

Evaluation of COVID-19 severity and post-acute-COVID-19 sequelae of dry eye disease in patients with SARS-CoV-2 infection

Avaliação da gravidade da COVID-19 e sequelas pós-COVID-19 aguda da síndrome do olho seco em pacientes com infecção por SARS-CoV-2

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ABSTRACT

Objective: To evaluate the prevalence and severity of dry eye disease in patients with a history of COVID-19 infection.

Methods: A total of 76 patients who had recovered from COVID-19 were included in the study. Dry eye disease was assessed using subjective and objective measures, including the Ocular Surface Disease Index questionnaire, tear break-up time, Schirmer test, and corneal staining.

Results: This study included 76 patients with a mean age of 54.55 ± 10.61 years. The results revealed a high prevalence of dry eye disease in post-COVID-19 patients, with a significant proportion experiencing moderate to severe symptoms. Patients with a history of intensive care unit hospitalization and those who received oxygen therapy or non-invasive ventilation had a higher risk of developing dry eye disease.

Conclusions: COVID-19 infection may be a risk factor for dry eye disease, particularly in patients with moderate to severe illness. Further research is warranted to elucidate the underlying mechanisms of this association and to devise effective preventive and therapeutic interventions for dry eye disease in post-COVID-19 patients.

RESUMO

Objetivo: Avaliar a prevalência e a gravidade da síndrome do olho seco em pacientes com histórico de infecção por COVID-19.

Métodos: Foram incluídos no estudo 76 pacientes que haviam se recuperado da COVID-19. A síndrome do olho seco foi avaliada por meio de medidas subjetivas e objetivas, incluindo o questionário Índice de Doenças da Superfície Ocular, o tempo de ruptura do filme lacrimal, o teste de Schirmer e a coloração da córnea.

Resultados: Este estudo incluiu 76 pacientes com idade média de $54,55 \pm 10,61$ anos. Os resultados revelaram uma alta prevalência da síndrome do olho seco em pacientes pós-COVID-19, com uma proporção significativa apresentando sintomas moderados a graves. Pacientes com histórico de internação na unidade de terapia intensiva e aqueles que receberam oxigenoterapia ou ventilação não invasiva apresentaram maior risco de desenvolver a síndrome do olho seco.

Conclusões: A infecção por COVID-19 pode ser um fator de risco para a síndrome do olho seco, particularmente em pacientes com doença de gravidade moderada a grave. São necessárias mais pesquisas para elucidar os mecanismos subjacentes a essa associação e para desenvolver intervenções preventivas e terapêuticas eficazes para a síndrome do olho seco em pacientes pós-COVID-19.

INTRODUCTION

Dry eye disease (DED) presents a multifaceted ocular condition characterized by visual disturbances, tear film instability, and pathological changes of the ocular surface. It is often associated with increased tear film osmolarity and ocular surface inflammation.⁽¹⁾ As concluded by the Tear Film and Ocular Surface Society Workshop in 2017,⁽²⁾ DED has emerged as a significant global health issue, affecting an estimated 20% to 50% of the global population and impacting ocular health, overall well-being, quality of life, and socioeconomic status.⁽³⁾ DED's economic burden to society is around 55 billion dollars in the USA.⁽⁴⁾

Dry eye disease is associated with numerous risk factors including but not limited to age, female sex, autoimmune disorders, endocrine disorders such as diabetes mellitus and thyroid disorders, use of contact lenses, dry environments, and increased digital screen time.⁽⁵⁻⁷⁾ Previous studies have suggested an association between COVID-19 viral load and evaporative DED in post-discharge COVID-19 patients.⁽⁸⁾

COVID-19, caused by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an infectious disease first identified in China in December 2019 and was announced as a global pandemic since March 2019.⁽⁹⁻¹¹⁾ The primary ocular symptoms observed in COVID-19 patients include dry eyes, decreased tear production,⁽¹²⁾ itching, redness, eye pain, and a sensation of a foreign body in the eye.⁽¹³⁾ However, the precise mechanism underlying the dry eye sensation in COVID-19 patients remains elusive and may not directly correlate with the presence of the SARS-CoV-2 virus. The use of face masks during the COVID-19 pandemic, especially when loosely fitted, along with the redirection of airflow towards the eyes, may exacerbate dry eye symptoms by accelerating tear film evaporation, in addition to causing inflammatory changes in the ocular surface.^(2,14,15) Inflammatory changes in the ocular surface during COVID-19 may result from direct viral infection or systemic inflammation, potentially leading to ocular surface inflammation and subsequent development of dry eye.⁽⁸⁾

Long COVID-19 or post-acute sequelae of COVID-19 infection consists of multisystemic manifestations that arise COVID-19 episode of infection. Long-term reservoirs of COVID-19 virus, coinfection with other microbial agent, in addition to immune, nervous system and endothelial dysfunction are suggested as possible mechanisms of this phenomenon.⁽¹⁶⁾ Ophthalmic manifestations related to long COVID-19 include blurred vision, dry eye symptoms, ocular surface irritation, and double vision.⁽¹⁷⁾

This study aims to evaluate ocular surface disturbances in post-acute sequelae of COVID-19 through the assessment of both subjective and objective symptoms and signs for diagnosing DED. Due to the lack of a standardized diagnostic tool, various methods are commonly employed. Understanding the interplay between COVID-19, dry eye syndrome, and treatment regimens is essential for comprehensive patient care. Our research seeks to investigate dry eye as a post-acute sequela of COVID-19 infection, aiming to provide more precise evidence regarding the association between dry eye and COVID-19 as a potential sequela or long-term effect

METHODS

This single-center cross-sectional observational study was conducted on patients with a history of COVID-19 who had been hospitalized and were evaluated at least one month after discharge. The study adhered to the principles outlined in the Declaration of Helsinki, and ethical approval was obtained from the Ethics Committee in Human Research at the Baqiyatallah Hospital in Tehran, Iran (IR.BMSU.BAQ.REC.1401.039). It is a single-institution prospective observational study.

The first group of our study consisted of discharged patients who had been previously hospitalized due to COVID-19. Signs, symptoms, and oropharyngeal swabs were employed for the diagnosis of the primary COVID-19 infection episode. Recovery was established through the resolution of the clinical signs of the COVID-19 infection in addition to two negative oropharyngeal swabs and the detection of anti-SARS-CoV-2 IgG antibodies in the blood sample of the patients. Following discharge, all COVID-19 patients were scheduled for a follow-up appointment at least 4 weeks later as part of a comprehensive post-acute COVID-19 sequelae assessment service involving various medical specialties.

Based on these criteria, participants were eligible for inclusion in the study if they had been discharged from the hospital for at least one month prior to the examination and were devoid of active symptoms of COVID-19 during the assessment. Exclusion criteria encompassed a pre-existing diagnosis of DED before contracting COVID-19, a history of refractive surgery, glaucoma surgery, and the use of medications known to exacerbate dry eye symptoms (such as antidepressants and glaucoma medications). Additionally, individuals with malpositioned eyelids, such as those with Bell's palsy or a history of surgery for entropion or ectropion, were excluded. Participants who expressed unwillingness to participate

at any stage of the research were also excluded from the study. All included patients filled the written consent form, and patients had no additional cost.

This study used the Ocular Surface Disease Index (OSDI) questionnaire (Allergan Inc., Irvine, CA, USA) as the primary tool for evaluating dry eye symptoms. Furthermore, the presence of DED was thoroughly assessed through patient recall and documentation of consistent use of lubricating eye drops. A comprehensive evaluation of potential confounding variables was conducted, including assessment of contact lens usage, best-corrected visual acuity (BCVA), gender, age, history of ocular surgeries, utilization of noninvasive or mechanical ventilation, history of autoimmune diseases, lid malposition, history of topical ocular medication usage, and blink rate per minute. Contact lens wearers abstained from using their lenses for a period of 30 to 60 days prior to their examination. Patients with a history of medications with adverse effects on ocular surface were excluded. For randomization, we evaluated the right eye of our patients unless the physical examinations deemed the right eye unsuitable for evaluation.

All subjects underwent a thorough ophthalmological assessment, comprising an evaluation of BCVA utilizing the Early Treatment Diabetic Retinopathy Study (ETDRS) technique and a slit-lamp examination. This examination was conducted independently by two experienced physicians, unaware of the participants' details.

Furthermore, tear break-up time (TBUT) was assessed before the administration of eye drops. The process was done by gently applying a fluorescein strip in the inferior cul-de-sac for 2 seconds. Then a cobalt blue filter was used to assess the time between blinking and the destabilization of the tear film. This procedure was repeated three times, and the average was recorded for analysis. Consistent with existing literature, a rapid TBUT (less than 10 seconds) was deemed indicative of abnormality. The level of conjunctival hyperemia was assessed by employing the Efron scale.

Schirmer type 1 test was done using a strip filter of paper in the inferior conjunctival cul-de-sac in the lateral corner of the eye for 5 minutes without prior administration of eye drops. A result less than 10 mm was considered as abnormal, and results less than 5 minutes were considered as a sign of moderate to severe dry eye.

Statistical analysis

The study findings will be presented using descriptive statistical measures, including mean $\pm$ standard deviation

for continuous variables and frequency percentages for categorical variables. Comparisons of quantitative data between groups were performed using the non-parametric Mann-Whitney U test, while comparisons of categorical data utilized the Chi-square test or Fisher's Exact test, as appropriate. Pearson's chi-square test was employed to classify the DED stage of the patients to mild, moderate, and severe based on predefined OSDI categories. Statistical analyses were conducted using SPSS version 25 software, with a significance level set at $p < 0.05$.

RESULTS

Demographics

This study included 76 patients. The mean age of the post-COVID-19 group was 57.00 ± 11.50 years. Majority of the participants were female (65.4%). In our study, 20% of the patients had a history of diabetes mellitus, 23% had a history of hypertension. All patients were hospitalized during the COVID-19 episode and 19.8% required intensive care unit (ICU) admission. A substantial majority (82.5% and 76.3%) received oxygen therapy and non-invasive ventilation, while a small percentage required mechanical ventilation (8.8%).

Dry eye parameters

The abnormal results of dry eye parameters included, reduced TBUT (16% low to moderate; 16% severe; 60% very severe), abnormal Schirmer test (92.5%), and abnormal tear height (95.7%). Conjunctival hyperemia (67.6%) and abnormal corneal staining (28.8%) were also common among participants. The OSDI scores showed that a substantial number of participants experience moderate to severe ocular surface disease symptoms (9.9% low scores; 13.8% moderate scores; 21.3% severe scores). The OSDI scores showed abnormal values for the patients previously afflicted by moderate-severe COVID-19 infection. Table 1 shows the breakdown of our results.

Although TBUT was decreased in patients admitted to the ICU admitted and with mechanical ventilation (4.30 ± 2.21 versus 6.068 ± 3.89) and (4.50 ± 1.22 versus 6.021 ± 3.87) respectively, none of these differences were found to be statistically significant (p -values: 0.174 and 0.347 respectively).

Furthermore, we found a significant negative correlation between OSDI and TBUT scores. ($r = -0.291$; $p = 0.033$). No significant correlation was found between OSDI scores and the Schirmer test or tear height parameters.

Of the specific ocular surface irritative symptoms, the presence of foreign body sensation had increased

Table 1. Demographic characteristics in post-COVID-19 dry eye patients

Parameters	Value
Age	57.00 ± 11.50
Gender	
Male	34.6
Female	65.4
ICU patients	20
Oxygen therapy patients	82.5
Mechanical ventilation patients	8.8
Comorbid disease	
Diabetes	19.8
Hypertension	23.1
OSDI	
Normal	55
Low-Moderate	9.9
Severe	13.8
Very severe	21.3
TBUT	
Normal	8
Low-Moderate	16
Severe	16
Very severe	60
Aqueous parameters	
Schirmer's test, mm	
Normal	7.5
Low-moderate	1.3
Severe	10
Very severe	81.3
Conjunctival hyperemia	67.9

Median ± interquartile interval or %.

OSDI: Ocular Surface Disease Index; TBUT: tear break-up time.

in the post-COVID-19 examinations (12.3% versus 29.6%, $p = 0.007$) but the presence of other symptoms including redness, tearing, and burning sensation remained as before.

Data regarding the medical treatment during the COVID-19 hospitalization were collected and none had significant effect on the measured primary and secondary outcomes.

None of the above-mentioned factors in addition to age, sex, O_2 therapy, or mechanical ventilation had significant confounding effects on multivariate analysis.

Conjunctival hyperemia

Mild conjunctival hyperemia was common amongst the examined patients (32.1% no hyperemia, 51.9% mild hyperemia, 9.9% moderate hyperemia, and 1.2% severe hyperemia).

Conjunctival hyperemia had significant positive correlation with the degree of corneal staining ($r = 0.393$; $p < 0.001$). Furthermore, moderate negative correlation was seen between TBUT ($r = -0.462$; $p = 0.001$), tear height ($r = -0.410$; $p < 0.001$), and conjunctival hyperemia. However, no significant correlation was found between conjunctival hyperemia and Schirmer or OSDI scores.

DISCUSSION

Our study reveals a notable prevalence of DED among individuals who have recovered from COVID-19, aligning with recent research findings.^(7,14,15) Our findings might suggest a potential link between COVID-19 infection and the development or exacerbation of DED as a post-acute sequela of COVID-19. The exact mechanisms behind this association remain unclear, but several hypotheses have been proposed.

One possibility is that the SARS-CoV-2 virus directly infects the ocular surface, leading to inflammation and damage to the tear film quality and ocular surface cells. Another hypothesis suggests that the systemic inflammation triggered by COVID-19 could indirectly affect the ocular surface, contributing to DED development. Additionally, the widespread use of face masks during the pandemic, particularly when worn loosely, might exacerbate DED symptoms by changing airflow and increasing tear evaporation. This relationship could also work in the opposite direction, as epithelial breakdown due to dryness has been suggested as a potential entry route for the COVID-19 infection.⁽¹⁸⁾ Furthermore, there is evidence that COVID-19 infection can result in worsening of meibomian gland dysfunction, which in turn, results in worsening of dry eye symptoms.⁽⁸⁾ Daryabari et al. reported positive COVID-19 PCR in tear and conjunctival swabs of COVID-19 patients, suggesting a potential infection route through the ocular surface for COVID-19 virus.⁽¹⁹⁾ Barros et al reported small-fiber neuropathy in COVID-19 patients similar to DED and diabetic patients which correlated with ocular irritation symptoms.⁽²⁰⁾

Our research aligns with recent studies highlighting the increased prevalence of DED in individuals recovering from COVID-19. For instance, a study by Napoli et al.⁽¹⁰⁾ identified a phenomenon termed “quarantine dry eye”, linking lockdown measures and increased screen time during the pandemic to a surge in DED symptoms. Similarly, Park et al.⁽²¹⁾ investigated mask-associated dry eye, suggesting that prolonged mask use can contribute to DED due to altered airflow and increased tear evaporation. Park et al.⁽²¹⁾ further emphasized the impact of the pandemic on eye strain and DED symptoms, particularly among individuals with pre-existing DED. Koprubasi et al. reported reduced Schirmer and TBUT test in addition to inflammatory cytologic changes in face mask users.⁽¹⁵⁾ Mastropsaqua et al. also had similar conclusion with the observation of increasing dendritic cell density and HLA-DR in ocular surface with increased use of face masks.⁽¹⁴⁾

The COVID-19 pandemic has also resulted in significant psychiatric distress around the world. He et al

reported a significant correlation between DED and anxiety and depression, with sleep disorders acting as mediator between these factors.⁽²²⁾

While our study did not specifically investigate the influence of masks or screen time, the observed prevalence of DED in our post-COVID-19 cohort is consistent with these studies, reinforcing the notion that COVID-19, whether through direct viral impact, systemic inflammation, or pandemic-related lifestyle changes, can significantly affect ocular surface health.

However, our research diverges from some previous studies in terms of the severity of DED observed. While we found a significant proportion of post-COVID-19 patients experiencing DED, the majority of cases were moderate to severe. This contrasts with studies like Gambini et al.,⁽¹²⁾ which reported a higher incidence of severe DED in their post-COVID-19 cohort. This discrepancy could be attributed to differences in study populations, diagnostic criteria, or the timing of DED assessment after COVID-19 recovery.

Several studies have focused on the changes in DED after COVID-19 infection as a post-acute sequela of COVID-19, alternatively named as long COVID.⁽¹²⁾ In a study evaluating post-COVID-19 DED, Ruan et al. concluded that recurrent COVID-19 infection may lead to higher OSDI scores in the affected patients.⁽²³⁾ Our findings also align with the systematic review by Williams et al., who studied burning eye syndrome after COVID-19 infection and concluded that this subset of neuropathic pain has a pooled prevalence of 9.9% in patients recovering from a COVID-19 episode, and the incidence is related to the COVID-19 episode severity.⁽²⁴⁾ In contrast to other studies, Szkodny et al. did not find any association between COVID-19 infection and the worsening of Schirmer, TBUT, and tear meniscus height measurements.⁽²⁵⁾ Of note, Antunes-Foschini et al. reported a significant decrease in the quality of life of the patients affected by the post-COVID-19 dry eye syndrome. These findings along with ours highlight the importance of the post-COVID-19 DED diagnosis and treatment.⁽²⁶⁾

Our study found more frequent subjective dry eye symptoms, based on OSDI questionnaire, in moderate-severe COVID-19 patients 4 weeks after the primary infection episode. This finding is similar to the previous reports of prevalent dry eye symptoms as a considerable component of long COVID-19 spectrum in more severe COVID-19 patients.⁽¹⁷⁾

Our findings underscore the importance of comprehensive eye examinations for individuals recovering from COVID-19, as early detection and management of

DED can help alleviate symptoms, prevent complications, and improve patients' quality of life. Further research is needed to elucidate the precise mechanisms underlying the association between COVID-19 and DED, which could pave the way for targeted interventions and preventive strategies.

Additionally, we evaluated the impact of corticosteroids, antivirals, age, and gender on the severity of dry eye in COVID-19 patients and compared with patients with pre-existing ocular surface diseases.

Our study has several limitations. First, the small sample size of our study limits the generalizability of our findings. Second, the cross-sectional design of our study limits our ability to conclude causality from our findings. Third, we relied on self-reported data for some variables, which is known to be subject to recall bias.

Future research should focus on larger, longitudinal studies to investigate our findings and the long-term effects of COVID-19 on ocular health. Additionally, studies exploring the potential therapeutic benefits of different DED treatments in post-COVID-19 patients would be valuable.

CONCLUSION

Our findings suggest that dry eye disease is relatively common among individuals recovering from COVID-19. However, due to cross sectional design and the absence of a control group, a causal relationship cannot be established. Further longitudinal and controlled studies are needed to better understand the potential association between COVID-19 and dry eye disease.

AUTHOR'S CONTRIBUTION

Conceptualization, Seyed-Hashem Daryabari; methodology, Seyed-Hashem Daryabari; software: Seyed Morteza Hosseini Imeni; validation, Seyed-Hashem Daryabari; formal analysis: Neda Shajirat; resources: Neda Shajirat; data curation: Neda Shajirat; Writing – original draft preparation: Seyed Aliasghar Mosavi; writing – review and editing: Seyyed Morteza Hosseini Imeni, Neda Shajirat; visualization: Seyyed Morteza Hosseini Imeni, Neda Shajirat; Supervision: Seyed-Hashem Daryabari; project administration: Seyed-Hashem Daryabari.

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