly lower ($p=0.003$) compared to non-cataract patients (14.25±17.95%). The relative percentage of neutrophils was higher ($p=0.01$) in COVID-19 patients with cataract (85.86±12.91%) compared to non-cataract patients (80.22±18.47%). RBC in 5 COVID-19 patients with chemosis (3.85±0.63 million cells per microliter) was

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significantly lower (p=0.024) compared to patients without chemosis (4.29±0.82 million cells per microliter). Other biochemical laboratory parameters were significantly related to ocular diseases. Serum potassium in COVID-19 patients with cataract (3.80±1.25 mmol/L) was significantly lower (p=0.014) compared to non-cataract patients (4.29±1.89 mmol/L). Serum albumin in COVID-19 patients with cataract (3.35±0.53 g/dL) was significantly lower (p=0.014) compared to non-cataract patients (3.73±0.68 g/dL). Oxygen saturation (SpO2) in 6 COVID-19 patients with Pterygium (94.37±5.23%) was higher (p=0.012) compared to patients without Pterygium (85.27±14.64%). Furthermore, D-dimer in COVID-19 patients admitted to the intensive care unit with Pterygium (5707.28±6598.56 ng/ml) was higher (p=0.034) compared to patients without Pterygium (1332.60±2438.75). However, serum lactate dehydrogenase in COVID-19 patients admitted to the intensive care unit with Pterygium (871.77±527.75 units per liter) was lower (p=0.024) compared to patients without Pterygium (1245.30±593.93 units per liter). Statistically speaking, the level of hemoglobin in COVID-19 patients admitted to the intensive care unit with fixed pupils (9.38±0.80 g/dL) was significantly lower (p=0.023) compared to those without fixed pupils (11.41±2.19 g/dL). Moreover, prothrombin time in COVID-19 patients admitted to the intensive care unit with fixed pupils (15.98±4.68 seconds) was significantly higher (p=0.020) compared to those without fixed pupils (13.03±1.34 seconds). However, the international normalized ratio in COVID-19 patients admitted to the intensive care unit with fixed pupils (1.64±0.82) was higher (p=0.015) compared to those without fixed pupils (1.14±0.18). Serum alkaline phosphatase in COVID-19 patients admitted to the intensive care unit with chemosis (481.65±648.20 units per liter) was significantly higher (p=0.01) compared to people without chemosis (185.63±82.21 units per liter).

A significant association was found between cup-to-disc ratio (in right and left eyes) and laboratory parameters. Cup-to-disc ratio was directly associated with CRP, BUN and ProBNP levels and inversely associated with serum calcium and total protein (Table 1). Furthermore, intraocular pressure showed a direct association with CRP, BUN, serum alkaline phosphatase and ProBNP levels and an inverse association with calcium, serum total protein and hemoglobin.

Table 1. Association between cup-to-disc ratio (based on the eye) and intraocular pressure (based on the eye) and laboratory parameters

Clinical and statistical variables	Hemoglobin	CRP	BUN	Serum alkaline phosphatase	Calcium	proBNP	Total serum protein
Cup-to-disc ratio in the right eye							
correlation coefficient	-0.163	0.302	0.330	0.110	-0.326	0.607	-0.454
p-value	0.203	0.021	0.014	0.408	0.009	0.000	0.020
Number	63	58	55	59	64	40	26
Cup-to-disc ratio in the left eye							
correlation coefficient	-0.156	0.270	0.302	0.101	-0.324	0.589	-0.328
p-value	0.222	0.041	0.025	0.446	0.009	0.000	0.102
Number	63	58	55	59	64	40	26
IOP in the right eye							
correlation coefficient	-0.277	0.339	0.280	0.262	-0.272	0.330	-0.533
p-value	0.022	0.007	0.030	0.037	0.026	0.033	0.004
Number	68	63	60	64	67	42	28
IOP in the left eye							
correlation coefficient	-0.386	0.265	0.244	0.256	-0.440	0.408	-0.510
p-value	0.001	0.036	0.060	0.041	0.000	0.007	0.006
Number	68	63	60	64	67	42	28

[DOR: 20.1001.1.15614107.1401.24.1.43.9]
[DOI: 10.22088/jbums.24.1.355]

Discussion

The results of our study showed that parameters related to blood cells are associated with ocular diseases in COVID-19 patients admitted to the intensive care unit. The presence of ocular manifestations such as redness, burning, itching, etc. in COVID-19 patients, delay in referral to medical centers, and economic and social issues in the COVID-19 pandemic are some of the factors that complicate the diagnostic and treatment methods in the presence of any sort of ocular disease (19). In addition, the hospitalization of patients in the intensive care unit due to the deterioration of the patient's physical and physiological condition makes diagnosis and treatment more difficult (20). The laboratory parameters always have the most important place in paraclinic units in the diagnosis of various diseases as specific and non-specific biomarkers. In this study, we tried to evaluate the association between laboratory parameters and ocular manifestations, as well as their sensitivity and specificity in the presence or absence of ocular manifestations. White blood cell count was significantly lower in COVID-19 patients with pinguecula compared to non-pinguecula patients. Pinguecula is a deposit of fat, protein or calcium in the conjunctiva of the eye, which is mainly caused by chronic irritation of the conjunctiva. According to the obtained results, white blood cell count has an inverse relationship with the presence of pinguecula complication. Pinguecula was first reported by Reinhold et al. in patients with COVID-19 (21).

As mentioned, the diagnosis and treatment of cataract in the COVID-19 pandemic has many challenges, including the delay in treatment (22, 23). Cataract, as a common disease in societies, has various causes, such as aging, and taking certain drugs such as corticosteroids, radiation, etc. Our study showed that blood cells are closely associated with cataracts; in COVID-19 patients admitted to the intensive care unit, the relative percentage of neutrophils in people with cataracts is higher, and therefore the relative percentage of lymphocytes in these people is lower than in people without cataracts. Cataract is also related to other laboratory variables. For example, hypokalemia is one of the common complications of COVID-19 (24). Our results showed that serum potassium in COVID-19 patients with cataract is significantly reduced compared to non-cataract patients. In other words, low potassium levels in the blood lead to cataracts. Moreover, changes in serum albumin levels have been reported in COVID-19 (25). In our study, serum albumin was significantly lower in COVID-19 patients with cataract compared to non-cataract patients.

In a study by Huang et al., serum lactate dehydrogenase and D-dimer were introduced as biochemical screening tests for COVID-19 (26). Our results also showed that D-dimer is higher in COVID-19 patients with pterygium admitted to the intensive care unit, while serum lactate dehydrogenase is lower in COVID-19 patients with pterygium admitted to the intensive care unit.

Chemosis is inflammation of the eye conjunctiva, which is generally caused by allergic sensitivities, viruses, excessive rubbing of the eyes, or some underlying diseases. Chemosis is one of the common eye symptoms in COVID-19 (27). Serum alkaline phosphatase is significantly higher in COVID-19 patients with chemosis admitted to the intensive care unit.

Due to the high prevalence of eye complications in patients with COVID-19, the diagnosis and treatment of ocular manifestations during this pandemic is faced with many challenges. Our results showed that ocular manifestations are associated with routine laboratory parameters and these relationships have high correlation coefficients. Diagnosis based on laboratory data along with clinical examinations can be helpful in diagnosing ocular manifestations in COVID-19 patients, especially patients admitted to the intensive care unit.

[DOR: 20.1001.1.15614107.1401.24.1.43.9]
[DOI: 10.22088/jbums.24.1.355]

Acknowledgment

Hereby, we would like to thank our colleagues at the intensive care unit of Ayatollah Rouhani Hospital in Babol, as well as the vice president of research and technology of Babol University of Medical Sciences for their support in the implementation of this research.

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[DOI: 10.22088/jbums.24.1.355]