

The Outbreak of Acute Primary Angle-Closure Cases During the COVID-19 Omicron Variant Pandemic at a Tertiary Eye Center in Shanghai

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Purpose: This study aimed to investigate the outbreak of acute primary angle-closure (APAC) during the COVID-19 Omicron variant pandemic in Shanghai.

Methods: This single-center retrospective observational study included all newly diagnosed patients with APAC in Eye, Ear, Nose, and Throat Hospital of Fudan University from December 15, 2022, to January 14, 2023 (pandemic group) during the COVID-19 pandemic of Omicron Variant, and from November 15, 2021, to February 14, 2022 (control group) when the infection rate of COVID-19 is very low in Shanghai. Demographic features, intraocular pressure, axial length, anterior chamber depth, lens thickness and pupil diameter were compared between the two groups.

Results: A total of 223 patients (261 eyes) were included in the pandemic group and 75 patients (82 eyes) in the control group. The number of APAC patients and eyes in the pandemic group is 8.92-fold and 9.55-fold of the monthly average number in the control group. The onset dates of acute angle-closure were mainly between December 17 and December 31, 2022. In the pandemic group, 72.65% of patients with APAC had a recent COVID-19 infection. Among the COVID-19-positive patients, 72% suffered APAC attacks within 24h of the occurrence of COVID-19 symptoms and 92% within 3 days. The pandemic group showed a longer time from symptoms to treatment and larger pupil diameter than the control group (7.92 ± 6.14 vs 3.63 ± 2.93 days, $p = 0.006$; 4.53 ± 1.17 vs 3.78 ± 1.24 mm, $p = 0.003$, respectively).

Conclusion: An outbreak of APAC attack was observed in our eye center during the COVID-19 Omicron variant pandemic in Shanghai. There may be a correlation between the onset of APAC and new COVID-19 Omicron variant infection, but the exact reason needs to be investigated further.

Keywords: acute primary angle-closure, COVID-19 pandemic, omicron variant, Shanghai

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first identified in December 2019 and has spread rapidly around the world.¹⁻⁴ Due to the strict preventive measures implemented in Shanghai, the COVID-19 infection rate was very low until the preventive measures were lifted in early December 2022. From mid-December 2022 to mid-January 2023, the population of COVID-19 Omicron variant infection increased dramatically and dropped gradually in Shanghai.⁵

The infection can range from asymptomatic, mild to life-threatening respiratory distress. Due to the uncontrolled systematic inflammatory response resulting from the release of large amounts of chemokines and pro-inflammatory cytokines named “cytokine storm”, COVID-19 must be considered as a systemic disease involving multiple human systems.⁶⁻⁸ Ophthalmologists all over the world have reported various manifestations of the infection in the eye. As

reported, about 31.6% COVID-19 affected patients had ocular manifestations consistent with conjunctivitis, including conjunctival hyperemia, chemosis, epiphora, or increased secretion.⁹ Besides conjunctivitis, viral keratoconjunctivitis, episcleritis, retinal vein occlusion, acute retinal necrosis, choroiditis, and some neuro-ophthalmic manifestations have been reported as COVID-19-related eye diseases.^{10–12} Some studies have reported that patients with COVID-19 suffered bilateral acute angle-closure attacks during hospitalization or after prone positioning.^{13–15} An Indian hospital reported a 62% increase in the proportion of visits that were true glaucoma emergencies during the COVID-19 lockdown period in India in 2020.¹⁶ A Hong Kong's hospital reported six cases of APAC, which was more than double of baseline in the second week of December 2022. All patients were newly COVID-19 affected.¹⁷ These reports indicated a relationship between COVID-19 and APAC attacks. Primary angle closure glaucoma (PACG) is an important reason for blindness in the Asian population.¹⁸ PACG is characterized by mechanical obstruction of the trabecular meshwork by apposition of the peripheral iris to the trabecular meshwork. APAC is usually due to a sudden occlusion of the trabecular network in the anterior chamber angle, resulting in a spike in intraocular pressure (IOP) and typical symptoms and clinical signs, such as ocular discomfort or pain, nausea or vomiting, or blurring of vision. Shallow anterior chamber, short axial length, elderly and female are considered as common risk factors for APAC.¹⁹ An outbreak of APAC attack was observed in our eye center from mid-December 2022 to late January 2023, which was the epidemic period of COVID-19 Omicron variant in Shanghai. After mid-January 2023, APAC cases decreased significantly. Thus, this study aimed to investigate the relationship between the onset of APAC and the COVID-19 Omicron variant infection and the clinical characteristics of APAC cases during the COVID-19 pandemic in Shanghai. In order to exclude the effect of season which was known as an influence factor for the onset of acute primary angle-closure^{20,21} and to make the sample size of two groups (the pandemic group and the control group) with good comparability, we collected and presented our hospital's clinical data of APAC cases during the COVID-19 pandemic of Omicron Variant (December 15, 2022–January 14, 2023) which were compared to those during the similar season of the previous year (November 15, 2021–February 14, 2022) when the infection rate of COVID-19 is very low in Shanghai.

Materials and Methods

This retrospective observational study included consecutive cases diagnosed with APAC in the outpatient and emergency departments in our hospital from December 15, 2022, to January 14, 2023. Consecutive cases of APAC from November 15, 2021, to February 14, 2022, were included as the control group. This study was approved by the Institutional Ethics Committee of Eye, Ear, Nose, and Throat Hospital of Fudan University, Shanghai, China, and conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all subjects.

APAC was diagnosed based on the following criteria: (1) the presence of at least two of the following symptoms: ocular or periocular pain, nausea and/or vomiting, ipsilateral migraine, or antecedent history of intermittent blurring of vision with halos; (2) intraocular pressure (IOP) spike more than 40 mmHg; (3) the presence of shallow anterior chamber with at least three of the following signs: obvious conjunctival hyperemia, corneal epithelial edema, enlarged pupil, and direct disappearance of light reflex; and (4) detecting angle-closure in at least two quadrants of the chamber angle on gonioscopy.²² Only patients with newly diagnosed of APAC were included in the study. Participants with any of the following criteria were excluded: pre-diagnosed APAC, secondary angle-closure because of lens subluxation, uveitis, iris neovascularization, ocular trauma, intraocular tumor, and history of intraocular surgery.

Data, including age, gender, place of residence, systemic medical history, COVID-19 infection history, time from COVID-19 infection to APAC onset, and time from APAC onset to treatment, were collected. All patients underwent complete ophthalmologic examinations at presentation, including best-corrected visual acuity (BCVA) in logMAR and slit lamp biomicroscopy. IOP was measured using Goldmann applanation tonometry, and the mean of 3 IOP measurements recorded for each eye was used. Axial length (AL) and lens thickness (LT) were measured using IOL Master (Carl Zeiss, Inc., Jena, Germany). The anterior chamber angle, anterior chamber depth (ACD), and pupil diameter (PD) were determined using ultrasound biomicroscopy (UBM, MD-300L, MEDA Co., Ltd., Tianjin, China). All patients underwent UBM examinations in a supine position in the same room light.

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 23.0) (IBM, Armonk, NY, USA). The Kolmogorov–Smirnov normality test was used to examine whether the variables were

normally distributed. Continuous normally distributed data were summarized with a mean \pm standard deviation (SD). Differences in the average between the two groups were evaluated using an independent sample *t*-test. To account for multiple testing, *p* values were adjusted using the Benjamini/Hochberg (B/H) method to control the false discovery rate (FDR). An association was considered statistically significant if the corresponding B/H-adjusted *p* value was less than 0.05, corresponding to an FDR of 5%. Categorical variables, such as sex, were assessed individually using Chi-squared test or Fisher's exact test. *p* < 0.05 indicated statistical significance.

Results

Demographic Characteristics of Patients with APAC in Both Groups

A total of 298 cases were included in this study, all in Shanghai. Among them, 75 patients with APAC (82 eyes) were recruited from November 15, 2021, to February 14, 2022 (the control group), and 223 patients (261 eyes) were recruited during the COVID-19 pandemic from December 15, 2022, to January 14, 2023 (the pandemic group). The number of APAC patients in the pandemic group is 8.92-fold of the monthly average number of APAC patients in the control group. And the number of APAC eyes in the pandemic group is 9.55-fold of the monthly average number of APAC eyes in the control group. The mean ages (mean \pm SD) of the patients in the control and pandemic groups were 67.05 \pm 8.95 years and 65.34 \pm 8.13 years, respectively. The control group included 16 (21.33%) males and 59 (78.67%) females, and the pandemic groups included 58 (26.01%) males and 165 (73.99%) females. The control group included 7 patients with APAC with bilateral onset (9.33%), and the pandemic group included 38 patients (17.04%). No significant differences in mean age, gender, left/right eyes, and laterality of the eyes were observed between patients in both groups (Table 1).

Figure 1 showed the correlation between the number of APAC patients and date of their APAC onset. APAC patient numbers remained relatively stable in the same period of previous year (December 15, 2021–January 14, 2022; blue line). However, the number of APAC patients increased rapidly and spiked on December 23, 2022 and then dropped gradually during the COVID-19 pandemic of Omicron Variant (December 15, 2022–January 14, 2023; orange line). This trend was similar to the data of new COVID-19 infections in Shanghai.

Ocular Biometry of Patients with APAC in Both Groups

The peak IOP was 48.25 \pm 7.23 mmHg in the control group and 46.01 \pm 8.20 mmHg in the pandemic group, respectively (*p* = 0.122). The axial lengths (AL) were 22.36 \pm 0.71 mm and 22.63 \pm 2.28 mm, the anterior chamber depths (ACD) were 1.58 \pm 0.29 mm and 1.62 \pm 0.24 mm, and the lens thickness (LT) were 4.99 \pm 0.44 mm and 5.02 \pm 0.32 mm in the

Table 1 Demographic Characteristics of Patients with APAC in Both Groups

Characteristics	Control Group November 15, 2021–February 14, 2022	Pandemic Group December 15, 2022–January 14, 2023	<i>p</i> value
Patients, n	75	223	
Eyes, n	82	261	
Mean age (mean \pm SD), years	67.05 \pm 8.95	65.34 \pm 8.13	0.124
Gender, n (%)			0.418 ^a
Male	16 (21.33)	58 (26.01)	
Female	59 (78.67)	165 (73.99)	
Affected eyes, n (%)			0.107 ^a
Bilateral	7 (9.33)	38 (17.04)	
Single	68 (90.67)	185 (82.96)	
Eyes, n (%)			0.205 ^a
Left	43 (52.44)	116 (44.44)	
Right	39 (47.56)	145 (55.56)	
COVID-19 infection history, n (%)	0	162 (72.65)	<0.001 ^b

Notes: All data were showed as mean \pm SD. ^aChi-squared test. ^bFisher's exact test.

Abbreviation: SD, standard deviation.

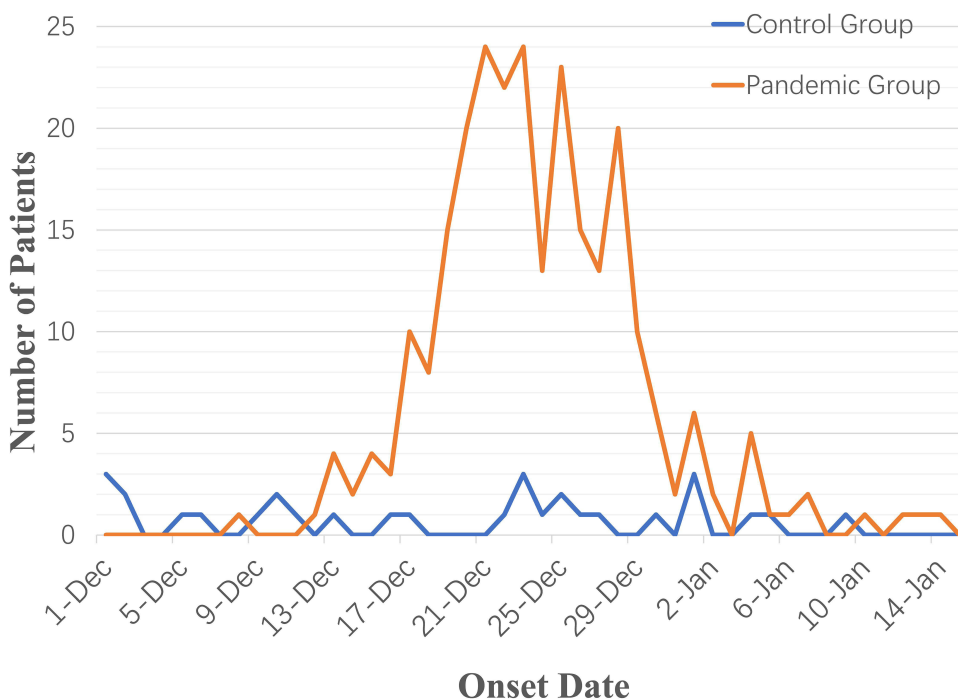


Figure 1 The onset date of patients with APAC recruited in the same period of different years with or without COVID-19 pandemic.

control and pandemic groups, respectively. No significant differences in AL, ACD, and LT were observed between the control and pandemic groups. However, the time from symptoms to treatment in the control group (3.63 ± 2.93 days) was significantly shorter than that in the pandemic group (7.92 ± 6.14 days, $p = 0.006$). Furthermore, the pupillary diameter was significantly larger in the pandemic group (4.53 ± 1.17 mm) than that in the control group (3.78 ± 1.24 mm, $p = 0.003$). All data are summarized in [Table 2](#).

Characteristics of Patients with COVID-19 in the Pandemic Group

In the pandemic group, 72.65% (162/223) of the patients (192 eyes) were diagnosed with COVID-19 infection, identified by a nucleic acid or antigen test in previous 2 weeks, whereas 61 patients (69 eyes) showed no evidence of COVID-19 infection in previous 2 weeks. The mean ages (mean \pm SD) were 65.25 ± 8.26 and 65.57 ± 7.83 years in the COVID-19-positive and COVID-19-negative groups, respectively. The COVID-19-positive group included 38 (23.46%) males and 124 (76.54%) females, and the COVID-19-negative group included 20 (32.79%) males and 41 (67.21%) females. In terms of bilateral onset, 30 patients with bilateral onset were in the COVID-19-positive group (18.52%) and 8 in the

Table 2 Ocular Biometry of Patients with APAC in Both Groups

Characteristics	Control Group November 15, 2021–February 14, 2022	Pandemic Group December 15, 2022–January 14, 2023	Unadjusted <i>p</i> value	B/H-Adjusted <i>p</i> value
Time from symptoms to treatment, days	3.63 ± 2.93	7.92 ± 6.14	<0.001	0.006*
Peak IOP, mmHg	48.25 ± 7.23	46.01 ± 8.20	0.061	0.122
AL, mm	22.36 ± 0.71	22.63 ± 2.28	0.340	0.408
ACD, mm	1.58 ± 0.29	1.62 ± 0.24	0.172	0.258
LT, mm	4.99 ± 0.44	5.02 ± 0.32	0.475	0.475
Pupil diameter, mm	3.78 ± 1.24	4.53 ± 1.17	<0.001	0.003*

Notes: *B/H-adjusted $p < 0.05$ indicates statistical significance.

Abbreviations: AL, axial length; ACD, anterior chamber depth; LT, lens thickness; IOP, intraocular pressure.

COVID-19-negative group (13.11%). No significant differences in mean age, gender, left/right eyes, and laterality of the eyes were observed between the COVID-19-positive and COVID-19-negative groups (Table 3).

The peak IOP was 45.97 ± 8.08 mmHg in the COVID-19-positive group and 46.10 ± 8.55 mmHg in the COVID-19-negative group. AL were 22.69 ± 2.58 mm and 22.41 ± 0.85 mm, ACD were 1.60 ± 0.25 mm and 1.63 ± 0.23 mm, and LT were 5.02 ± 0.32 mm and 5.04 ± 0.33 mm in the COVID-19-positive and COVID-19-negative groups, respectively. No significant differences in AL, ACD, LT and the time from symptoms to treatment were observed between the two groups. Furthermore, the pupillary diameter was significantly larger in the COVID-19-positive group (4.64 ± 1.19 mm) than that in the COVID-19-negative group (4.19 ± 1.05 mm). All data are summarized in Table 4.

Additionally, most of COVID-19 infection patients presented systemic symptoms including fever, sore throat, nasal obstruction, tiredness and so on. The time from the occurrence of COVID-19 related systemic symptoms to APAC onset was statistically analyzed (Figure 2). Among all patients in the COVID-19-positive group, 149 (92%) experienced an APAC attack within three days of COVID-19 related systemic symptoms occurrence, whereas 117 (72%) of these patients experienced an attack within one day. These results indicate that APAC onset may be related to COVID-19 infection. Representative images obtained from single and bilateral eyes with APAC onset are shown in Figures 3 and 4, respectively.

Discussion

This study showed an obvious increase in APAC onset in the Eye, Ear, Nose, and Throat Hospital of Fudan University, the biggest eye center in Shanghai, from December 15, 2022, to January 14, 2023. The number of patients newly diagnosed with APAC was 8.92-fold of the monthly average number of APAC patients in the control group, and the number of eyes that suffered APAC attack was 9.55-fold of the monthly average number of APAC eyes in the control

Table 3 Demographic Characteristics of Patients with APAC in the Pandemic Group

Characteristics	COVID-19-Positive	COVID-19-Negative	p value
Patients, n	162	61	
Eyes, n	192	69	
Mean age (mean \pm SD), years	65.25 ± 8.26	65.57 ± 7.83	0.790
Gender, n (%)			0.157 ^a
Male	38 (23.46)	20 (32.79)	
Female	124 (76.54)	41 (67.21)	
Affected eyes, n (%)			0.586 ^a
Bilateral	30 (18.52)	8 (13.11)	
Single	132 (81.48)	53 (86.89)	
Eyes, n (%)			0.706 ^a
Left	84 (43.75)	32 (46.38)	
Right	108 (56.25)	37 (53.62)	

Note: ^aChi-squared test.

Table 4 Ocular Biometry of Patients with APAC in the Pandemic Group

Characteristics	COVID-19-Positive	COVID-19-Negative	Unadjusted p value	B/H-Adjusted p value
Time from symptoms to treatment, days	8.42 ± 6.21	6.55 ± 5.76	0.03	0.090
Peak IOP, mmHg	45.97 ± 8.08	46.10 ± 8.55	0.923	0.923
AL, mm	22.69 ± 2.58	22.41 ± 0.85	0.431	0.647
ACD, mm	1.60 ± 0.25	1.63 ± 0.23	0.359	0.647
LT, mm	5.02 ± 0.32	5.04 ± 0.33	0.606	0.727
Pupil diameter, mm	4.64 ± 1.19	4.19 ± 1.05	0.008	0.048*

Notes: *B/H-adjusted $p < 0.05$ indicates statistical significance.

Abbreviations: AL, axial length; ACD, anterior chamber depth; LT, lens thickness; IOP: intraocular pressure.

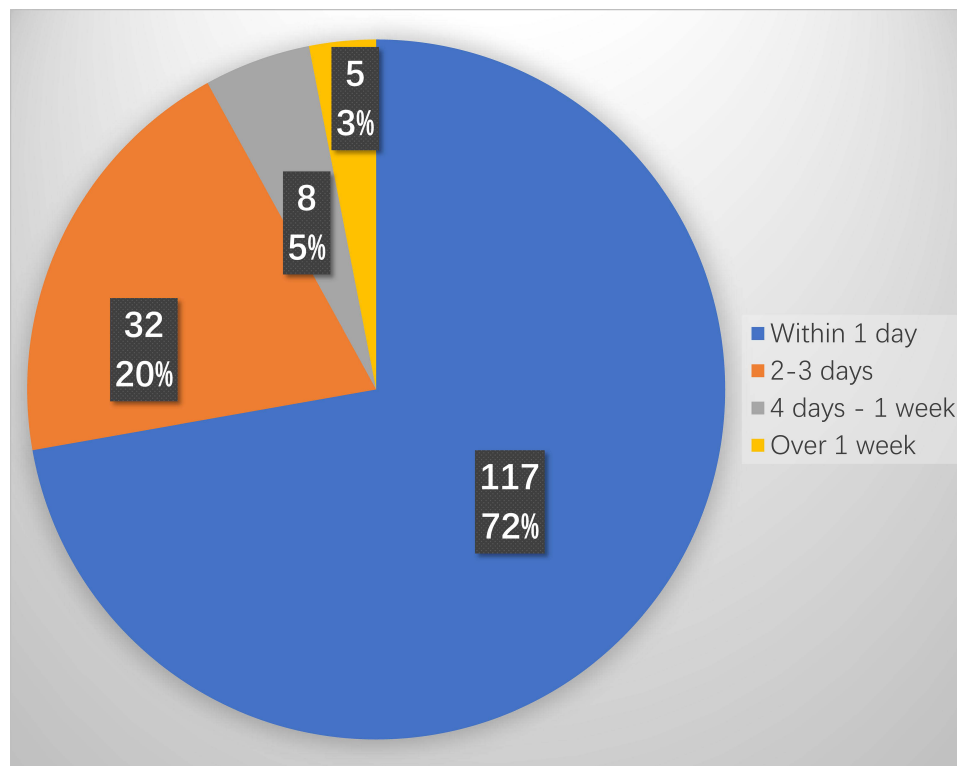


Figure 2 The days of APAC onset after COVID-19 related systemic symptoms in the COVID-19 positive patients.

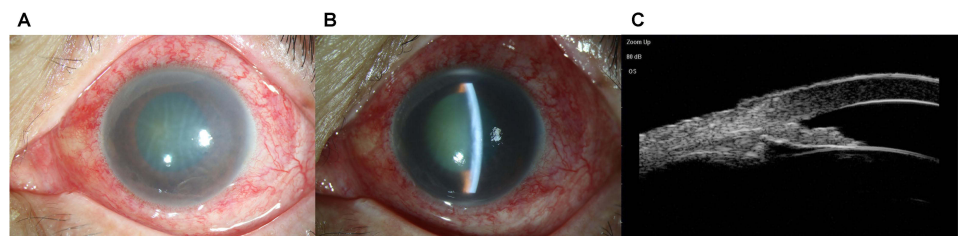


Figure 3 A 67-year-old woman with APAC attack after COVID-19 infection. **(A and B)**: Slit lamp images showed apparent conjunctival hyperemia, corneal epithelial and stromal edema, enlarged pupil, and shallow anterior chamber in left eye. **(C)**: Ultrasound biomicroscopy image showed iris trabecular contact, closed angle, and shallow anterior chamber.

group. The onset dates of APAC were mainly between December 17, 2022, and December 30, 2022, when COVID-19 rapidly spread in Shanghai.⁵ 72.65% of patients newly diagnosed with APAC attack had a previous COVID-19 infection history. APAC symptoms started within 24h of fever caused by COVID-19 infection in 72% of patients with a COVID-19 infection history. The median onset time of APAC with a previous COVID-19 infection history was December 24, the same as when the COVID-19 infection reached its peak in Shanghai.⁵ These data suggest that there may be a correlation between the onset of APAC and new COVID-19 Omicron variant infection in the population.

COVID-19 has spread worldwide since 2019. Some APAC cases have been reported in COVID-19-positive patients or after vaccination against COVID-19 in Hong Kong, Korea, Italy, India, and Russia.^{11,13–15,17,23–25} An Indian hospital reported a 62% increase in the proportion of visits that were true glaucoma emergencies during the COVID-19 lockdown period. However, secondary open-angle glaucoma and neovascular glaucoma were the main emergency diagnoses. The number of APAC cases did not increase during the COVID-19 lockdown period.¹⁶ During Wuhan's COVID-19 pandemic from the end of 2019 to the beginning of 2020, a mild increase in the number of APAC cases was observed compared to the next year.²⁶ Our study showed an obvious outbreak of APAC cases in clinics during the COVID-19 Omicron variant

pandemic, which is comparable with a recent report from other hospital in Shanghai and Guangdong.^{27,28} This may be due to the higher prevalence of PACG among Eskimos, Chinese, and Mongolians. Additionally, Asia accounts for about 77% of all worldwide PACG cases. Chinese ocular anatomic characteristics are a very important reason.²⁹ Chinese have some ocular anatomic risk factors for angle-closure such as shallow anterior chamber, short AL, and narrow anterior angle.^{30–33} This can be explained why no outbreak of APAC in western countries during COVID-19 pandemic in last 3 years. Since December 2022, almost all epidemic strains in China were of the Omicron variant,⁵ with a higher infection rate than previous variants. The COVID-19 pandemic from the end of 2022 to the beginning of 2023 in China had a very fast speed of spread, and the COVID-19 infection ratio of the population reached 70–80% in about one month which is much faster and higher infection ratio than that in Wuhan 3 years' ago. The outbreak of COVID-19 infection cases in such a short time in China is another important reason. Moreover, SARS-CoV-2 mutates all the time, and new strains are gradually generated. The main strains of SARS-CoV-2 in different countries were different. The China CDC analysis showed a predominance of Omicron lineages BA.5.2 and BF.7 among locally-acquired infections at the end of 2022. And in Shanghai, the main strains of the Omicron variant were BA.5.2 (accounting for 63%) and BF.7 (accounting for 37%).⁵ Different variants and strains have different pathogenic mechanisms. In Hong Kong, the main strains of the Omicron variant were BA.2 and BA.4 in the 2022.³⁴ The spread of different strains might be one of the reasons why there was no similar outbreak of APAC in Hong Kong and other Asian countries, which suffered the COVID-19 pandemic and had similar ocular anatomic risk factors for angle-closure.

The clinical characteristics of patients newly diagnosed with APAC in Shanghai during the COVID-19 pandemic were very similar to those reported in the previous year. Age, gender ratio, and bilateral acute attack ratio were very close in the two groups. Additionally, these data are very similar to those of previous reports in China or Korea in the non-pandemic period.^{26,35–37} However, the time from symptoms to treatment in the pandemic group was 7.92 ± 6.14 days, which was significantly longer than that in the control group (3.63 ± 2.93 days). In the pandemic group, the time from symptoms to treatment in COVID-19-positive patients was 8.42 ± 6.21 days, which was longer than that in COVID-19-negative patients (6.55 ± 5.76 days). Considering that APAC occurred at the same time of COVID-19 infection in most of the patients in the pandemic period, we proposed that, under severe systemic symptoms of COVID-19 such as fever and cough, many COVID-19-positive patients delayed APAC treatment. Besides that, the COVID-19 pandemic caused psychological panic to everyone.³⁸ Even patients with a COVID-19-negative history are delaying their acute angle-closure attack treatment. As we known, rapid reduction of IOP is key to the treatment of APAC including antiglaucomatous drugs, laser treatment or surgery.³⁹ Delayed treatment in the pandemic group might affect the final treatment results of APAC.

The anatomic parameters of eyeballs suffering APAC attacks were compared between the pandemic and control groups. Axial length, anterior chamber depth, and lens thickness were very close in both groups. However, the average pupil diameter of pandemic cases was 4.53 ± 1.17 mm, which was larger than that in the control group (3.78 ± 1.24 mm). In the pandemic group, the average pupil diameter in the COVID-19-positive group was 4.64 ± 1.19 mm, which was larger than that in the COVID-19-negative group. These findings are consistent with those of a previous study.²⁶ Furthermore, the larger pupil diameter in the pandemic group, especially in the COVID-19-positive group, may be due to two reasons. First, the time from symptoms to treatment was longer in the pandemic group, especially in the COVID-19-positive group. Delayed treatment can lead to a longer time of high IOP, which causes more severe iris ischemia and pupillary sphincter damage, forming a larger pupil. Second, COVID-19 infection can cause direct damage, excessive inflammatory response, hypoxia, and other pathophysiological mechanisms, which may lead to more severe iris ischemia and a larger pupil.^{40–42}

The reason why COVID-19 Omicron variant infection led to more APAC attacks is still unknown. COVID-19 is a systemic disease that can cause human respiratory infection and affect multiple organs. These organs include the kidney, liver, nervous system, spleen, etc. The coronavirus entry is through the angiotensin-converting enzyme 2 receptor (ACE-2 receptor).⁴¹ Coronavirus S protein binds to the cellular transmembrane protein, ACE-2 receptor, which promotes S protein activation by host protease and is responsible for viral entry.^{43,44} ACE-2 is not only expressed in the lungs, kidney, cardiovascular, but also highly expressed in ocular tissues, including conjunctiva, cornea, ciliary body, aqueous humor and retina.^{45–48} Conjunctivitis is most frequently reported as COVID-19 related eye disease. Besides ocular surface, the novel coronavirus may change the ciliary body shape or aqueous circulation through ACE-2 and lead to

intraocular pressure elevation. A re-positive case of SARS-CoV-2 associated with glaucoma has been reported.⁴⁹ However, this glaucoma case is not an angle-closure glaucoma case. It is well known that anatomy is the very important basis of acute angle-closure attacks. Acute angle-closure attacks are difficult to occur without a highly risky anatomic structure, even in eyeballs in COVID-19-positive patients.^{50,51} However, the onset of APAC requires a triggering factor in addition to these anatomic factors. Previous studies have reported that hantavirus infections cause bilateral acute angle-closure through non-pupillary blocking factors (ciliary body edema, anterolateral rotation of the iris-lens diaphragm).⁵² Similar to hantavirus, COVID-19 infection may be a very important trigger of acute angle-closure attacks. As shown in [Figure 4](#), the initial presentation included subconjunctival hemorrhage and severe corneal stromal edema in some acute angle-closure cases with COVID-19 infection, which is hard to explain by APAC attacks only. COVID-19-affected conjunctivitis must occur, and COVID-19-affected uveitis might play a role in inducing acute angle-closure attacks. A case report showed that ciliary body swelling was observed in acute angle-closure cases after vaccination against COVID-19.¹¹ The swollen ciliary body may lead to anterior shifting of the lens and trigger APAC attacks. Moreover, hypersecretion of aqueous humor may be a contributing risk factor in the eyes after vaccination against COVID-19.⁵³ We proposed that COVID-19-affected eyes should have a similar ciliary body swelling and hypersecretion of aqueous humor as COVID-19-vaccinated eyes. The main strains of the Omicron variant of this COVID-19 pandemic in Shanghai might be more susceptible to the eyes, which needs further studies to identify. In Hong Kong's cases reported that cough mixture or flu medication uses were detected in all these six APAC patients with newly COVID-19 affection.¹⁷ Commonly used cold medication including antitussive and nasal decongestants are common triggers to pupil dilation and can lead to APAC attack.^{54–57} In addition, some Chinese medicines containing ingredients such as pseudoephedrine and chlorpheniramine may also cause pupil dilation. Besides that, drinking a lot of water after fever,⁵⁴ hyponatremia⁵⁸ may also trigger APAC attacks during the COVID-19 pandemic period. Additionally, a high proportion of anxiety and depression was found in people during the COVID-19 pandemic.^{59,60} And it is increasingly acknowledged that APAC is highly associated with anxiety and depression.^{55,61,62} Moreover, lifestyle behaviors, including restricted physical activity and increased indoor and screen time caused by the COVID-19 pandemic, may play a role in APAC.⁶³ All these factors

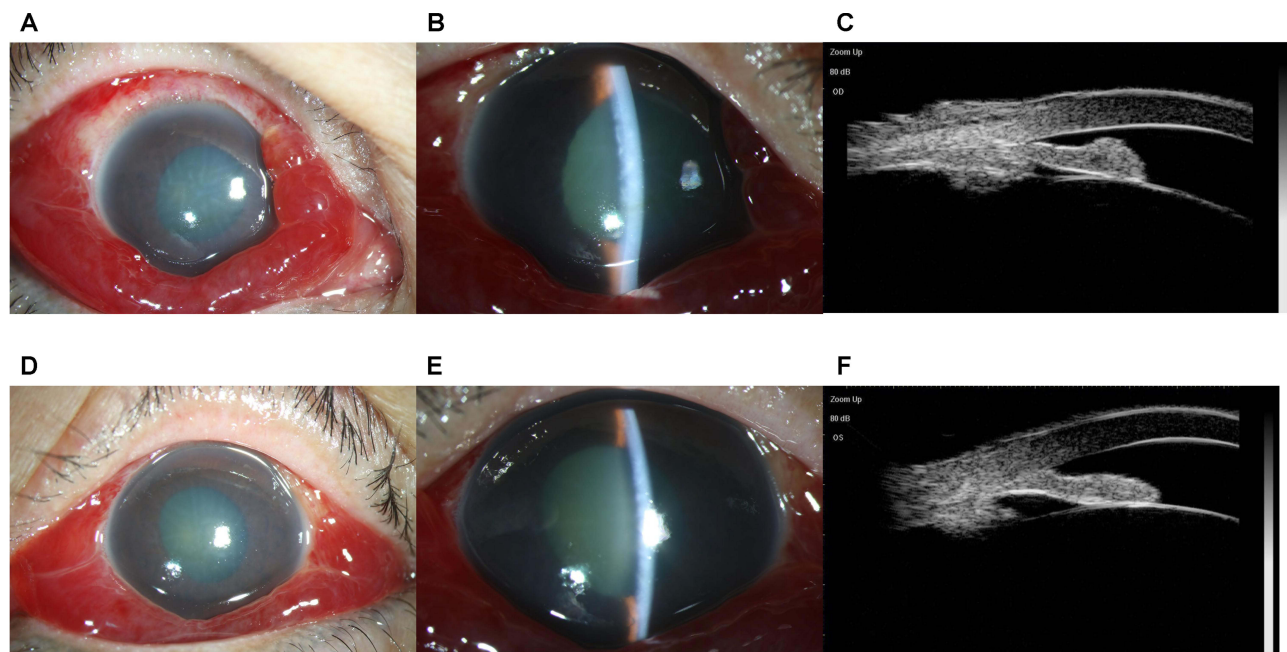


Figure 4 A 59-year-old woman presented to our clinic with complaints of reduced visual acuity, ocular pain, nausea, and vomiting in both eyes one day after COVID-19 infection. **(A and B)**: Slit lamp images showed obvious conjunctival hyperemia and hemorrhage, corneal epithelial and stromal edema, enlarged pupil, and shallow anterior chamber in right eye. **(C)**: Ultrasound biomicroscopy images showed iris trabecular contact, closed angle, and shallow anterior chamber in the same eye. **(D–F)**: The patient experienced the same APAC attack in the left eye simultaneously.

may contribute to the outbreak of APAC attacks during the COVID-19 Omicron variant pandemic in Shanghai, but the exact reason remains to be further studied.

The present study has several limitations. First, this study was a single-center study based on the largest eye center in Shanghai, and we cannot exclude the influence of the patient choice preferences for Medical Care, the crowding of primary institution during the COVID-19 pandemic, and epidemic control policies. Therefore, the outbreak of APAC cases in this study is limited to our center and cannot represent all medical institutions nationwide. Long-term follow-up, multicenter and large sample clinical study are needed in the future research. Second, this study only used basic clinical characteristics for analysis, which indicate that there may be a correlation between the onset of APAC and new COVID-19 Omicron variant infection, but the exact reason remained unknown. Future work will include anterior aqueous humor analysis or animal studies. However, whether the virus has an effect on the prognosis of the APAC requires long-term observation.

Conclusion

An outbreak of APAC attack was observed in our eye center during the COVID-19 Omicron variant pandemic in Shanghai. Among COVID-19-positive patients, 92% suffered acute angle-closure attacks within 3 days of the occurrence of COVID-19 symptoms. Age, gender, bilateral ratio, and most of the anatomical characteristics during the COVID-19 pandemic were similar to those in the previous year. However, the time from symptoms to treatment of acute angle-closure attacks in this pandemic period was obviously longer, and the pupillary diameter was significantly larger than those in the previous year. There may be a correlation between the onset of APAC and new COVID-19 Omicron variant infection, but the exact reason needs to be investigated further.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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