• Clinical Research •

Evaluation of dry eye disease symptomatology and mental health status among patients with different COVID-19 statuses

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Abstract

● **AIM:** To evaluate dry eye disease (DED) symptomatology and mental health status in different COVID-19 patients.

● **METHODS:** A cross-sectional observational design was used. Totally 123 eligible adults (46.34% of men, age range, 18-59y) with COVID-19 included in the study from August to November, 2022. Ocular Surface Disease Index (OSDI), Five-item Dry Eye Questionnaire (DEQ-5), Hospital Anxiety and Depression Scale (HADS), and Pittsburgh Sleep Quality Index (PSQI) were used in this study.

● **RESULTS:** OSDI scores were 6.82 (1.25, 15.91) in asymptomatic carriers, 7.35 (2.50, 18.38) in mild cases, and 16.67 (4.43, 28.04) in recurrent cases, with 30.00%, 35.56%, and 57.89%, respectively evaluated as having DED symptoms (χ^2=7.049, P=0.029). DEQ-5 score varied from 2.00 (0, 6.00) in asymptomatic carriers, 3.00 (0, 8.00) in mild cases, and 8.00 (5.00, 10.00) in recurrent cases, with 27.50%, 33.33%, and 55.26%, respectively assessed as having DED symptoms (χ^2=8.532, P=0.014). The prevalence of clinical anxiety (50.00%) and depression (47.37%) symptoms were also significantly higher in patients with recurrent infection (χ^2=24.541, P<0.001; χ^2=30.871, P<0.001). Recurrent infection was a risk factor for high OSDI scores [odds ratio, 2.562; 95% confidence interval (CI), 1.631-7.979; P=0.033] and DEQ-5 scores (odds ratio, 3.353; 95%CI, 1.038-8.834; P=0.043), whereas having a fixed occupation was a protective factor for OSDI scores (odds ratio, 0.088; 95%CI, 0.022-0.360; P=0.001) and DEQ-5 scores (odds ratio, 0.126; 95%CI, 0.039-0.405; P=0.001).

● **CONCLUSION:** Patients with recurrent COVID-19 have more severe symptoms of DED, anxiety, and depression.

● **KEYWORDS:** COVID-19; dry eye disease; recurrent infection; mental health

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INTRODUCTION

In early May and November 2022, large-scale and persistent waves of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) rapidly emerged in Beijing, China. To tackle this new rapid surge of coronavirus disease 2019 (COVID-19) with a sudden and rapid influx of patients in acute care, centralized treatment of asymptomatic carriers and mild cases was conducted to protect the health and safety of uninfected individuals. The temporary centralized isolation wards named Fangcang shelter hospitals were designed to quickly and centrally isolate patients with COVID-19. These facilities provide a variety of services, including specialized medical care, accurate disease monitoring, supplying food, and daily consumable support[1]. Quarantine, social distancing, stay-at-home orders, and lockdowns effectively controlled

the SARS-CoV-2 spread, which might also have had adverse psychological and social effects[2]. A study reported that 34.1% of the participants who experienced quarantine or isolation had at least one psychological symptom[3]. Owing to this large-scale, long-lasting, recurring pandemic and the consequent considerable disruptions to daily life, people have been under unprecedented stress; they may also have serious mental problems, such as depression, anxiety, and insomnia[4-5]. Many studies have investigated the psychological conditions of all strata during the COVID-19 pandemic[6]. Dry eye disease (DED) is a common ocular surface disease that affects visual quality and quality of life[7]. Current research is focused on DED in post-COVID-19 infection patients[8-12] and eye strain due to lifestyle changes in the COVID-19 era[13-14], indicating that ocular surface changes during COVID-19 should be alerted, emphasized, and monitored. DED is related to psychosocial factors, including anxiety, depression[15-17], and sleep disorder[18-19]. However, thorough assessments of patients with mild-to-moderate COVID-19 isolated from their families and communities are limited. Therefore, the authors aimed to evaluate the ocular changes and psychological effects of social isolation in asymptomatic carriers, patients with mild disease, and recurrent cases under centralized treatment for SARS-CoV-2 infection.

SUBJECTS AND METHODS

Ethical Approval This study adhered to the tenets of the Declaration of Helsinki, was approved by the Institutional Ethics Committee of Beijing You'an Hospital (No. 2022097), Capital Medical University, and was enlisted in the Chinese Clinical Trial Registry (registration number: ChiCTR2200062435). All participants provided written informed consent before participating in the study.

Patients diagnosed with COVID-19 between August and November 2022 and treated in isolation wards in single-patient rooms at Beijing Xiaotangshan Fangcang Shelter Hospital were enrolled in this cross-sectional, observational, and regional survey. The authors distributed 125 paper-based combined questionnaires, including the Ocular Surface Disease Index (OSDI), Five-item Dry Eye Questionnaire (DEQ-5), Hospital Anxiety and Depression Scale (HADS), and Pittsburgh Sleep Quality Index (PSQI), to patients with COVID-19. Totally 123 valid questionnaires were received with a valid response rate of 98.40%. And 123 valid responses were obtained with a 100% effective rate. Inclusion criteria were: 1) patients ≥18y; 2) logical and completed questionnaire responses. The exclusion criteria were 1) age <17y, 2) illogical questionnaire responses.

COVID-19 diagnosis required positive SARS-CoV-2 nucleic acid test results from respiratory secretion samples, that is, the real-time polymerase chain reaction (PCR) assay for the viral nucleic acid nucleocapsid protein gene cycle threshold (NCt) value and open reading frame 1ab gene cycle threshold (OCt) values were less than 35. Participants were 18-59y and with normal cognitive function, able to communicate effectively, with no previous known history of ocular surface or intraocular disease, no corneal contact lens wear, and no history of ocular surgery.

The criteria for classifying patients with COVID-19 were as follows: asymptomatic carriers, no obvious clinical symptoms and pneumonia imaging changes; mild cases, mild symptoms without pneumonia imaging changes; and recurrent cases, NCt and OCt values less than 35 after recovery from the last infection.

Those with a combination of serious cardiac, hepatic, cerebral, renal, or other major physical illnesses, previous psychological or psychiatric disorders, or recent major psychological trauma were excluded. The data involved were de-identified. Data were analyzed from December 10, 2022, to January 2, 2023.

Measurements At the beginning of centralized isolation, the SARS-CoV-2 nucleic acid Ct values were defined as NCt1 and OCt1, and the values on the fifth day of hospitalization were defined as NCt2 and OCt2. Four questionnaires were administered on the fifth day.

Evaluation of Dry Eye Disease DED is characterized by various symptoms such as dryness, foreign body sensation, burning sensation, blurred eyesight, and visual fatigue. The classic screening questionnaires for DED (since many participants did not elicit symptoms unless specifically asked) included OSDI and DEQ-5[20], which could accurately quantify ocular surface symptoms and assist in determining the necessity of additional DED assessment in daily clinical work.

Ocular Surface Disease Index The OSDI, one of the most widely used patient-reported outcome dry eye questionnaires in clinical settings with good sensitivity and specificity[21], focuses on evaluating the common symptoms of DED and their frequency of occurrence and can assist in grading the dryness severity. The questionnaire included 12 questions: questions 1-5 on symptoms of eye discomfort (sensitivity to light, feeling gritty, eye soreness or eye aches, blurred eyesight, poor vision), questions 6-9 on limitations of daily activities (reading books, driving at night, working with the computer, watching television), and questions 10-12 on environmental triggers (windy conditions, low humidity conditions, air-conditioned conditions), and the DED screening criteria was a score ≥13.

Five-Item Dry Eye Questionnaire The DEQ-5[22] was used to evaluate ocular dryness and tearing symptoms and the severity of these symptoms 2h before bedtime for the rapid assessment and epidemiological investigation of DED. The questionnaire comprised five items: the frequency of eye discomfort, eye dryness, and watery eyes, and late-day intensity of eye

discomfort and eye dryness within 2h of going to bed, and the dry eye screening criteria was a score ≥6.

Assessment of Anxiety and Depression

Hospital anxiety and depression scale The HADS is a reliable self-assessment scale with good reliability and validity for screening clinically significant anxiety and depression and assessing the severity of these mood disorders in hospitalized patients without disorders[23]. The scale contained 14 items, seven of which assessed depression and seven measured anxiety. The cut-off value for each subscale was eight, and a score greater than or equal to this indicated anxiety or depression.

Assessment of Sleep Quality

Pittsburgh sleep quality index The PSQI was a self-assessment questionnaire designed to assess the quality of sleep in psychiatric clinical practice and research activities[24]. The questionnaire included 19 separate items that yield scores for seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction and the sum of the scores was the PSQI score. The threshold value of the PSQI score was five, and a total score greater than this indicated a sleep disorder.

The reliability and validity of the questionnaires were confirmed using Cronbach α (0.783) and the Kaiser-Meyer-Olkin test (0.633).

Statistical Analysis Statistical analyses were performed using the SPSS software (version 26.0; IBM, Armonk, New York, USA). The χ^2 test or Fisher's exact test was used to compare enumeration data expressed as *n* (%) between the groups. The measurement data were tested for normality using the Shapiro-Wilk test. The Mann-Whitney *U* test was performed for non-normally distributed data presented as the median (interquartile range (IQR) for comparison between two groups; the Kruskal-Wallis *H* test was used for multiple group comparisons. The correlation between the measured data was determined using Spearman rank correlation analysis. Dichotomous logistic regression analysis was used to explore the factors influencing the OSDI or DEQ-5 scores. Statistical significance was set at $P<0.05$.

RESULTS

Comparison of Demographic Characteristics and Ocular Conditions of Patients with Different Clinical Types of COVID-19 The authors enrolled 123 eligible patients in the study (46.34% men and 53.66% women aged 18-59y). The mean age was 40.77±11.82y (IQR 32-52y). The 123 patients included 40 asymptomatic carriers, 45 patients with mild disease, and 38 patients with recurrent disease. The participants' age, sex, original demographic characteristics, and ocular conditions are presented in Table 1. The authors obtained 123 validated questionnaires from 135 paper-based questionnaires, with an answer rate of 91.11%. No significant differences were observed in age, sex, marital status, fertility status, education level, occupational status, refractive status, wearing glasses, or duration of daily video display terminals (VDT) use between the three groups.

Comparison of Ct Values and OSDI, DEQ-5, HADS, and PSQI Scores of Patients with Different Clinical Types of COVID-19 Intergroup comparisons among the three clinical types of COVID-19 are presented in Table 2. The differences in NCt1, OCt1, NCt2, OCt2, OSDI scores, DEQ-5 scores, HADS scores and subcategories of anxiety and depression scores, PSQI scores and subsets of subjective sleep quality scores, use of sleeping medication scores, and daytime dysfunction scores were significant among the three groups and between recurrent cases and asymptomatic carriers ($P<0.05$). In addition to the PSQI and subjective sleep quality scores, a significant difference was observed between recurrent and mild cases for the indicators ($P<0.05$). However, no significant difference was observed in any variable between asymptomatic carriers and mild cases.

Comparison of Dry Eye, Anxiety, Depression, and Sleep Disorder Symptoms in Patients with Different Clinical Types of COVID-19 Recurrent cases had more pronounced DED symptoms than asymptomatic carriers and mild cases, as evidenced by a higher percentage of OSDI (57.89%) and DEQ-5 scores (55.26%) above the threshold ($\chi^2=7.049$, $P=0.029$; $\chi^2=8.532$, $P=0.014$). The prevalence of clinical anxiety (50.00%) and depression (47.37%) were also significantly higher in patients with recurrent infection ($\chi^2=24.541$, $P<0.001$; $\chi^2=30.871$, $P<0.001$). The percentage of participants with sleep disorder symptoms was not significantly different among the three groups, as presented in Table 3.

Binary Logistic Regression Analysis of Factors Associated with Dry Eye Symptoms Binary logistic regression analysis (Tables 4 and 5) revealed that having a fixed occupation was a protective factor for OSDI scores [odds ratio (OR), 0.088; 95% confidence interval (CI), 0.022-0.360; $P=0.001$] and DEQ-5 scores (OR, 0.126; 95%CI, 0.039-0.405; $P=0.001$), whereas recurrent infection was a risk factor for OSDI scores (OR, 2.562; 95%CI, 1.631-7.979; $P=0.033$) and DEQ-5 scores (OR, 3.353; 95%CI, 1.038-8.834; $P=0.043$).

Correlation Analysis of NCt2 and OCt2 Values with OSDI, DEQ-5, HADS, and PSQI Scores NCt2, OCt2, and the questionnaires were assessed on the same day. The results of their correlation analysis with each questionnaire index in patients with first-time infection (asymptomatic carriers and mild cases) and recurrent positives are presented in supplemental materials. NCt2 and OCt2 had no significant correlation with any questionnaire indicator in the different populations.

Table 1 Comparison of demographic characteristics and ocular conditions of patients with different clinical types of COVID-19

Variables	Group			Fisher's exact test/χ^2	*P*
	Asymptomatic carriers (*n*=40)	Mild cases (*n*=45)	Recurrent cases (*n*=38)		
Age	34 (28, 52)	42 (35.5, 53.5)	44 (36.25, 53)	1.723	0.423
Sex				3.115	0.211
Men	22 (55.00%)	16 (35.56%)	18 (47.37%)		
Women	18 (45.00%)	29 (64.44%)	19 (52.63%)		
Marriage status				1.118	0.578
Single	6 (15.00%)	9 (20.00%)	4 (10.53%)		
Married	34 (85.00%)	36 (80.00%)	25 (89.47%)		
Fertility status				0.699	0.638
Infertility	11 (27.50%)	10 (22.22%)	12 (31.58%)		
Fertile	29 (72.50%)	35 (77.78%)	26 (68.42%)		
Education levels				5.244	0.263
Junior high school or below	11 (27.50%)	20 (44.44%)	8 (21.05%)		
High school	17 (42.50%)	18 (40.00%)	21 (55.26%)		
University or higher	12 (30.00%)	7 (15.56%)	9 (23.68%)		
Occupational status				5.099	0.074
Employed	30 (75.00%)	37 (82.22%)	35 (92.1%)		
Unemployed	10 (25.00%)	8 (17.78%)	3 (7.89%)		
Refractive status				4.755	0.093
Normal	17 (42.50%)	30 (66.67%)	23 (60.53%)		
Myopia/hyperopia/astigmatism	23 (57.50%)	15 (33.33%)	15 (39.47%)		
Wearing glasses				1.622	0.444
Without glasses	24 (60.00%)	33 (73.33%)	23 (60.53%)		
Wearing glasses	16 (40.00%)	12 (26.67%)	15 (39.47%)		
Duration of daily VDT use				0.015	0.992
≤6h	9 (22.50%)	13 (28.89%)	10 (26.32%)		
>6h	31 (77.50%)	32 (71.11%)	28 (73.68%)		

COVID-19: Coronavirus disease 2019; VDT: Video display terminals.

Table 2 Comparison of Ct values and OSDI, DEQ-5, HADS, and PSQI scores of patients with different clinical types of COVID-19

Variables	Group			χ^2	*P*
	Asymptomatic carriers (*n*=40)	Mild cases (*n*=45)	Recurrent cases (*n*=38)		
NCt1	20.81 (17.53, 23.08)	21.39 (18.40, 23.01)	32.83 (30.27, 36.10)[a,b]	60.706	<0.001
OCt1	22.12 (20.00, 25.00)	21.95 (20.07, 24.41)	33.19 (31.10, 35.81)[a,b]	60.375	<0.001
NCt2	31.18 (21.25, 33.65)	31.37 (28.34, 35.95)	37.07 (35.30, 38.23)[a,b]	35.868	<0.001
OCt2	32.91 (22.21, 35.39)	31.63 (29.43, 36.35)	35.29 (34.20, 37.87)[a,b]	33.790	<0.001
OSDI score	6.82 (1.25, 15.91)	7.35 (2.50, 18.38)	16.67 (4.43, 28.04)[a,b]	6.807	0.033
DEQ-5 score	2.00 (0, 6.00)	3.00 (0, 8.00)	8.00 (5.00, 10.00)[a,b]	13.359	0.001
HADS score	6.00 (2.00, 7.50)	4.00 (0, 10.50)	19.00 (7.00, 23.25)[a,b]	16.248	<0.001
Anxiety score	1.00 (1.00, 4.00)	3.00 (0, 6.00)	10.00 (4.00, 11.75)[a,b]	17.484	<0.001
Depression score	2.00 (1.00, 5.00)	1.00 (0, 5.00)	9.00 (0.50, 11.75)[a,b]	13.073	0.001
PSQI score	2.00 (1.00, 7.00)	5.00 (2.00, 8.50)	7.50 (2.00, 12.75)[a]	7.401	0.025
Subjective sleep quality score	1.00 (0, 1.00)	1.00 (0, 1.00)	2.00 (1.00, 3.00)[a]	10.300	0.006
Sleep latency score	0 (0, 2.00)	1.00 (0, 3.00)	2.00 (0, 3.00)	3.414	0.181
Sleep duration score	0 (0, 2.00)	1.00 (0, 1.00)	1.00 (1.00, 2.00)	4.936	0.085
Habitual sleep efficiency score	0 (0, 1.00)	0 (0, 1.00)	0 (0, 2.00)	3.333	0.189
Sleep disturbances score	1.00 (0.50, 1.00)	1.00 (0, 1.00)	1.00 (1.00, 1.00)	1.187	0.552
Usage of sleeping medication score	0	0	1 (0, 1.25)[a,b]	15.610	<0.001
Daytime dysfunction score	0	0	0.50 (0, 1.00)[a,b]	9.477	0.009

[a]Statistically significant difference between recurrent and asymptomatic carriers (P<0.05); [b]Statistically significant differences between recurrent and mild cases (P<0.05). OSDI: Ocular Surface Disease Index; DEQ-5: Five-item Dry Eye Questionnaire; HADS: Hospital Anxiety and Depression Scale; PQSI: Pittsburgh Sleep Quality Index; COVID-19: Coronavirus disease 2019; OCt2: Open reading frame 1ab gene cycle threshold; NCt2: Nucleocapsid protein gene cycle threshold.

Table 3 Comparison of dry eye, anxiety, depression, and sleep disorder symptoms in patients with different clinical types of COVID-19

Variables	Group			χ^2	*P*
	Asymptomatic carriers (*n*=40)	Mild cases (*n*=45)	Recurrent cases (*n*=38)		
Dry eye symptoms					
OSDI score ≥13	12 (30.00%)	16 (35.56%)	22 (57.89%)	7.049	0.029
DEQ-5 score ≥6	11 (27.50%)	15 (33.33%)	21 (55.26%)	8.532	0.014
Anxiety symptoms					
HADS-anxiety score ≥8	2 (5.00%)	6 (13.33%)	19 (50.00%)	24.541	<0.001
Depression symptoms					
HADS-depression score ≥8	1 (2.50%)	5 (11.11%)	18 (47.37%)	30.871	<0.001
Sleep disorder symptoms					
PSQI score >5	12 (30.00%)	18 (40.00%)	20 (52.63%)	4.150	0.126

OSDI: Ocular Surface Disease Index; DEQ-5: Five-item Dry Eye Questionnaire; HADS: Hospital Anxiety and Depression Scale; PQSI: Pittsburgh Sleep Quality Index.

Table 4 Binary logistic regression analysis of factors associated with dry eye symptoms (OSDI score ≥13)

Variables	Uni-variable		Multi-variable	
	OR (95%CI)	*P*	OR (95%CI)	*P*
Demographics				
Age	1.023 (0.991-1.055)	0.170	-	-
Sex	1.023 (0.497-2.106)	0.950	-	-
Marriage status	0.499 (0.190-1.311)	0.158	-	-
Fertility status	1.109 (0.501-2.455)	0.798	-	-
Education levels (junior high school or below)				
High school	2.141 (0.863-5.313)	0.101	3.091 (0.986-9.689)	0.053
University or higher	2.700 (1.004-7.260)	0.049	2.650 (0.716-9.805)	0.144
Occupational status	0.302 (0.111-0.823)	0.019	0.088 (0.022-0.360)	0.001
Ocular parameters				
Refractive status	2.301 (1.102-4.802)	0.026	4.292 (0.830-22.193)	0.082
Wearing glasses	2.821 (1.307-6.084)	0.008	0.903 (0.173-4.713)	0.904
Duration of daily VDT use	0.905 (0.403-2.032)	0.808	-	-
Clinical typing of COVID-19 (asymptomatic carriers)				
Mild cases	1.287 (0.518-3.201)	0.587	1.981 (0.636-6.172)	0.238
Recurrent positive cases	3.208 (1.261-8.163)	0.014	2.562 (1.631-7.979)	0.033
Symptomology				
Anxiety symptoms	4.358 (1.769-10.738)	0.001	2.195 (0.361-13.358)	0.393
Depression symptoms	4.186 (1.637-10.7040)	0.003	1.767 (0.264-11.824)	0.557
Sleep disorder symptoms	3.420 (1.605-7.286)	0.001	1.768 (0.670-4.661)	0.250

OR: Odds ratio; CI: Confidence interval; COVID-19: Coronavirus disease 2019; OSDI: Ocular Surface Disease Index; VDT: Video display terminals.

DISCUSSION

From this study, compared with asymptomatic carriers and mild cases, populations with recurrent SARS-CoV-2 positive results had more severe symptoms of DED, anxiety, and depression. Recurrent positivity was a risk factor for DED symptoms, whereas fixed occupation was a protective factor.

The proportion of SARS-CoV-2 transmission or infection through the ocular surface was low; however, the ocular surface was also a potential route[25-26]. One study reported that patients with moderate-to-severe COVID-19 had a much higher possibility of transmitting the virus through their tears[27], suggesting the involvement of the ocular surface in the initial phase of COVID-19. Several studies have investigated ocular surface disturbance symptoms in post-COVID-19 patients, including those with DED, indicating the long-term effects of this infectious disease on the ocular surface[8-12].

The authors conducted the first timely self-report survey of centrally isolated patients with COVID-19 without pulmonary pathologies. The authors identified significant dry eye scores [OSDI: 16.67 (4.43, 28.04) and DEQ-5: 8[5,10]] and symptoms (57.89% of OSDI scores above the threshold and 55.26% of DEQ-5) in the re-positive cohort. However, dry eye scores and symptoms were less prominent in asymptomatic carriers [OSDI: 6.82 (1.25, 15.91), 30.00%; DEQ-5: 2 (0, 6), 27.50%]

Table 5 Binary logistic regression analysis of factors associated with dry eye symptoms (DEQ-5 score ≥6)

Variables	Uni-variable		Multi-variable	
	OR (95%CI)	*P*	OR (95%CI)	*P*
Demographics				
Age	1.031 (0.999-1.065)	0.060	-	-
Sex	1.034 (0.500-2.139)	0.928	-	-
Marriage status	0.459 (0.174-1.208)	0.115	-	-
Fertility status	0.856 (0.388-1.888)	0.699	-	-
Education levels (junior high school or below)				
High school	1.411 (0.583-3.415)	0.445	-	-
University or higher	1.645 (0.626-4.139)	0.312	-	-
Occupational status	0.211 (0.075-0.598)	0.003	0.126 (0.039-0.405)	0.001
Ocular parameters				
Refractive status	1.724 (0.829-3.587)	0.145	-	-
Wearing glasses	2.000 (0.934-4.281)	0.074	-	-
Duration of daily VDT use	0.695 (0.310-1.559)	0.377	-	-
Clinical typing of COVID-19 (asymptomatic carriers)				
Mild cases	1.318 (0.520-3.343)	0.561	1.328 (0.467-3.778)	0.594
Recurrent positive cases	3.625 (1.406-9.343)	0.008	3.353 (1.038-8.834)	0.043
Symptomology				
Anxiety symptoms	3.900 (1.608-9.458)	0.003	1.319 (0.221-7.888)	0.761
Depression symptoms	4.593 (1.790-11.781)	0.002	2.356 (0.374-14.846)	0.361
Sleep disorder symptoms	2.907 (1.370-6.169)	0.005	1.511 (0.574-3.978)	0.404

OR: Odds ratio; CI: Confidence interval; COVID-19: Coronavirus disease 2019; DEQ-5: Five-item Dry Eye Questionnaire; VDT: Video display terminals.

and mild cases [OSDI: 7.35 (2.50, 18.38), 35.56%; DEQ-5: 3 (0, 8), 33.33%]. Binary logistic regression analysis was used to explore the factors associated with OSDI and DEQ-5 scores exceeding the screening criteria, and recurrent positivity was a risk factor for both. This result could be explained by the long-COVID and recurrent positive SARS-CoV-2 detection phenomena.

The WHO Clinical Case Definition Working Group on Post-COVID-19 Conditions identified long-COVID as sustained post-infection sequelae that occurred within 3mo from the onset and lasted for 2mo[28]. Long-COVID is considered a multi-organ disease, including fatigue, dyspnea, chest pain, cognitive dysfunction, and arthralgia, which may be associated with cellular injury, inflammatory cytokines produced by a robust innate immune response, and a SARS-CoV-2-induced procoagulant state[29]. Post-infection ocular implications may also be part of long-COVID. At a mean period of 3.7mo after diagnosis, patients with long-COVID underwent corneal confocal microscopy, which revealed corneal small nerve fiber loss and increased dendritic cell density[30]. In addition, post-COVID-19 patients have significantly reduced vascular density in the macular and papillary regions, along with retinal nerve fiber layer thickness damage on optical coherence tomography angiography[31]. Regarding the ocular surface, a cohort study revealed that post-COVID-19 patients had a significantly higher prevalence of dry eye disease on both subjective and objective assessments than healthy controls, as evidenced by their higher OSDI scores, lower Schirmer test results, shorter tear break-up times, and higher tear osmolarity[9]. Wan *et al*[12] enrolled 228 patients in Hong Kong and discovered that meibomian gland dysfunction and ocular surface staining abnormalities were more common and severe in post-COVID-19 patients.

This study revealed that the people with repeat-positive tests for SARS-CoV-2 were mostly discharged and discontinued isolation recently and were sent back to centralized isolation wards according to relevant policies. The Ct values were higher in this group [NCt1 32.83 (30.27, 36.10), OCt1 33.19 (31.10, 35.81)], indicating a lower viral load. Two consecutive negative results of approximately 17% (65/383) tested positive for SARS-CoA-2 with a median Ct of 32.8, similar to these results. The median length of SARS-CoA-2 RNA shedding was 24d from symptom onset, coinciding with the readmission timing after discharge[32]. An increase in reports of recurrent positive real-time-PCR assays for SARS-CoV-2 has caused widespread concern[33-34] and may be associated with prolonged viral RNA shedding in some infected individuals[35].

From this study, people with rebound-positive reverse transcription-polymerase chain reaction (RT-PCR) test results had higher HADS scores, including anxiety and depression

subcategory scores, higher PSQI scores, and a significantly larger proportion of clinical anxiety symptoms (50.00%) and depressive symptoms (47.37%). The association between depression, anxiety, and DED has been well-documented[36-37]. The chronic discomfort and pain caused by DED symptoms might negatively impact cognitive processes, sleep, the performance of daily activities, emotional well-being, and workability[38-39]. DED can lead to visual perception and performance disturbances, with the latter inducing and exacerbating the symptoms of anxiety and depression[40-41]. Additionally, many countries and regions have required infected individuals and their contacts to be isolated at home or in dedicated quarantine facilities since COVID-19 began. Social isolation has negative psychological effects, including post-traumatic stress disorder, confusion, and anger; stressors include extended quarantine periods, fear of infection, frustration, boredom, inadequate supplies, insufficient information, financial loss, and stigma[42]. For recurrent positive cases, increased anxiety and depression could be explained due to re-exposure to such stressors. Binary logistic regression analysis revealed that fixed occupation was a protective factor against DED symptoms; thus, people with stable jobs might not have had aggravated DED symptoms affecting their psychological condition, as they did not experience the occupational uncertainty (pay cuts and unemployment) associated with centralized isolation.

In this study, Ct values conducted on the day of administration of the questionnaire were not significantly correlated with each score, unlike in a previous study[12], which revealed that Ct values were the only variable independently associated with any ocular symptoms within 4wk of diagnosis. This disparity was possibly due to the limited number of participants in this study and the different times at which assessments were performed.

This study had several limitations. First, the sample size was too small to generalize the results; however, the authors investigated the pandemic in the Chinese centralized isolation wards unprecedentedly. Despite the relatively small number of patients, the relationships between these factors were well demonstrated. Moreover, this study provided ophthalmologists with better access to unique and irreplaceable situations during COVID-19. Second, questionnaires were only administered to patients with COVID-19 during hospitalization, whereas these conditions were not investigated before the COVID-19 infection and after discharge. Third, due to the coronavirus infection control policy, objective examinations of ocular manifestations, tear, or conjunctival sac sampling were not performed, and these self-reported symptoms might have been biased. It would be interesting to investigate the development of post-infection dry eye or conjunctivitis over a longer period of time.

In conclusion, this study revealed that recurrent positivity was a risk factor for DED symptoms in patients with COVID-19 in centralized isolation wards, who had more severe DED, anxiety, and depressive symptoms than asymptomatic carriers and mild cases. Future research should focus on systematic eye examinations, psychological interventions, and longitudinal studies of related mechanisms; ocular and systemic changes should be evaluated in centralized isolation wards.

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