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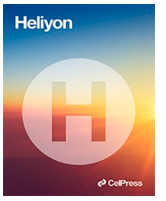

Research article

Acute angle-closure glaucoma before, during, and after the outbreak of COVID-19 in China

Yu Mao [a,1], Yanqian Xie [a,1], Guoxing Li [a], Rongrong Le [a], Shuxia Xu [a], Peijuan Wang [a], Xiaojie Wang [a], Qi Zhang [a], Shaodan Zhang [a,b,*], Yuanbo Liang [a,b]

[a] National Clinical Research Center for Ocular Diseases, The Eye Hospital, School of Ophthalmology and Optometry, Wenzhou Medical University, Wenzhou, China
[b] Glaucoma Research Institute, Wenzhou Medical University, Wenzhou, China

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ABSTRACT

Objectives: Acute angle-closure glaucoma (AACG) is a major cause of irreversible and severe visual function loss. Robust rise in AACG was observed in the ophthalmic outpatient clinics concomitant with the outbreak of COVID-19 infection in China after the relaxing of "zero-COVID policy" in early December 2022. Here we compared the demographic and clinical profiles of patients with AACG before, during and after the COVID-19 outbreak. Underlying mechanisms were tentatively investigated.

Methods: This is a retrospective comparative study. Consecutive cases with newly diagnosed AACGs in a tertiary eye hospital were retrospectively collected during December 17, 2022 to January 8, 2023. Data from the same period in 2018–2019 and 2019–2020, 2020–2021 and 2021–2022, and 2023–2024 were collected as pre-pandemic, pandemic-control, and post-pandemic control, respectively. For the patients in 2022–2023 outbreak group, COVID-19 infection was confirmed by reversed transcriptase-polymerase chain reaction or antibody test for severe acute respiratory syndrome coronavirus disease 2 (SARS-CoV-2) from nasopharyngeal swabs. Ocular parameters, serum electrolytes and coagulative parameters were compared between COVID-19 positive and negative AACGs in observational group. SARS-CoV-2 nucleic acid in the aqueous humor was detected.

Results: A total of 106 AACG cases were diagnosed during the outbreak period in 2022–2023. In contrast, 18 (in 2018–2019) and 22 (in 2019–2020) cases were included during pre-pandemic period, and 21 (in 2023–2024) during the post-pandemic period. Only 13 and 4 newly onset AACG were included in 2020–2021 and 2021–2022 during the pandemic-control period, respectively. Younger age and higher proportion of bilateral involvement were detected in COVID-19 outbreak group than that of other groups ($p = 0.034$ and $p = 0.080$). Sixty-eight (64.2 %) patients in the outbreak group had a confirmed COVID-19 infection. Intervals between infection and AACG attack was 52 ± 85h (0-15d). Fifty-three patients (77.9 %) reported the

Abbreviations: AACG, acute angle-closure glaucoma; APTT, activated partial thromboplastin time; ACE, angiotensin-converting enzyme; COVID-19, coronavirus disease 2019; IOP, intraocular pressure; LPI, laser peripheral iridectomy; MPV, mean platelet volume; PT, plasma prothrombin time; PACG, primary angle-closure glaucoma; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SD, standard, deviation; TT, thrombin time.

* Corresponding author. National Clinical Research Center for Ocular Diseases, The Eye Hospital of Wenzhou Medical University, Glaucoma Research Institute of Wenzhou Medical University, Wenzhou, 325027, Zhejiang, China.
E-mail address: shaodan_zhang@eye.ac.cn (S. Zhang).

[1] These authors contribute equally to this work.

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applications of ibuprofen or other antipyretic medications and 25 (36.8 %) reported large volume water intake before AACG attack. COVID-19-positive AACG patients had higher level of D-dimer than their negative counterparts (1.13 ± 2.60 mg/L vs. 0.46 ± 0.43 mg/L, p = 0.083). No difference in IOP, serum electrolytes, and coagulative parameters other than D-dimer was observed between COVID-19 positive and negative cases. SARS-CoV-2 were negative in the aqueous humor from 14 COVID-19 positive and 8 negative patients.

Conclusion: COVID-19 infection surged the onset of AACG in patients at risk. Mental stress, water intake, increased choroidal thickness due to SARS-CoV-2 induced ACE receptor activation, and hyper-coagulation, may contribute to the disease onset. Ocular involvement should not be ignored in both routine and new systemic emergent conditions.

1. Introduction

Following the adjustment and relaxing of the "dynamic zero-COVID policy" in early December 2022, the infection of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in China surged [1–3]. The coronavirus disease 2019 (COVID-19) mainly occurs as a lower respiratory tract infection and could lead to multi-organ involvement. Although ocular manifestations are not perceived as typical and severe symptoms of COVID-19, ocular surface has been suggested as a site of infection with responsible for COVID-19 [4–6]. Since its first description in 2020, accumulating evidence reported COVID-19 related ocular manifestations in affected individuals, mainly including conjunctival hyperemia, ocular surface inflammation, retinal and choroidal lesions [7–12]. The disease is not only manifested as an acute inflammatory process, but also can lead to microvascular thrombosis in the retina and choroid, exerting long-term impact on the visual prognosis of the patients. Surged onset of various of previously uncommon conditions, including acute macular neuroretinopathy (AMN), multiple evanescent white dot syndrome, seasonal hyperacute panuveitis (SHAPU), have been observed during the outbreak of Omicron after China's relaxation from the "zero-COVID" policy in December 2022, suggesting an unique pathogenic mechanism of SARS-CoV-2 [13–15]. Recently, robust attack of acute angle-closure glaucoma (AACG) following the outbreak of COVID-19 has also been consistently reported by various studies [16–20]. However, the exact mechanisms are still far from being fully understood. In the present study, we further investigated the advocative effect of COVID-19 infection on AACG attack by comparing the prevalence of AACG in a tertiary eye hospital before, during and after the outbreak of omicron. Possible underlying mechanisms were also tentatively investigated.

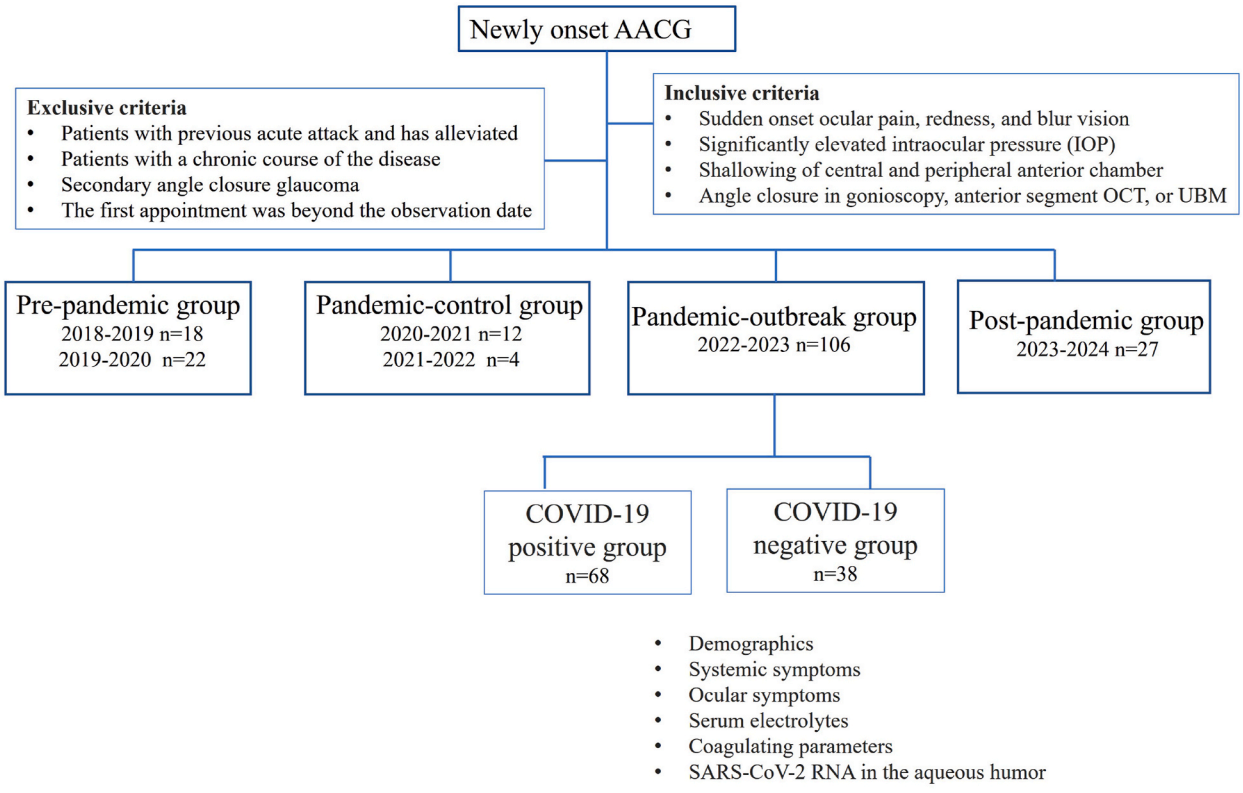

Fig. 1. Flow chart of the study.

2. Methods

2.1. Study design and ethic approval

This is a retrospective study. This study was conducted in accordance with the tenets of the Declaration of Helsinki. The Ethics Committee of the Eye hospital of Wenzhou Medical University approved this study (2022-244-K-197) and waived the informed consent, as all data were retrospectively collected and analyzed in de-identified fashion.

2.2. Study population

Consecutive patients with newly diagnosed AACG in Eye Hospital of Wenzhou Medical University in southeast China between December 17, 2022 to January 8, 2023 were enrolled and defined as COVID-19 outbreak group. Data from the same period during 2018–2019 and 2019–2020 was used as pre-pandemic control, while that from 2020 to 2021 and 2021–2022 as pandemic-control group, and 2023–2024 as post-pandemic group. Diagnosis of AACG required a complain of sudden onset ocular pain, redness, and blur vision; significantly elevated intraocular pressure (IOP); shallowing of central and peripheral anterior chamber; evidence of angle closure in gonioscopy, anterior segment OCT, or UBM. Advocative factors for acute angle closure attack were also interviewed. For the 2022–2023 outbreak group, patients were divided into COVID-19 positive and COVID-19 negative group depending on the PCR or antibody test for COVID19. Information on demographics, systemic COVID-19 symptoms, and ocular symptoms were collected. Serum electrolytes and coagulating parameters were extracted from the medical record. Aqueous humor (approximately 0.1 cc) was collected from 22 patients during paracentesis or at the beginning of the surgery. Aqueous samples were analyzed for SARS-CoV-2 viral ribonucleic acid (RNA) using real-time reverse transcriptase chain reaction (Fig. 1).

2.3. Statistical analysis

Statistical analyses were performed by SPSS 24.0 software (SPSS Inc., CHI, USA). Continuous data with normal distribution were presented as mean ± standard, deviation (SD). Comparison of gender, history of laser peripheral iridectomy (LPI), AACG aura, and frequency of bilateral attack between groups were performed using the Chi-square test or fisher's exact test. ANOVA was performed for the comparing of age and intraocular pressure among groups, while independent *t*-test was used to investigate the difference in age, ocular biometry parameters and serum biochemical measurements between COVID-19 positive and negative patients. A p value < 0.05 was considered as statistically significant.

3. Results

3.1. Numbers of newly-diagnosed AACG during different period

During pre-pandemic period in 2018–2019 and 2019–2020, a total of 18 and 22 newly onset AACG were diagnosed, respectively. The mean age at presentation was 68.7 ± 12.7 years (5 males, 27.8 %) and 71.8 ± 11.5 years (6 males, 27.3 %), and the IOP was 46.3 ± 8.66 mmHg and 42.2 ± 13.6 mmHg, respectively. Two cases (9.1 %) in 2019–2020 group were reported as bilateral attack. During the pandemic-control period, 12 AACG (mean age, 67.9 ± 6.7 years, 25 % males) presented in 2020–2021, and 4 (mean age 74.3 ± 12.3 years, 25 % males) presented in 2021–2022. The presenting IOP was 41.8 ± 11.2 mmHg and 45.7 ± 10.9 mmHg, respectively. One case (8.3 %) in 2020–2021 group was reported as bilateral attack. None of the patients in pandemic-control group reported a previously COVID-19 infection or fever prior to their AACG attack in control groups. In the post-pandemic period of 2023–2024, 27 newly onset AACG was diagnosed, with a mean age of 66.4 ± 11.8 years (22.2 % males). The presenting IOP was 41.2 ± 13.7 mmHg. Two cases (7.4 %) presented with bilateral attack in this series. Twelve (44.4 %) of these patients reported a previous COVID-19 infection or fever one year ago during the outbreak period. One (3.70 %) case experienced influenza and fever within one week

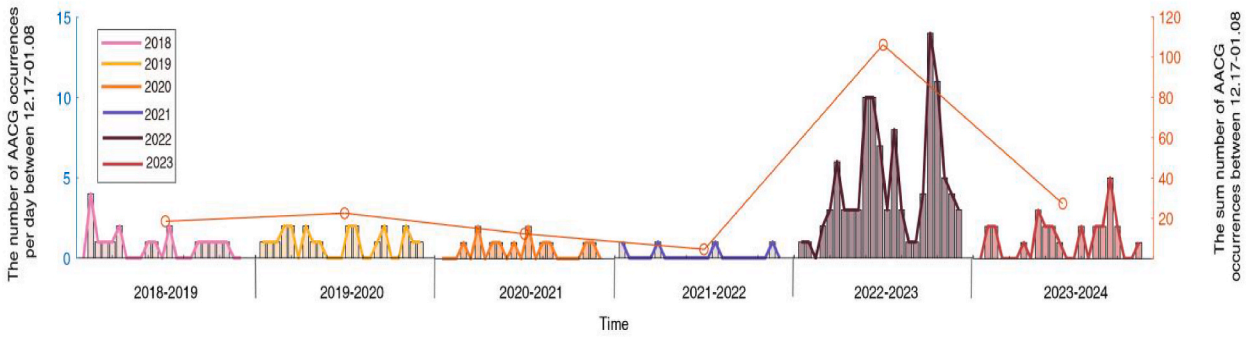

Fig. 2. Nembers of newly onset acute angle-closure glaucoma during different periods.

before this attack. Four (14.8 %) of these AACGs reported symptoms of previous aura.

Surged attack of AACG was observed during the COVID-19 outbreak period in 2022–2023. A total of 106 newly onset AACG presented to the outpatient clinics during this period (Fig. 2). The mean age of the affected patients was 65.5 ± 9.0 years (21.7 % males) and the mean presenting IOP was 39.7 ± 14.0 mmHg. Twenty patient (18.9 %) presented with bilateral attack. Twenty-nine (27.4 %) patients reported a previous aura within one year and 4 cases (3.8 %) have received bilateral LPI before. Younger age and higher proportion of bilateral attack and pervious aura were observed in the COVID-19 outbreak group compared with other groups. However, the presenting IOP and time intervals between AACG attack and presentation showed no difference among groups (Table 1).

3.2. Demographic and clinical features of the AACGs during COVID-19 outbreak period

During the COVID-19 outbreak period in 2022–2023, sixty-eight (64.2 %) patients with AACG reported confirmed COVID-19 infection. Age (65.6 ± 9.2 years vs. 65.3 ± 8.8 years, p = 0.877) and gender distribution (16.2 % males vs. 31.6 % males, p = 0.086) showed no difference between COVID-19-positive and -negative AACGs. Sixty-five (95.6 %) COVID-19 positive AACG reported a history of fever and 52 had cough (76.5 %). Other symptoms of COVID-19 infection mainly included headache (67.6 %), sored muscle (63.2 %), and tired (85.3 %). Average onset of AACG after COVID-19 infection was 52 ± 85h (range, 0h to15d) (Fig. 3). Mean body temperature was 38.5 ± 0.84 °C (37.5 °C–42 °C). Fifty-three (77.9 %) patients reported the applications of ibuprofen or other antipyretic medications and 25 (36.8 %) reported large volume water (>500 ml) intake before AACG attack. In contrast, 5 cases (13.2 %) among COVID-19 negative patients reported a history of large volume water intake. None of them have taken flu medications. Presenting IOP (40.5 ± 13.8 mmHg vs. 38.2 ± 14.5 mmHg, p = 0.433), axial length (22.3 ± 0.64 mm vs. 22.2 ± 0.61 mm, p = 0.797), anterior chamber depth (from central anterior surface of the cornea to the anterior surface of the lens, 2.40 ± 0.27 mm vs. 2.39 ± 0.23 mm, p = 0.872), and lens thickness (4.88 ± 0.43 mm vs. 4.87 ± 0.37 mm, p = 0.906) in affected eyes showed no significant difference between COVID-19-positive and negative cases.

Both systolic (129.79 ± 21.38 mmHg vs. 133.63 ± 15.64 mmHg, p = 0.481) and diastolic pressure (77.62 ± 10.70 mmHg vs. 78.26 ± 8.91 mmHg, p = 0.817) were comparable between COVID-19 infected and non-infected AACG patients at their presentation. Serum sodium (140.6 ± 2.99 mmol/L vs. 140.7 ± 2.32 mmol/L, p = 0.839), potassium (4.06 ± 0.43 mmol/L vs. 4.00 ± 0.53 mmol/L, p = 0.631), chloride (104.6 ± 3.5 mmol/L vs. 105.0 ± 3.7 mmol/L, p = 0.650), calcium (2.39 ± 0.08 mmol/L vs. 2.38 ± 0.09 mmol/L, p = 0.646), magnesium (0.92 ± 0.08 mmol/L vs. 0.92 ± 0.07 mmol/L, p = 0.947) showed no difference between COVID-19-positive and negative AACG patients. However, a relatively high serum phosphorus (1.18 ± 0.14 mmol/L vs. 1.08 ± 0.17 mmol/L, p = 0.015) was detected in COVID-19 infected cases. Coagulative indexes, including plasma prothrombin time (PT, 10.9 ± 0.55s vs. 11.2 ± 1.74s, p = 0.303), INR (0.95 ± 0.05 vs. 0.98 ± 0.16, p = 0.306), activated partial thromboplastin time (APTT, 27.0 ± 2.27s vs. 27.0 ± 2.29s, p = 0.980), fibrinogen (Fbg-c, 3.26 ± 0.63 g/L vs. 3.29 ± 0.71 g/L, p = 0.822) and thrombin time (TT, 19.1 ± 0.79s vs. 19.2 ± 0.81s, p = 0.643) showed no significant difference between groups. Although not statistically significant, COVID-infected AACG patients had higher D-dimer (1.13 ± 2.60 mg/L, range 0.10–13.92 mg/L) than their negative counterparts (0.46 ± 0.43 mg/L, range 0.12–1.86 mg/L) (p = 0.083). A total of 36 % COVID-19 positive AACGs demonstrated D-dimer above the upper limit of the normal range (>0.55 mg/L) compared with 21 % among the negative cases (Table 2).

Table 1
Characteristics of patients with acute angle-closure glaucoma during different period.

	Control period					COVID-19 outbreak period (2022–2023)				
	Pre-pandemic		Pandemic-control		Post-pandemic	Total	COVID-19 positive	COVID-19 negative	P value	P value
	2018–2019	2019–2020	2020–2021	2021–2022	2023–2024					
N	18	22	12	4	27	106	68(64.2 %)	38(35.8 %)	/	/
Age (mean ± SD)	68.7 ± 12.7	71.8 ± 11.5	67.9 ± 6.7	74.3 ± 12.3	66.4 ± 11.8	65.47 ± 9.0	65.6 ± 9.2	65.3 ± 8.8	0.877	0.034
Genger (male, %)	5(27.8 %)	6(27.3 %)	3(25 %)	1(25 %)	6(22.2 %)	23 (21.7 %)	11 (16.2 %)	12 (31.6 %)	0.086	0.986
Bilateral attack	0	2 (9.1 %)	1 (8.33 %)	0	2(7.4 %)	20(18.9 %)	14(20.6 %)	6(15.8 %)	0.545	0.080
IOP (mmHg)	46.3 ± 8.66	42.2 ± 13.6	41.8 ± 11.2	45.7 ± 10.9	41.2 ± 13.7	39.7 ± 14.0	40.5 ± 13.8	38.2 ± 14.5	0.433	0.306
Previous aura	1 (5.56 %)	0	2 (16.7 %)	0	4(14.8 %)	29(27.4 %)	19(27.9 %)	10(26.3 %)	0.857	0.006
History of LPI	0	0	1(8.33 %)	0	2(7.4 %)	4(3.8 %)	3(4,4 %)	1(2.6 %)	>0.999	0.470
Time interval between AACG attack and presentation (d, range)	5.08 ± 6.55 (0.5–27)	5.68 ± 7.22 (0.5–31)	8.83 ± 11.2 (0.25–30)	9.0 ± 6.58 (1–17)	9.0 ± 6.58 (1–17)	6.70 ± 7.69 (0.5–60)	6.40 ± 5.06 (0.5–60)	7.26 ± 11.2 (0.5–60)	0.587	0.734

SD, standard deviation; IOP, intraocular pressure; LPI, laser peripheral iridotomy.

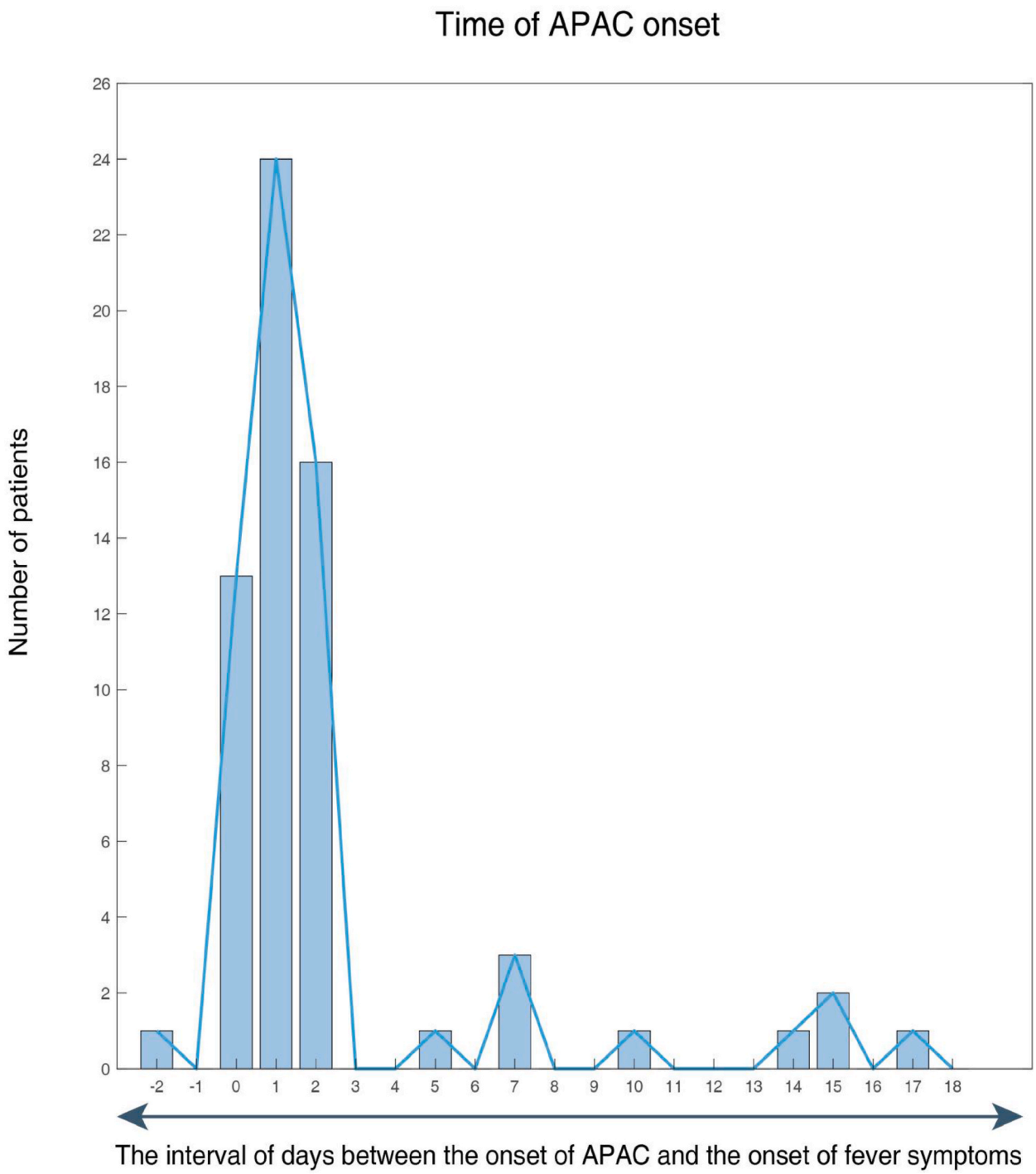

Fig. 3. The interval of days between the onset of APAC and the onset of fever symptoms in 2022–2023. Negative number in the horizontal axis means APAC onset before fever symptoms appeared. Positive number in the horizontal axis means APAC onset after fever symptoms appeared.

Finally, 54.4 % of the COVID-19-positive versus 42.0 % of the COVID-19-negative AACGs received incisional glaucoma surgeries ($p = 0.224$). The IOP at the last follow-up was 13.7 ± 5.51 mmHg versus 13.6 ± 2.89 mmHg for the COVID-19-positive and -negative AACGs, respectively ($p = 0.959$). No medication was need for the IOP control in both groups.

Table 2
Ocular biometry and blood biochemical test of patients with acute angle-closure glaucoma during COVID-19 outbreak.

	Total	COVID-19 positive	COVID-19 negative	P value
Axial length(mm)	22.3 ± 0.63	22.3 ± 0.64	22.2 ± 0.61	0.797
Anterior chamber depth(mm)	2.39 ± 0.26	2.40 ± 0.27	2.39 ± 0.23	0.872
Lens thickness(mm)	4.88 ± 0.42	4.88 ± 0.43	4.87 ± 0.37	0.906
Systolic pressure(mmHg)	130.9 ± 19.9	129.8 ± 21.4	133.6 ± 15.6	0.481
Distolic pressure(mmHg)	77.8 ± 10.2	77.6 ± 10.7	78.3 ± 8.91	0.817
Sodium (mmol/L)	140.6 ± 2.81	140.6 ± 2.99	140.7 ± 2.32	0.839
Potassium (mmol/L)	4.05 ± 0.46	4.06 ± 0.43	4.00 ± 0.53	0.631
Chloride (mmol/L)	104.7 ± 3.53	104.6 ± 3.49	105.0 ± 3.71	0.650
Calcium (mmol/L)	2.39 ± 0.08	2.39 ± 0.08	2.38 ± 0.09	0.646
Magnesium (mmol/L)	0.92 ± 0.08	0.92 ± 0.08	0.92 ± 0.07	0.947
Phosphorus (mmol/L)	1.15 ± 0.16	1.18 ± 0.14	1.08 ± 0.17	0.015
D-dimer (mg/L)	0.94 ± 2.24	1.13 ± 2.60	0.46 ± 0.43	0.083
PT (s)	11.0 ± 1.02	10.9 ± 0.55	11.2 ± 1.74	0.303
TT (s)	19.2 ± 0.79	19.1 ± 0.79	19.2 ± 0.81	0.643
APTT (s)	27.0 ± 2.25	27.0 ± 2.27	27.0 ± 2.29	0.980
Fbg-C (g/L)	3.27 ± 0.63	3.26 ± 0.65	3.29 ± 0.71	0.822
INC	0.96 ± 0.10	0.95 ± 0.05	0.98 ± 0.16	0.306

PT, plasma prothrombin time; INR, international ratio; APTT, activated partial thromboplastin time; Fbg-c, fibrinogen; TT, thrombin time.

3.3. SARS-CoV-2 detection in the aqueous humor of the AACGs during COVID-19 outbreak period

Aqueous humor samples were collected from 14 COVID-19-positive (7.14 % male, mean age 65 ± 9 years) and 8 negative (12.5 % male, mean age 66 ± 8 years) patients, which were all negative for SARS-CoV-2 nucleotide acid detection.

4. Discussion

In present study, we observed a concurrent "outbreak" of AACG and COVID-19 infection in predisposed patients after the relaxing and adjustment of the "dynamic-zero" policy in China, suggesting a potent relationship between these two conditions. The prevalence of AACG attack among COVID-19 infected individuals may still be underestimated because some AACGs patients with severe COVID-19 infection may present to respiratory clinics, even intensive care unit, instead of the ophthalmology clinics. The novelty of the

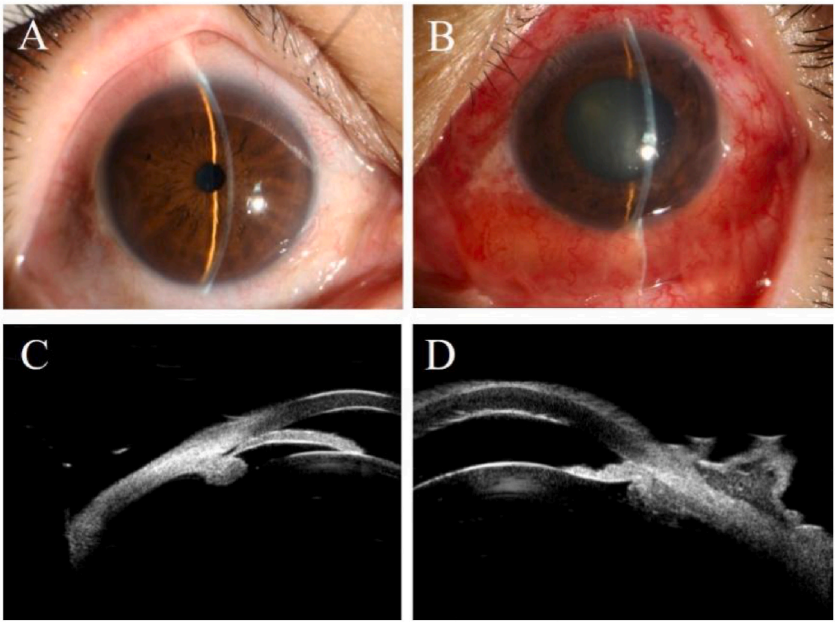

Fig. 4. Severe conjunctival congestion and edema in the acute attacked eye in a COVID 19 positive patients. (A) Slit lamp findings in the contralateral eye showed shallowed central anterior chamber. (B) Slit lamp findings in the affected eye showed diffused conjunctival congestion, highly elevated congestive conjunctiva in the inferior hemi-field. (C) UBM image in the contralateral eye demonstrated anteriorly rotated ciliary body, iris bombe and nearly closed peripheral anterior chamber angle. (D) UBM image in the affected eye showed the highly congestive conjunctiva and closed peripheral anterior chamber angle.

present study lies in that we reported similar AACG attack during the post-pandemic period in 2023–2024 with that of the pre-pandemic group, when the infection of influenza virus, adenovirus, rhinovirus and other respiratory diseases was very popular in Wenzhou. It suggests that the provocative effects and pathological mechanism of COVID-19 on the AACG attack are quite different from that of other influenza virus. AACG may be an ocular manifestation of COVID-19 infection in predisposed patients. However, the precise mechanism of AACG onset following COVID 19 infection are still unknown.

Robust increase of AACG attack was consistently reported from various tertiary eye hospitals in China during December 2022 to January 2023. A total of 171 cases were diagnosed at Eye, Ear, Nose and Throat Hospital of Fudan University in Shanghai from December 15, 2022 to January 11, 2023 [17]. Compared with that in the same period of 2020 and 2021, the number of newly diagnosed AACG at the Zhongshan Ophthalmic Center of Sun Yat-sen University was 6.63 and 6.42 times during the COVID-19 outbreak period [18]. In a tertiary hospital in Beijing, 95 eyes of 88 patients with APAC were diagnosed during the COVID-19 outbreak. A significant increase in the number of APAC cases was observed during the COVID-19 outbreak compared with the same months over a 5-year period [19]. In our present study, the number of newly diagnosed AACG was over 5 times of that before the pandemic. Other evidence supporting COVID-19 as a provocative factor of AACG is that 64.2 %–88.9 % of the affected cases in the outbreak group had a history of COVID-19 infection according to different reports [17–19]. The interval between COVID-19 infection and the onset of AACG was highly consistent between our study (52h) and that from other researchers (2–3 days on average) [18–20]. Our current study and other related studies consistently reported a younger age and higher proportion of bilateral eye involvement in the outbreak group than that in the control groups [17,18]. Meanwhile, keratic precipitates, deeper anterior chamber depth, more dilated pupil and more congestive conjunctiva were observed in the COVID-19 positive patients compared to the COVID-19 negative cases [17]. In our study, a trend of severe conjunctival congestion and edema in the affected eye of COVID-19 positive patients was also observed (Fig. 4A–D). These findings strongly suggested a potent relationship between COVID-19 infection and the AACG attack.

Evidence of direct infection of SARS-CoV-2 in the ocular tissues and fluids have been widely reported [21–23]. Presence of SARS-CoV-2 Viral RNA in the aqueous humor despite negative nasal swab testing (19.3 %) was reported by Koo and colleagues [24]. Differing from these studies, our present study, as well as studies of Roberts, List, Maya Hada, and Srinivasan Sanjay, reported negative evidence of SARS-CoV-2 in the aqueous humor in affected individuals [25–28]. Consistently, Kamalipour and colleagues reported positive RT-PCR SARS-COV-2 results from 3.57 % conjunctival, 6.67 % vitreous, but 0 % aqueous humor samples from postmortem ocular specimens of patients with severe COVID-19 disease [29]. Most recently, Li et al. revealed that after recovering from COVID-19, no SARS-CoV-2 RNA was detected in vitreous humor, but anti-CoV-2 IgM was detected in 6.1 % and IgG in approximately 80 % of vitreous humor samples [30]. Additionally, proteomic analysis of the aqueous humor from a most recently study also revealed that an activated immune response, neuro-inflammatory response, and viral infection system were associated with PAACGs upon COVID-19 attack [31]. It raises the possibility that SARS-CoV-2-derived immunoinflammatory mechanism, in addition to or instead of virus infection itself, may contribute to the provocation of AACG.

SARS-CoV-2 virus is believed to use an angiotensin-converting enzyme (ACE)-related carboxypeptidase receptor to enter the cells [32]. Activity of ACE2 was found in vitreous body, ciliary body, choroid and retina in porcine, nonhuman primate and human eyes [33–35]. The virus may directly or indirectly activate local ACE receptors, resulting in upregulated aqueous humor production, dilated vessel diameter, and inflammatory responses. It has been recently reported that choroidal thicknesses were significantly higher in the active disease period than control group but were comparable between after recovery and control groups among COVID19 infected population [36]. COVID19 virus may evoke AACG attack by directly upregulated the aqueous humor production and increase the volume of vitreous and choroid. SARS-CoV-2 related local or systemic ACE receptor activation as a provocative factor for AACG attack need further investigation.

One may attribute the surged AACG attack during observation period to a delayed visit of these patients due to previous policy-control. However, time interval between AACG attack and presentation to the hospital showed no difference among pre-pandemic, policy-control and policy-relaxing groups in present study. Second, COVID-19-related respiratory infection may be a provocative factor to AACG similar with influenza. In a prospective study on the epidemiology of acute primary angle-closure glaucoma in the Hong Kong Chinese population, an upper respiratory tract infection (23.6 %) and utilization of antitussive agents (34.7 %) prior to an acute PACG attack were noted. However, overall analysis revealed an inverse correlation between the monthly attack rate and the monthly rate of influenza [37]. Some ingredients of nonprescription oral cold and flu medications may induce AACG. Mechanism of cold and flu medications induced AACG attack is proposed to be related with their anticholinergic components with anticholinergic properties [38]. Active components, including the anticholinergics atropine, scopolamine and hyoscyamine, can cause crowded angles by pupillary dilatation [39]. Paracetamol and Oseltamivir may also contribute to the attack of acute angle-closure glaucoma by causing ciliary body and choroid effusion [40,41]. Under this condition, anterior rotation of the ciliary body may lead to narrowing or closure of the angle, and subsequent IOP elevation. In the present study, 77.9 % (53/68) patients reported applications of ibuprofen or other antipyretic medications. However, ibuprofen-induced AACG has not been previously reported and anticholinergic characteristics of these medications are difficult to identify. To note, in present study, 27.8 % cases among the AACG patients with COVID19 infection and 13.2 % among those of non-infection reported a history of large volume water intake. Significantly increased choroidal thickness and IOP, and decreased anterior chamber depth have been consistently observed after the water drinking provocative test in eyes with angle closure [42]. Therefore, the effect of large volume water intake on the AACG attack in present population should not be excluded, either [42,43]. Meanwhile, mental stress associated with depression, burden of taking care of the affected family members, and fearing for being infected may also be the advocative factors for AACG attack [44–46].

Hyponatremia is perceived as the most common electrolyte disorder in COVID-19 infection [47]. It was detected in 30 % of patients with pneumonia due to COVID 19 infection [48,49]. Recently, Özmen and colleagues reported three cases that developed acute angle-closure glaucoma on the background of hyponatremia due to COVID 19 infection in Turkey [50]. The authors deduced that

osmotic gradient between blood and aqueous humor due to hyponatremia can increase intraocular pressure and lead to shallowing of the anterior chamber. However, serum sodium, as well as other electrolytes were all within the normal range and showed no difference between COVID-19 positive and negative cases in present study. This is because only patients with mild COVID infection are more likely to present to the ophthalmology clinics. Nonetheless, results from present study may suggest mechanisms other than electrolyte imbalance for the onset of AACG following COVID 19 infection.

It has been consistently reported that the early stage of COVID-19 infection can be associated with high D-dimer, indicating infection induced coagulopathy [51,52]. D-dimer level was considered to be positively correlated with the prognosis of COVID-19 [53]. In present study, although not statistically significant, higher D-dimer was observed in COVID-19 positive AACGs than their counterpart. Recently, Li and colleagues reported shorter activated partial thromboplastin time (APTT), prothrombin time (PT), and thrombin time (TT) but significantly higher D-dimer and mean platelet volume (MPV) in patients with primary angle-closure glaucoma (PACG) compared with the control group. They proposed that hyper-coagulation status is significantly associated with patients with PACG and may play an important role in the onset and development of PACG [54]. However, the excised mechanism of hyper-coagulation state induced angle-closure is still waited to be investigated.

Limitations of this study should be mentioned. Firstly, aqueous humor was only obtained from 14 COVID-19-positive and 8 -negative patients. Meanwhile, the method used in our present study for the SARS-CoV-2 detection may be not sensitive enough for a specimen with very limited volume. Therefore, direct infection of SARS-CoV-2 in the anterior chamber still could not be excluded. Secondly, reasons for the significantly decreased AACG attack during pandemic-control period were not explored, which may mainly be due to the transportation restriction, fear of being infected, and the suspension of routine visits. Finally, although various possible mechanisms have been deduced, the exact mechanism of COVID-19-induced AACG attack still cannot be clearly elucidated base on the present study.

5. Conclusions

In conclusion, we observed a striking increase of acute angle-closure glaucoma attack concurrent with the surged COVID19 infection after the pandemic prevention policy adjustment. Mental stress, large volume water intake, increased choroidal thickness due to SARS-CoV-2 induced ACE receptor activation, and hyper-coagulation state may be the possible mechanisms for the disease onset. Ocular involvement should not be ignored in both routine and new systemic emergent conditions. Health education and prophylactic strategies should be delivered to patients at risk to prevent acute angle closure attack and subsequent severe visual function loss.

Ethics approval and consent to participate

This study was conducted in accordance with the tenets of the Declaration of Helsinki. The Ethics Committee of the Eye hospital of Wenzhou Medical University approved this study (2022-244-K-197) and waived the requirement for the informed consent, as all data were retrospectively collected and analyzed in de-identified fashion.

Availability of data and materials

All data supporting the findings are included in this article. The datasets during the study that are not presented in this article are available from the corresponding author on reasonable request.

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CRediT authorship contribution statement

Yu Mao: Writing – original draft, Software, Methodology, Investigation, Formal analysis. **Yanqian Xie:** Writing – original draft, Methodology, Investigation, Formal analysis. **Guoxing Li:** Validation, Resources, Methodology, Conceptualization. **Rongrong Le:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Shuxia Xu:** Software, Resources, Methodology, Data curation. **Peijuan Wang:** Writing – review & editing, Methodology, Investigation, Data curation. **Xiaojie Wang:** Methodology, Investigation, Formal analysis. **Qi Zhang:** Resources, Methodology, Conceptualization. **Shaodan Zhang:** Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Yuanbo Liang:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

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.

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