Heliyon 10 (2024) e39497

Contents lists available at ScienceDirect

Heliyon

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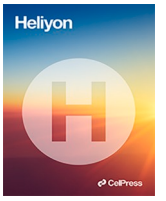

Research article

Optical quality changes of the eye during peak SARS-CoV-2 pandemic in young adults

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ARTICLE INFO

Keywords:
Corneal morphology
Coronavirus
Backscatter
Corneal aberration
Optical quality

ABSTRACT

Introduction: To determine whether severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection affects corneal morphology and optical quality.
Methods: In this cross-sectional study, ophthalmological indicators were examined during the peak of SARS-CoV-2 infection after adjusting for public health control measures. Participants were divided into control (remained uninfected), A (infected during follow-up), and B (infected prior to the first consultation) groups. Effects of varying SARS-CoV-2 infection levels were determined using reverse transcription polymerase chain reaction. Changes in corneal morphology, backscatter, and aberrations were measured. Corneal parameters, such as flat keratometry, steep keratometry, and surface variance, vertical asymmetry, height asymmetry, and height decentration indices were considered.
Results: Overall, 110 participants (208 eyes, 42.7 % male; age 17–31 years) were enrolled. Eighteen (16.3 %) were infection-free during the outbreak with unchanged corneal morphology, backscatter, and aberration. In group A, 34.73 ± 9.30 days after infection, the backscatter of the anterior corneal layer and central layer (both $p = 0.000$) decreased. Total low-order aberration, defocus, horizontal coma, and spherical aberration of the cornea increased ($p < 0.05$), while corneal morphology after infection did not change ($p > 0.05$). In group B, a decrease in backscattering in the corneal middle layer and an increase in horizontal coma ($p < 0.05$) were noted.
Conclusion: Backscattering of the anterior and intermediate layers of the cornea decreased and corneal aberrations increased after SARS-CoV-2 infection, which affected corneal optical quality. However, corneal morphology and thickness remained unchanged. Ophthalmological indicators and optical quality should be monitored during SARS-CoV-2 infection.

1. Introduction

On December 7, 2022, mainland China ended its community-based dynamic zeroing coronavirus disease-2019 (COVID-19) policy to adjust and optimize its public health control measures [1]. After rapid and total opening, this change accompanied with an unexpected sudden incidence peak in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection [2]. The rapid spread was

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https://doi.org/10.1016/j.heliyon.2024.e39497
Received 3 July 2024; Received in revised form 15 September 2024; Accepted 16 October 2024
Available online 17 October 2024

primarily driven by the Omicron variants BF.7 (75.71 %) and BA.5.2 (16.29 %), which accounted for the infection wave that swept the entire mainland China [3,4].

Although SARS-CoV-2 primarily affects the respiratory system, the ocular surface has been reported and identified as a potential entry point for the virus [5,6]. Evidence increasingly shows that the virus can reside in tear film and conjunctival secretions and infect the eye, causing ocular symptoms [7]. Given that the cornea, as the outermost structure of the eye, plays a critical role in visual quality, any impact on its shape or transparency could lead to significant visual disruptions.

During COVID-19 infection, some patients have complained and expericed ocular symptoms such as conjunctival congestion and foreign body sensation, which could increase the risk of hand-eye contact and subsequent infection [8,9]. SARS-CoV-2 enters cells through angiotensin-converting enzyme 2 (ACE2) receptors, with transmembrane serine protease 2 (TMPRSS2) aiding entry, and these receptors are found in various parts of the eye, including the conjunctiva, cornea, and limbus [10,11]. This raises concerns and hypothesis that SARS-CoV-2 could potentially alter the corneal structure, even in the short term, leading to changes in optical quality [12].

During the peak of infections from November 2022 to February 2023, we observed reports of decreased visual quality among some patients during infection [13,14]. These clinical observations may suggest a possible association between COVID-19 and changes in corneal morphology and properties. To date, no studies have explored the effects of SARS-CoV-2 infection on corneal structure and optical quality. Given the possibility of future infection waves and new variants [2], understanding how COVID-19 may affect the cornea, particularly regarding optical quality and visual function, is essential. This study aims to examine the relationship between corneal characteristics and optical quality during the peak period of SARS-CoV-2 infections, offering insights for future clinical management.

2. Methods

This cross-sectional study was approved by the Ethics Committee of Tianjin Eye Hospital (ID: KY-2023019) and followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) reporting guidelines. This study is also registered on ClinicalTrials.gov (NCT05882383) and adhered to the tenets of the Declaration of Helsinki. Participants at the Tianjin Eye Hospital were recruited from November 25, 2022, to December 3, 2022, and a thorough and comprehensive eye examination was conducted free of charge. All participants, including those under 18 years of age, provided written informed consent, duly obtained from both the participants themselves and their respective parents or legal guardians. No incentives were offered to encourage participation. All participants underwent a full ophthalmic examination by skilled ophthalmologists to confirm that they had no corneal abnormalities, including inflammation, scar, congenital anomalies, and haze. The inclusion criteria for participants were as follows: age $\geq$17 years; refractive stability (change $\pm$ 0.50 diopter [D] or less) for at least 2 years; no history of wearing corneal contact lenses; no history of ophthalmic medication use within the past three months; and normal intraocular pressure. The exclusion criteria were as follows: any degree of corneal opacity; a history of eye trauma or eye surgery; glaucoma; keratoconus; diabetes; immune dysfunction; or systemic connective tissue disease. Participants were required to complete two visits with an interval of one month and submit samples for real-time reverse transcription polymerase chain reaction (rRT-PCR) testing at least twice a week. Participants who were lost to follow-up were excluded from this study. Whether the participants had undergone rRT-PCR testing, as well as the testing timings and results were recorded in detail. The last participant was followed up on February 20, 2023. The presence of rRT-PCR positivity during the follow-up indicated SARS-CoV-2 infection and PCR-negativity, and no symptoms of infection during the follow-up period indicated no infection. Participants with symptoms but without PCR test results were excluded from the study. All participants were confirmed to have no history of PCR positivity before November 25, 2022, or ocular and systemic diseases except for refractive errors.

Participants were divided into three groups according to the rRT-PCR results and the presence or absence of symptoms of infection during follow-up: the control group (uninfected during follow-up), group A (infected during follow-up), and group B (infected before the first visit). Corneal topography was performed using a rotating Scheimpflug device (Pentacam HR, Oculus, Wetzlar, Germany) by the same skilled examiner from 2 p.m. to 5 p.m. in the same examination room in triplicate, to obtain the mean value. Corneal morphological parameters, corneal vertex and thinnest-point thickness, corneal backscatter, and corneal aberration-related parameters were extracted. Moreover, flat keratometry (K1), steep keratometry (K2), index of surface variance (ISV), index of vertical asymmetry (IVA), index of height asymmetry (IHA), and index of height decentration (IHD) were used to assess corneal morphology. Corneal backscatter of the anterior layer (surface layer, 120 μm), posterior layer (innermost layer, 60 μm), and intermediate layer (the section between the anterior and posterior layers) in the corneal range of 0–2 mm was used to assess corneal transparency. Corneal optical quality was evaluated by examining the corneal aberrations with a diameter of 6 mm, including the total values of corneal low-order and high-order aberrations. Moreover, the Zernike vectors, such as astigmatism, defocus, spherical aberration, coma, and trefoil, which had a significant influence on visual quality, were analyzed.

All statistical analyses were performed using SPSS (version 26.0, SPSS Inc., IBM Corp., Armonk, NY, USA), and continuous variables were expressed as mean $\pm$ standard deviation. The Kolmogorov–Smirnov test was used to evaluate data normality. A paired-sample *t*-test was used when the data were normally distributed; otherwise, the Wilcoxon test was performed. Analysis of variance was used to assess differences between all groups, and the Bonferroni correction was applied to address the problem of multiple comparisons. Pearson's correlation analysis was used to analyze the correlation between corneal backscatter and aberration changes. Differences with p-values $<$0.05 were considered statistically significant.

3. Results

3.1. Participant demographics and grouping

This study included 208 eyes from 110 participants, consisting of 63 females (57.3 %) and 47 males (42.7 %), with an average age of 23.26 ± 5.32 years. The participants were divided into three groups: the control group with 36 eyes from 18 participants, Group A with 67 eyes from 39 participants, and Group B with 105 eyes from 53 participants. In Group A, participants had their first visit before SARS-CoV-2 infection and their second visit approximately 34.73 ± 9.30 days post-infection. Fig. 1 presents the study details and main findings of Group A. In Group B, the first and second visits occurred at 16.45 ± 6.17 days and 45.38 ± 5.69 days post-infection, respectively. Comparisons between the groups during both visits are provided in Supplementary Table S1.

3.2. Visual acuity and corneal morphology

No significant differences were observed in uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) among the groups throughout the follow-up period. Additionally, there were no significant changes in corneal morphological parameters, including keratometry, Index of Surface Variance (ISV), Index of Vertical Asymmetry (IVA), Index of Height Asymmetry (IHA), and Index of Height Decentration (IHD), in any group after SARS-CoV-2 infection. Corneal thickness also remained stable across all groups post-infection. Detailed information on these parameters can be found in Supplementary Table S2.

3.3. Corneal aberrations

In the control group, no significant changes were observed in visual aberrations, maintaining baseline stability throughout the study. However, in Group A, following SARS-CoV-2 infection, there were significant increases in several visual aberrations, including low-order aberrations (p = 0.001; 95 % CI, −0.219 to −0.056), defocus (p = 0.023; 95 % CI, −0.246 to −0.019), horizontal coma (p = 0.007; 95 % CI, 0.005–0.029), and spherical aberration (p = 0.043; 95 % CI, −0.033 to −0.001). In Group B, significant increases were noted in total high-order aberration (p = 0.027; 95 % CI, −0.036 to −0.002) and vertical coma (p = 0.000; 95 % CI, −0.048 to −0.021), with no significant differences in low-order aberrations between the two visits (Table 1).

3.4. Corneal backscatter

No significant changes were observed in corneal backscatter in the control group. In Group A, significant reductions in corneal backscatter were noted in both the anterior (p = 0.000; 95 % CI, 0.436–1.478) and intermediate layers (p = 0.000; 95 % CI,

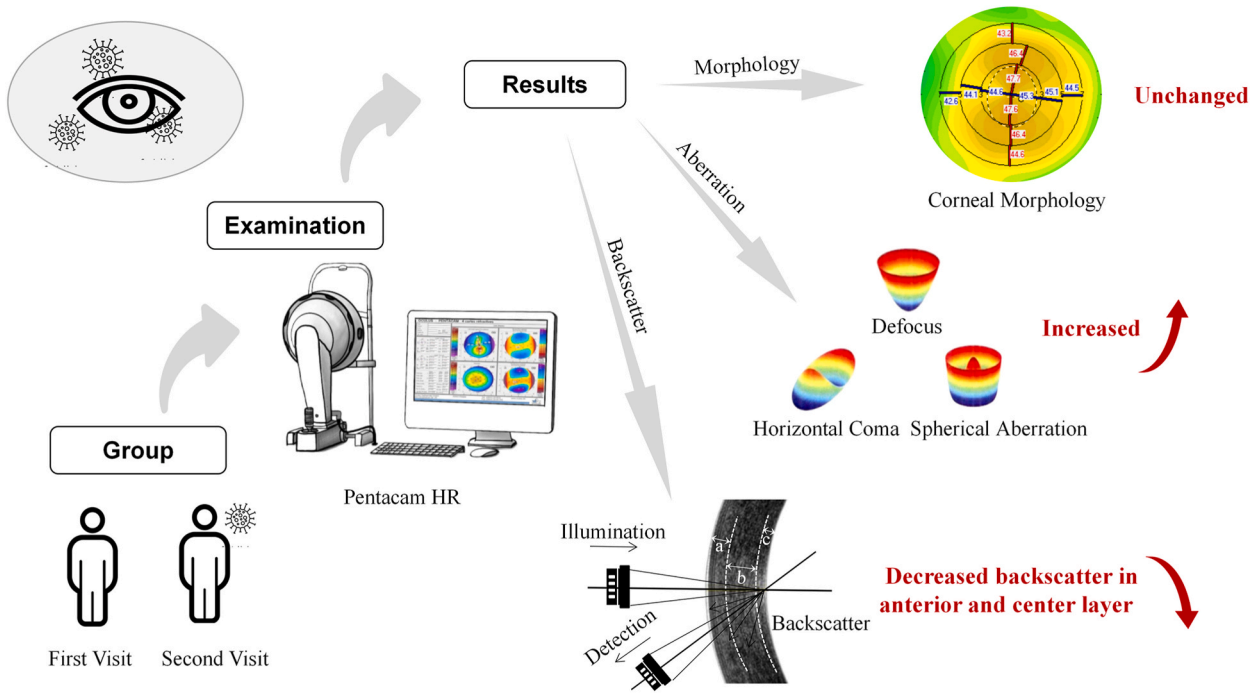

Fig. 1. Flowchart of the results of group A.
a: Anterior 120 μm of the cornea; b: Central part of the anterior and posterior layers; c: Posterior 60 μm of the cornea.

Table 1
The comparison of changes in the respective groups during fowllow up.

		First Visit	Second Visit	p	Upper CI	Lower CI
Control group (n = 36)						
Corneal aberration	RMS LOA	1.80 ± 0.62	1.76 ± 0.61	0.254	−0.034	0.123
	RMS HOA	0.39 ± 0.09	0.40 ± 0.10	0.454	−0.047	0.021
	Z 2 2	−1.31 ± 0.64	−1.24 ± 0.66	0.105	−0.239	0.024
	Z 2 0	0.67 ± 0.26	0.66 ± 0.31	0.493	−0.076	0.155
	Z 2 -2	0.05 ± 0.24	0.07 ± 0.26	0.831	−0.083	0.067
	Z 3 3	0.02 ± 0.07	0.02 ± 0.09	0.274	−0.016	0.056
	Z 3 1	0.00 ± 0.12	−0.00 ± 0.13	0.684	−0.031	0.020
	Z 3 -1	0.36 ± 0.21	0.26 ± 0.20	0.650	−0.035	0.022
	Z 3 -3	−0.07 ± 0.07	−0.09 ± 0.07	0.259	−0.017	0.062
	Z 4 0	0.22 ± 0.04	0.22 ± 0.05	0.496	−0.013	0.025
Group A (n = 67)						
Corneal aberration	RMS LOA	1.54 ± 0.54	1.67 ± 0.63	0.001[a]	−0.219	−0.056
	RMS HOA	0.38 ± 0.12	0.39 ± 0.17	0.414	−0.037	0.015
	Z 2 2	−1.04 ± 0.68	−1.08 ± 0.72	0.127	−0.014	0.113
	Z 2 0	0.61 ± 0.39	0.74 ± 0.51	0.023[a]	−0.246	−0.019
	Z 2 -2	0.00 ± 0.41	−0.05 ± 0.37	0.127	−0.010	0.078
	Z 3 3	−0.01 ± 0.10	−0.02 ± 0.11	0.876	−0.028	0.032
	Z 3 1	−0.01 ± 0.11	−0.02 ± 0.12	0.007[a]	0.005	0.029
	Z 3 -1	0.02 ± 0.17	0.03 ± 0.17	0.338	−0.028	0.010
	Z 3 -3	−0.06 ± 0.14	−0.05 ± 0.13	0.361	−0.043	0.016
	Z 4 0	0.19 ± 0.08	0.20 ± 0.09	0.043[a]	−0.033	−0.001
Group B (n = 105)						
Corneal aberration	RMS LOA	1.77 ± 0.63	1.78 ± 0.65	0.596	−0.081	0.047
	RMS HOA	0.39 ± 0.09	0.41 ± 0.09	0.027[a]	−0.036	−0.002
	Z 2 2	−1.21 ± 0.81	−1.24 ± 0.81	0.119	−0.006	0.054
	Z 2 0	0.71 ± 0.44	0.74 ± 0.48	0.392	−0.087	0.034
	Z 2 -2	0.02 ± 0.37	0.00 ± 0.37	0.288	−0.015	0.051
	Z 3 3	0.01 ± 0.09	−0.00 ± 0.10	0.068	−0.001	0.037
	Z 3 1	−0.00 ± 0.12	−0.00 ± 0.12	0.822	−0.009	0.011
	Z 3 -1	−0.00 ± 0.18	0.03 ± 0.18	0.000[a]	−0.048	−0.021
	Z 3 -3	−0.08 ± 0.09	−0.09 ± 0.11	0.133	−0.005	0.035
	Z 4 0	0.22 ± 0.08	0.22 ± 0.09	0.441	−0.013	0.006

RMS LOA: Root Mean Square of Lower-Order Aberrations RMS HOA: Root Mean Square of Higher-Order Aberrations; CI: confidence interval; Z2 2: Astigmatism; Z2 0: Defocus; Z2 -2: Astigmatism; Z3 3: x-Trefoil; Z3 1: Horizontal Coma; Z3 -1: Vertical coma; Z3 -3: y-Trefoil; Z 4 0: spherical aberration.

[a] : *p* value less than 0.05.

0.333–0.704) after SARS-CoV-2 infection. In Group B, the backscatter in the middle corneal layer remained significantly lower at the second visit compared to the first (p = 0.001; 95 % CI, 0.072–0.267). The comparison of corneal backscatter changes among different groups is shown in Fig. 2.

3.5. Correlation between backscatter and aberrations

Changes in anterior corneal backscatter were significantly correlated with changes in defocus (p = 0.000, r = −0.368), horizontal

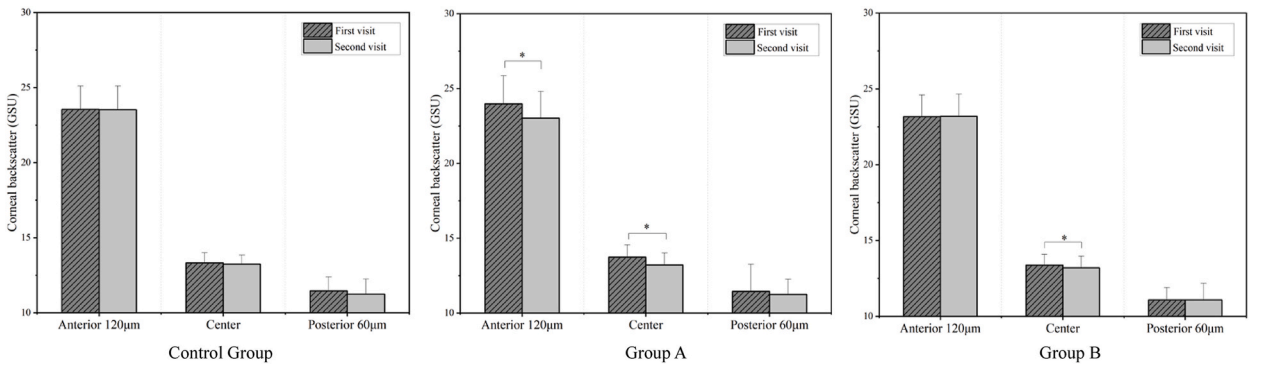

Fig. 2. Comparison of Corneal Backscatter Changes Among Different Groups.
GSU: Greyscale Units; *: The difference between the two visits was statistically significant (p < 0.05).

coma (p = 0.000, r = −0.301), vertical coma (p = 0.002, r = 0.24), and spherical aberration (p = 0.030, r = −0.166), as detailed in Table 2.

4. Discussion

During the COVID-19 outbreak, participants who presented at the clinic complained about a decline in visual quality and eye discomfort but no abnormal causes were found by routine ophthalmic examination [14], prompting the need for this study. This is the first study to assess whether the properties of the cornea are affected by SARS-CoV-2 infection. None of the participants in the study had been infected with COVID-19 before the fast large-scale outbreak (November 25, 2022), which excluded any impact of previous infection on the results. This cross-sectional study demonstrates that the optical quality of the cornea decreases after SARS-CoV-2 infection, although the corneal morphology remains unaffected.

Though the cornea is typically considered an immune-privileged tissue, immune responses can still occur due to the infiltration of monocyte-derived macrophages and $CD4^+$ and $CD8^+$ T cells into the anterior chamber [15]. SARS-CoV-2 infection has been linked to several ocular symptoms, including conjunctival congestion, dry eyes, blurred vision, and foreign body sensations, along with increased eye rubbing [8]. While these symptoms could result from frequent hand-eye contact during infection, our study found no significant changes in corneal thickness or morphological parameters, suggesting that short-term discomfort does not necessarily affect corneal structure. However, more subtle microstructural changes could still be present, potentially impacting optical quality and warranting further investigation.

Corneal backscattering, also known as corneal densitometry, are currently a commonly used indicator of corneal transparency and can be used to diagnose edema, haze, and keratitis that are not detectable by slit lamps and other conventional methods [16–18]. The ultrastructure of the eye allows for optical transparency, and changes in the ultrastructure observed after infection can be indirectly reflected by the corneal backscattering [19]. In our study, significant reductions in corneal backscattering were observed in the anterior and intermediate layers post-infection, while the inner layer showed no notable changes. Previous studies have suggested that the observed effects of SARS-CoV-2 on the cornea are likely attributable to corneal nerve damage [20,21]. SARS-CoV-2 infection appears to induce nerve degeneration, as evidenced by reductions in corneal nerve fiber density, length, and branching [20]. Notably, backscattering in the anterior corneal layer demonstrated a faster recovery than in the intermediate layer, where changes persisted over a longer period. The sustained reduction in backscattering within the intermediate layer may be attributable to the loss of corneal nerve fibers and the increase in dendritic cell density, as demonstrated by confocal microscopy 3.7 months post-infection [21]. These findings suggest that the intermediate layer of the cornea experiences a more prolonged recovery process following SARS-CoV-2 infection.In addition to changes in corneal backscattering, we also noted alterations in wavefront aberrations, which objectively measure visual quality [22]. Specifically, we observed an increase in horizontal coma and Spherical aberration shortly after infection. Such findings suggest that ultrastructural changes in the cornea caused by SARS-CoV-2 infection may contribute to visual disturbances, a hypothesis that warrants further validation through follow-up studies. Given the instability in wavefront aberrations post-infection, refractive surgeries guided by wavefront measurements should be approached with caution in the short term. Further research is needed to explore post-infection visual quality more thoroughly. Moreover, increased corneal aberrations may be linked to reduced tear film stability, potentially caused by disturbances on the ocular surface [23]. These disruptions could lead to localized variations in the corneal surface and reduced image quality [13,24]. Additionally, changes in anterior-layer backscattering correlated with increased corneal defocus, coma, and spherical aberration. Thus, during the early stages of the pandemic, surgeries requiring precise wavefront measurements were not recommended. Larger-scale studies are necessary to fully understand the optical quality changes associated with SARS-CoV-2 infection.

Several limitations must be acknowledged. First, this was a single-center study involving a single ethnicity. Moreover, due to the change in epidemic control measures, fewer participants were routinely tested for SARS-CoV-2, resulting in a limited sample size.

Table 2
Correlation analysis between cornea backscatter change and aberration change after infection (n = 172).

	Anterior 120 μm Δ		Center Δ		Posterior 60 μm Δ	
	R[b]	P	R[b]	P	R[b]	P
RMS LOA	-0.081	0.291	0.057	0.461	0.051	0.512
RMS HOA	-0.021	0.789	-0.069	0.374	-0.103	0.183
Z 2 2	0.071	0.355	-0.012	0.873	0.009	0.909
Z 2 0	-0.368	0.000[a]	0.048	0.531	0.087	0.257
Z 2 -2	0.050	0.514	0.108	0.161	-0.061	0.434
Z 3 3	-0.030	0.702	0.078	0.31	-0.061	0.428
Z 3 1	-0.301	0.000	-0.085	0.271	-0.012	0.876
Z 3 -1	0.240	0.002[a]	-0.003	0.969	0.100	0.196
Z 3 -3	-0.136	0.078	-0.130	0.092	-0.009	0.092
Z 4 0	-0.166	0.030[a]	-0.151	0.051	-0.097	0.207

RMS LOA: Root Mean Square of Lower-Order Aberrations RMS HOA: Root Mean Square of Higher-Order Aberrations; Z2 2: Astigmatism; Z2 0: Defocus; Z2 -2: Astigmatism; Z3 3: x-Trefoil; Z3 1: Horizontal Coma; Z3 -1: Vertical coma; Z3 -3: y-Trefoil; Z 4 0: spherical aberration; a: p value less than 0.05;

[b] :Pearson's correlation analysis; Δ: The difference between the two visits

Second, the vaccination status of participants was not controlled, which may have influenced the findings, and future studies should systematically consider this factor to enhance methodological rigor. Lastly, long-term follow-up was not conducted to determine when the corneal aberrations and structural changes in the cornea would be ameliorated. This study aimed to present important findings promptly, given the pressing nature of the pandemic.

5. Conclusion

We found that SARS-CoV-2 infection affected the optical quality of the eye, with decreased backscattering in the anterior and intermediate layers of the cornea and increased corneal aberrations. However, no changes were observed in corneal morphology and corneal thickness. These results have important clinical implications in helping ophthalmologists, especially refractive surgeons, assess and predict possible risks to the cornea due to SARS-CoV-2 infection. Optical quality needs to be monitored during the COVID-19 pandemic, particularly post-COVID era.

CRediT authorship contribution statement

He Tian: Writing – original draft, Software, Resources, Methodology, Investigation, Data curation. **Qian Fan:** Writing – review & editing, Supervision, Methodology, Investigation. **Wenjing Gao:** Writing – review & editing, Supervision, Software, Methodology, Investigation. **Yan Wang:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Funding acquisition.

Statement of ethics

This study was carried out in accordance with the recommendations of tenets of the Declaration of Helsinki with written informed consent from all subjects. This study was reviewed and approved by the Ethics Committee of the Tianjin Eye Hospital of Nankai University (ID: KY-2023019), date (2023-03-01). All participants/legal guardians provided written informed consent for the publication of their anonymised Medical records and images.

Medical writing and editorial assistance

This paper did not receive any medical writing support and editorial assistance.

Data availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Data statement

The data that support the findings of this study are available from the corresponding author, Y.W., upon reasonable request.

Funding sources

This work was supported by the grants from the National Program on Key Research Project of China (2022YFC2404502), National Natural Science Foundation of China (82,271,118), Tianjin Science and technology project (21JCZDJC01190), Tianjin Health Research Project (TJWJ2022XK036), Tianjin Key Medical Discipline (Specialty) Construction Project (TJYXZDXK-016 A).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to thank Mingdong Zhang for data collection.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e39497.

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