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Incidence and association of ocular manifestations with the disease severity in COVID-19 patients of northern region of India

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Abstract:

PURPOSE: Our study aims to find the incidence of ocular manifestations and to investigate the relation of ocular manifestations with the disease severity among coronavirus disease 2019 (COVID-19) patients.

MATERIAL AND METHODS: Our study is a cross-sectional study done between May 15, 2020, and April 15, 2021, at Hind Institute of Medical Sciences, Lucknow, India. All COVID-19 patients who got admitted to our center between May 15, 2020, and April 15, 2021, were included in our study. We included 261 patients in our study. Diagnosis of COVID-19 was made by testing the nasal and pharyngeal swabs by (reverse transcriptase-polymerase chain reaction [RT-PCR]). An RT-PCR test positive was the criteria for admission in the COVID ward. Statistical analyses were performed using the Mann–Whitney *U*-test, Chi-square test, and Kolmogorov–Smirnov test. $P < 0.01$ was considered statistically significant.

RESULTS: We included 261 patients in our study. Out of 261 patients, ocular manifestations were found in 43 (16.4%) patients. The patients with ocular manifestations had higher neutrophil counts, erythrocyte sedimentation rate (ESR), procalcitonin (PCT), C-reactive protein (CRP), and D-dimer values ($P < 0.001$). Patients with ocular manifestations were relatively more symptomatic concerning fever and myalgia.

CONCLUSION: The incidence of ocular manifestations in COVID-19 patients was 16.4%. Ocular manifestation was significantly associated with raised neutrophil counts, CRP, ESR, PCT, and D-dimer values. Ocular manifestation was also significantly associated with higher body temperature and higher mean age. The findings of the study are suggestive of more severe disease in patients of COVID-19 with ocular manifestations.

Keywords:

Conjunctivitis, coronavirus disease 2019, C-reactive protein, erythrocytic sedimentation rate, red eye

Introduction

At present, most of the countries of the world are facing a pandemic caused by a new coronavirus, namely severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). Since it started in 2019, it is named coronavirus disease 2019 (COVID-19).^[1] In December 2019, the

first case of COVID-19 was reported in Wuhan, China.^[2] The first case in India was reported in March 2020. The World Health Organization (WHO) declared it as a “Public Health Emergency” on January 30, 2020, and “Pandemic” on March 11, 2020. To date, the total number of confirmed COVID-19 cases reported in India is more than 16.6 million with more than 0.18 million deaths. Being a densely populated country with the average medical infrastructure, it is important to

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stop the transmission of COVID-19 in India and to identify the disease severity (mild, moderate, severe). The WHO had published guidelines for the protection and prevention of the spread of the disease.^[3]

Bats are known to be the primary carriers of coronaviruses. To date, 7 types of coronaviruses have been identified to infect human beings, namely HKU, 229E, OC43, NL63, Middle East respiratory syndrome coronavirus, SARS-COV, and SARS-COV2. COVID-19 is caused by SARS-COV2.^[4] Most of the coronaviruses are known to cause respiratory tract infections but some cause gastrointestinal infections and ocular infections.^[5,6]

Mainly, SARS-COV among the coronaviruses causes ocular manifestations.

SARS-COV RNA was found in tear samples of three patients in 2004, suggesting its ocular involvement.^[5,7] Many theories are explaining various routes of ocular involvement through direct conjunctival inoculation, hematogenous route, or nasolacrimal duct. Studies have proven that SARS-COV-2 has comparable epidemiological and pathological functions as SARS-COV. Both have structural and genomic similarities, due to these similarities, we can suspect ocular manifestations in COVID-19 as well.^[8,9]

On PubMed and Google search, there are limited publications on COVID-19 with ocular manifestations.^[10-16] Our study focuses on the incidence of ocular manifestations and its correlation with acute phase markers of COVID as C-reactive protein (CRP), D-dimer, erythrocyte sedimentation rate (ESR), procalcitonin (PCT), and neutrophil values. Our study also tries to find the association of age, degree of fever, and infection severity with ocular involvement.

Methods

This cross-sectional study was conducted at the Hind Institute of Medical Sciences, Lucknow, India, following the ethical standards of the Declaration of Helsinki. We included all the 261 patients in our study who got admitted to the COVID ward of our institute from May 15, 2020, to April 15, 2021. Diagnosis of COVID-19 was made after a positive reverse transcriptase-polymerase chain reaction (RT-PCR) test report of nasal and throat swabs. A positive RT-PCR test was the only criteria for admission in the COVID ward of our institute.

Complete blood count, D-dimer, CRP, PCT; lactose dehydrogenase (LDH); ESR, chest X-ray, and temperature charting were done and recorded. As per clinical symptoms, few patients were advised (high-resolution computed tomography) thorax.^[12] Ocular symptoms

if any were recorded. Fever and cough at the time of presentation were also recorded. Elderly age was marked as 65 years of age or above. Fever was marked as body temperature more than 37.3°C. All the ocular symptoms and findings were recorded by the same ophthalmologist in a proper personal protective equipment kit. The statistical analysis was done by using SPSS statistics software version 22 (Armonk, IBM, Chicago USA). Statistical calculations were done by using the Kolmogorov–Smirnov test and Chi-square test. Mann–Whitney *U*-test was used to test the differences between the outcomes of the two groups. *P* < 0.05 was considered statistically significant.

Ethical approval

The study was conducted following the ethical standards of the Declaration of Helsinki and was approved by the ethics committee of Hind Institute of Medical Sciences. (HIMS/IRB/2020-21/1110). The IRB agreed to waive written patient consent.

Results

A total of 261 patients were included in our study out of which 178 (68.2%) were males and 83 (31.8%) were females. The mean age of the patients was 31 years (minimum 3 years and maximum 81 years). Male patients had a mean age of 34.2 years, whereas female patients had a mean age of 24.1 years. Out of 261 patients, ocular involvement was found in 43 (16.4%) patients. Fever was recorded in 70 (26.8%) patients at the time of presentation. Cough was recorded in 48 (18.3%) patients. 158 (60.5%) patients were asymptomatic. 5 (1.9%) patients reported respiratory distress.

Table 1 shows the ocular findings and symptoms recorded in the patients having ocular manifestations in COVID-19.

Table 1: The ocular findings and symptoms recorded in the patients having ocular manifestations in coronavirus disease-2019

	n (%)
Ocular findings	
Conjunctival congestion	42 (16)
Conjunctival chemosis	8 (3)
Conjunctivitis (follicular)	7 (2.7)
Episcleritis	4 (1.5)
Ocular symptoms	
Blurring	3 (1.1)
Photophobia	22 (8.4)
Burning sensation	26 (9.9)
Foreign body sensation	36 (13.7)
Itching	5 (1.9)
Eye ache	21 (8)
Watering	28 (10.7)

Conjunctival congestion/hyperemia was the most common finding present in almost all the patients having ocular involvement, whereas foreign body sensation was the most common symptom followed by watering, burning sensation, and photophobia.

Table 2 shows the comparison between patients with ocular involvement and those without ocular involvement concerning age, fever, and laboratory findings.

In our study, the patients having ocular manifestations were relatively older, had more probability of fever, had a higher neutrophil count, neutrophil/lymphocyte ratio, and higher values of inflammatory markers such as CRP, D-dimer, PCT, LDH, and ESR ($P < 0.05$). All these findings were suggestive of more severe disease in patients with ocular involvement.

Discussion

COVID-19 is a pandemic affecting a major fraction of the population in the whole world. India has been badly struck by this pandemic. Ophthalmologists had been curious to find any ocular involvement in this disease as the lung is the main organ that came into the limelight in earlier days of the pandemic. Various articles on ocular manifestations of COVID-19 have been published to date.^[10-16] All these researches and studies started when a doctor of Wuhan was found infected with COVID-19 in 2020 and he had conjunctivitis at the same time. This produced a stir among the Ophthalmologists.

Pathophysiology of SARS-COV2 states inflammatory response as the most significant component, which results in the damage of airways.^[17] Viral load and host immune response together contribute to the severity of the disease.^[18] Some studies tell us about the role of ESR, PCT, and CRP to predict the onset of inflammation or infection.^[19] Many studies concluded that symptomatic COVID-positive patients had elevated immune markers such as CRP, PCT, and ESR.^[20,21] CRP is an acute immune marker with a half-life of 5–7 h and it begins to rise within 4–6 h of

the onset of inflammation.^[22] Its serum level indicates the measure of active inflammation, lung involvement, and the severity of the disease in patients with SARS-COV2 infection.^[23] PCT is released by either lungs or intestines. PCT levels increases during bacterial infection.^[24] Its level rises within 4–6 h of inflammation and remains elevated for 1–2 days after the inflammation subsides. Raised PCT levels in COVID patients indicate secondary bacterial infection and hence a more severe disease.^[25,26] ESR starts to rise within 24 h of the onset of inflammation, but it is less specific than CRP.^[27] D-dimer is produced as a result of the degradation of fibrin; it is present in the blood after a blood clot undergoes fibrinolysis. An increase in D-dimer values suggests a more severe COVID infection. LDH is an enzyme found in almost all cells of our body, this enzyme converts glucose into energy. Whenever cells are destroyed, this enzyme is poured into plasma and its level increases. Elevated LDH levels in COVID-positive patients signify cellular destruction in the body, hence a more severe COVID infection. Flu or influenza with added secondary bacterial infection also produces similar picture of the disease; hence, it needs to be ruled out and diagnosis of COVID-19 has to be established by RT-PCR tests.

In a prospective study done by Xia *et al.*,^[10] it was found that the SARS-COV2 virus can be present in tears or secretions of COVID RT-PCR-positive patients. It was proposed that chances are higher in patients having conjunctivitis, but its absence in nonconjunctivitis patients was not ruled out.

In a cross-sectional study done by Feng *et al.*, in the United states,^[16] mean age of the patients was 61.7 years, ocular manifestations were found in 9.5% of cases, and the most common manifestation was conjunctival injection. This study concluded that the factors associated with severe systemic COVID-19 disease were not associated with developing ocular manifestations. Results of our study contradict this study; reason might be difference in immunity and immune response among different population groups of different parts of the

Table 2: The comparison between patients with ocular involvement and those without ocular involvement concerning age, fever, and laboratory findings

	Patients with ocular manifestations (n=43)	Patients without ocular involvement (n=218)	P
Mean age (years)	52.1±11.32	26.8±15.97	<0.001
Fever over 37.3°C, n (%)	28 (65.11)	42 (19.26)	<0.001
Mean neutrophil count (/mm ³)	7659.23±4818.23	4723.16±2139.71	<0.001
Neutrophil/lymphocyte ratio	8.12±10.4	3.21±2.1	<0.001
Mean monocyte count (/mm ³)	488.2±179.5	481.3±199.4	>0.05
Mean CRP (mg/L)	61.25±41.2	15.81±7.98	<0.001
Mean ESR (mm/h)	49.21±18.6	19.57±11.8	<0.001
Mean LDH (U/L)	494.38±118.7	272.45±94.9	<0.05
Mean D-dimer (µg/L)	1632.24±549.3	1032.52±608.45	<0.05
Mean PCT (µg/L)	0.41±0.21	0.18±0.11	<0.001

CRP=C-reactive protein, ESR=Erythrocyte sedimentation rate, LDH=Lactose dehydrogenase, PCT=Procalcitonin

world. Various new strains of coronavirus (Alpha in the United Kingdom, Beta in South Africa, Gamma in Brazil, Delta in India, and Omicron in multiple countries) are also being detected among different regions of the world. The prevalence of different variants in different regions of the world might be another reason for difference in results in our study.

In another study done by Abrishami *et al.*,^[15] in northeast region of Iran, the authors concluded that ocular manifestations were observed in 64.8% of COVID-19 patients whereas in our study incidence of Ocular manifestation was 16.4%, hyperemia was the most common manifestation similar to our study and they suggested a strong association of ocular manifestations with COVID-19. The results from various studies suggested different incidence of ocular manifestations in different regions of the world in COVID-19 patients.^[15,16]

We wanted to know the incidence of ocular manifestations in COVID-19 patients of northern region of India and its association with the disease severity. In our study, the incidence of ocular involvement was 16.4%. The incidence of ocular manifestations was more in elderly patients (mean age 52.1 years) and the patients having fever (temperature >37.3°C). There might be many reasons for it such as age-related changes, dry eye disease, meibomian gland dysfunction, and compromised immunity.^[28,29] All the thrombo-inflammatory markers as CRP, ESR, PCT, D-dimer, and neutrophil counts were significantly raised in patients with ocular involvement, indicating more severity of the disease. Still, the complete pathogenesis of the SARS-CoV 2 virus is under study and is not known to us.^[30] The severity of the disease depends upon the viral load, cytokine storm, and the cellular immune response of the host.^[31] There have been studies suggesting that increased neutrophil count and decreased lymphocyte count are associated with more severe disease and a poor prognosis.^[30]

In our study, we found that inflammatory markers as CRP, PCT, and ESR were significantly more elevated in patients with ocular manifestations as compared to patients without ocular manifestations. Neutrophil: lymphocyte ratio was found significantly higher in patients with ocular manifestations. Incidence of fever (temperature >37.3°C) and mean age were also higher in patients with ocular manifestations. Levels of D-dimer and LDH were significantly raised in patients having ocular manifestations as compared to those without ocular involvement.

The limited sample size and lack of conjunctival evaluation with RT-PCR are the limitations of our study. A larger number of patients with COVID-19 from different centers would further help us to define

the ocular manifestations and their association with the disease severity. Regardless, the findings of our study are the early results shared to serve as a starting/basic platform for research into ocular involvement and immunological responses of COVID-19. Older age, high fever, increased neutrophil/lymphocyte ratio, and high levels of acute-phase immune markers were associated with an increased risk of developing ocular manifestations. Care must be taken when evaluating patients with those characteristics to prevent ocular complications and viral spread since other organ involvements might be alternative routes of transmission.

The small sample size is a limitation; more studies in the future with a larger number of patients are required to reach any conclusion.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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