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Daily activities change is linked to acute angle closure occurrence in COVID-19 co-infected patients

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Abstract

Objectives To analyze the influence of daily activity-related factors associated with COVID-19 infection on the occurrence of acute angle closure (AAC).

Methods A multicenter hospital-based study was conducted at 23 ophthalmic centers in 17 provincial-level regions across China to recruit patients with confirmed AAC during the post-lockdown time of COVID-19 (P-TOC) from Dec 7, 2022, to Jan 17, 2023, and three lockdown time of COVID-19 (TOC) periods, which included the TOC-2022 (Sep 7, 2022 - Dec 6, 2022), TOC-2021(Sep 7, 2021 - Jan 6, 2022) and TOC-2020 (Sep 7, 2020 - Jan 6, 2021). Patient information, including demographic, a questionnaire on daily activity changes during the AAC period, COVID-19 history, and eye examination results, was collected.

Results The study involved 3216 AAC cases, with 76.2% being female and 78.9% aged over 60 years. AAC occurrences during P-TOC was nearly tripled compared to the corresponding months in TOC-2021 and TOC-2020. Patients with AAC comorbidity and COVID-19 had significantly higher water intake (37.3% vs. 2.2%, p < 0.001) and poorer sleep quality (49.16% vs. 4.07%, p < 0.001) than those without COVID-19 comorbidity, while about 58.4% of these patients received antipyretic analgesic drugs for symptom management. The COVID-19 group showed higher intraocular pressure as well as worse uncorrected distance visual acuity, when compared to non-COVID-19 patients.

Conclusions The relationship between AAC occurrence and daily activity factors associated with COVID-19 suggests that patient management should account for changes in daily activities.

Keywords Acute angle closure, Daily activity, COVID-19

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Introduction

Glaucoma is the leading cause of global blindness, affecting an estimated 111.8 million people by 2040 [1]. In China, primary angle-closure glaucoma (PACG) is the most common type, with acute angle-closure (AAC) representing a subgroup characterized by a sudden closure of the peripheral iris against the anterior chamber angle either through apposition or synechial adhesion. This results in elevated intraocular pressure (IOP) and symptoms like headache, blurred vision, eye pain, and potentially irreversible vision loss [2].

Following the end of China's "dynamic zero COVID" policy on Dec 7 [3], 2022, a nationwide surge in new outbreaks driven by the SARS-CoV-2 omicron variants BA5.2 and BF.7 occurred due to relaxed restrictions [4]. A significant portion of our country's medical resources were directed towards treating COVID-19 patients. However, after this policy change, we observed an increase in admissions for AAC at our hospital (Eye Hospital of Wenzhou Medical University). Previously, only a few case reports or small-scale studies from single centers had described AAC cases with COVID-19 infection, indicating a potential correlation between them [5-8]. Nevertheless, the exact cause of this rise in AAC remains unclear, as does the direct relationship between viral infection and its onset. Some researchers propose that emotional distress and stress may act as triggering factors; experiencing COVID-19 and quarantine can create stressful conditions and negative emotions. Concerns about COVID-19 might have led some individuals to delay or avoid seeking medical care [9, 10], which contradicts the observed increase in AAC patients.

A crucial aspect for investigation is the potential link between COVID-19 and AAC occurrence, particularly daily activity factors post-infection that may correlate with increased AAC cases and underlying mechanisms. Thus, we did a nationwide hospital-based observational study involving 23 ophthalmic centers across 17 provincial-level regions in China. This objective of this study is to analyze the impact of daily activity factors following post-COVID-19 infection on the occurrence of AAC. Additionally, as a secondary endpoint, we evaluated the relationship between COVID-19 infection and AAC severity.

Methods

The data were collected from 23 ophthalmic centers in 17 provincial-level regions across China, including two second-level specialized hospitals, twelve tertiary general hospitals, and nine tertiary specialized hospitals that primarily handled emergent ophthalmic cases within their respective localities. The study population comprised adults 18 years or older who had been diagnosed with AAC. AAC was defined by the presence of the following three conditions: (a) at least two symptoms such as ocular or periocular pain, nausea and/or vomiting, and a history of intermittent blurring of vision with halos; (b) IOP>21mmHg; (c) the presence at least one sign among conjunctival hyperemia, cornea edema, mid-dilated unreactive pupil, or shallow anterior chamber. Further, we excluded secondary angle closure, such as dislocated lens-induced glaucoma, neovascular glaucoma, or glaucoma after retinal laser treatment or surgery. Independent investigators searched the patient database for terms such as "acute angle-closure," "acute angle-closure glaucoma," "primary angle-closure glaucoma combined with an acute attack," and International Classification of Disease-10 code H40.203 in inpatient reports. In our study, an admission referred to a single AAC episode, encompassing the entire process from admission to discharge at a single hospital. Only the primary diagnosis was included to avoid double-counting admissions.

Patients with confirmed AAC were included in the post-lockdown time of COVID-19 (P-TOC) from December 7, 2022, to January 6, 2023 (P-TOC-1), and three lockdown time of COVID-19 (TOC) periods, which included the TOC-2022 from September 7, 2022, to December 6, 2022, the TOC-2021 from September 7, 2021, to January 6, 2022, and the TOC-2020 from September 7, 2020, to January 6, 2021. Considering the time interval between the onset of AAC and COVID-19, we extended the time for another 11 days until January 17, 2023 (P-TOC-2). The study's timeline is illustrated in Fig. 1. The affected eye was selected for data collection for patients with unilateral AAC. For patients with bilateral AAC, information from both eyes was collected. Data included each patient's demographic characteristics, medical history, COVID-19, and eye examination information.



Fig. 1 Study timeline. The study conducted over four time periods: TOC-2020 (September 7, 2020 to January 6, 2021), TOC-2021 (September 7, 2021 to January 6, 2022), TOC-2022 (September 7, 2022 to December 6, 2022), and P-TOC [(includes P-TOC-1 (December 7, 2022 to January 6, 2023) and P-TOC-2 (January 7, 2023 to January 17, 2023)]. The lockdown period was scheduled from 2020 until December 6, 2022 (Lockdown time), with the lifting of restrictions commencing on December 7, 2022 (Post-lockdown time)

For AAC patients with onset between December 7, 2022, and January 17, 2023 (P-TOC-1+P-TOC-2), we collected COVID-19 information through laboratory testing and telephone surveys. This included results from nucleic acid test using polymerase-chain-reaction or SARS-CoV-2 antigen tests, symptoms of COVID-19 infection, water intake (the increase in water intake during the onset of AAC was defined as a daily increment of 200 ml or more exceeding the individual's habitual intake, while a decrease was considered if there was a reduction of 200 ml or more per day. Any changes falling within this range were categorized as unchanged), eye use time in dark environments (the increase in the duration of eye usage in dark environments during the onset of AAC was defined as a daily increment of one hour beyond an individual's habitual time, while a decrease was considered if there was a reduction of one hour per day. Any changes falling within this range were categorized as unchanged), usage details of antipyretic analgesic drugs (timing, frequency, and type), and sleep quality (subjective evaluation of sleep quality during AAC onset compared to non-AAC onset: improved, unchanged, or worsened).

Additionally, based on the nucleic acid/antigen test results and clinical symptoms assessment criteria were used to classify AAC patients into two groups: the COVID-19 group (Definite-COVID-19+Suspected-COVID-19) and non-COVID-19 group. Definite-COVID-19 was defined as symptomatic COVID-19 infection consistently confirmed by positive oral/nasopharyngeal swabs through polymerase-chain-reaction testing or positive SARS-CoV-2 antigen test. Suspected-COVID-19 was defined as having a fever (temperature>37.3°C) with known contact with individuals infected with COVID-19 plus four or more symptoms, such as dry cough, sore throat, shortness of breath, dyspnea, sudden worsening of preexisting respiratory symptoms, anosmia, dysgeusia, nausea, vomiting, headache, diarrhea, and conjunctivitis.

The eye examination information included uncorrected distance visual acuity (UDVA), intraocular pressure (IOP, measured by Non-contact Tonometer), slit lamp examination (grading cornea edema from 1 to 4; where 1=no corneal edema, 2=mild corneal edema, 3=moderate corneal edema, and 4=severe corneal edema). Axial length was measured using the IOL Master, while ultrasound biomicroscopy was used to evaluate anterior chamber depth. Additionally, we assessed the time elapsed from onset to presentation in the included AAC patients.

The study received approval from the institutional ethics review committee at the Eye Hospital of Wenzhou Medical University (2023 Science Ethic No.13). Patient informed consent was waived for this retrospective non-interventional study in accordance with Chinese regulations.

Statistical analysis

All analyses were performed using the SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were reported with frequency and percentage and compared using the Chi-Square test. Normally distributed measurement data were presented with mean±standard deviation (SD). A one-way analysis of variance was employed to compare three groups with normally distributed samples and equal variances. Considering the similarities between eyes, we used generalized estimating equations to estimate the differences in ocular manifestation between the COVID-19 group and the non-COVID-19 group. All analyses were considered significant at a type 1 error probability<0.05.

Results

A total of 3216 AAC cases were included; 76.2% were female, and 78.9% were age over 60 years old (average age: 66.89 ± 9.26 years). The numbers of AAC cases per time period was as follows: 826 for TOC-2020, 856 for TOC-2022, and a combined total of 1280 for TOC-2022 and P-TOC-1, plus an additional 254 for P-TOC-2.

Figure 2a shows the changes in new-onset AAC admissions over time. Hospital admissions remained stable during the TOC-2020 and TOC-2021 periods, with no significant difference in AAC numbers between these two timeframes (Fig. 2b). A similar trend was noted in TOC-2022. However, following the relaxation of the zero-COVID-19 policy on December 7, 2022, there was a substantial surge in AAC admissions—an almost three-fold increase (621, 225, and 191 respectively; see supplemental Table 1) during P-TOC-1 compared to the same period in 2020 and 2021 (Fig. 2c, while the exponential smoothing model predicted a value of 210, the actual recorded number was 621). Additionally, this rise in AAC cases coincided with a notable increase in COVID-19 infections.

Table 1 summarizes the demographics characters and medical history of confirmed AAC cases before and after the relaxation of the zero-COVID-19 Policy. Compared to AAC patients post-policy implementation, those prior to its relaxation had a higher mean age (67.27 ± 9.33 vs. 65.88 ± 9.00 , p<0.001) and a lower proportion of females (74.37% vs. 81.26%, p<0.001). Additionally, there were fewer individuals with a glaucoma family history (1.24% vs. 3.20%, p<0.001) and a lower COVID-19 infection rate (22/2341 vs. 474/875, p<0.001).

From December 7, 2022, to January 17, 2023, a total of 875 AAC patients were included in the study. Among them, 474 (54.2%) were categorized as COVID-19 group: 433 with Definete-COVID-19 infection and 41 with Suspected-COVID-19 infection; 270 (30.8%) were in the Non-COVID-19 group, and 131 (15.0%) were in the unidentified group. The most frequently



Fig. 2 Changes in the number of new-onset acute angle closure (AAC) admissions during the study period. (**a**) depicts the trends in blue, representing the observed number of new-onset AAC cases, while the red trends represent AAC patients with comorbidity with COVID-19. (**b**) displays monthly cases of new AAC admissions categorized into three time periods (2020–2021, 2021–2022, and 2022–2023). (**c**) presents both actual and predictive values obtained from an exponential smoothing model for assessing the number of new-onset AAC cases. Further details can be found in the main text. COVID-19=Coronavirus Disease 2019

reported symptoms associated with COVID-19 infection were fever, fatigue, and malaise. The mean age was similar between groups: 65.97 ± 8.62 years in COVID-19 group versus 66.14 ± 8.91 years in non-COVID-19 group (p=0.794). A telephone survey indicated that 37.3% (177/474) of COVID-19 patients increased their water intake compared to only 2.2% (2/270) in the non-COVID-19 group. Differences in self-reported sleep quality and the time of eye use in a dark environment were also observed between groups. Approximately 58.4% (279/474) of COVID-19 patients received antipyretic analgesic—most commonly Paracetamol,

 Table 1
 Demographics characters and medical history among confirmed acute angle closure cases before and after relaxing the zero-COVID-19 policy

	Before relaxing the zero-COVID-19 Policy	After relaxing the zero-COV- ID-19 Policy	<i>P</i> value
Number of acute angle closure cases	2341	875	
Age (mean \pm SD), years	67.27±9.33	65.88 ± 9.00	< 0.001
Gender, N (% female)	1741(74.37%)	711(81.26%)	< 0.001
History of systemic diseases	N (% Yes)		
Hypertension	879(37.55%)	319(36.46%)	0.569
Diabetes	230(9.82%)	83(9.49%)	0.773
Pulmonary diseases	51(2.18%)	15(1.71%)	0.409
Heart diseases	153(6.54%)	43(4.91%)	0.087
Thyroid diseases	29(1.24%)	15(1.71%)	0.302
Anti-anxiety-depression drug, N (% Yes)	17(0.73%)	3(0.34%)	0.218
Alcohol, N (% Yes)	82(3.50%)	15(1.71%)	0.002
Smoking status, N (% Current/Former smoker)	77(3.29%)	16(1.83%)	0.012
History of Allergy, N (% Yes)	151(6.45%)	55(6.29%)	0.865
Family history of glau- coma, N (% Yes)	29(1.24%)	28(3.20%)	<0.001
History of COVID-19 vaccination, N (% Yes)	1187(50.70%)	571(65.26%)	< 0.001
Infection of COVID-19, N (%)			
Definite -COVID-19	17(0.73%)	415(47.43%)	< 0.001
Suspected-COVID-19	5(0.21%)	59(6.74%)	
Non-COVID-19	2312(98.76%)	270(30.86%)	
Unknown	7(0.30%)	131(14.97%)	

COVID-19=Coronavirus Disease 2019, SD=standard deviation

Pseudoephedrine Hydrochloride, Dextromethorphan Hydrobromide and Chlorphenamine Maleate Tablets, and cold medications—while only one patient (1/270) from the non-COVID-19 group received such treatment during their care (Table 2).

Table 2 presents the clinical characteristics of comorbidity in AAC patients with COVID-19 and non-COVID-19 after the relaxation of the zero-COVID-19 policy. The COVID-19 group showed higher IOP (40.8±16.6mmHg vs. 35.3 ± 17.2 mmHg, p=0.001) and worse UDVA (1.47 ± 0.83 vs. 1.29 ± 0.82 , p=0.016) compared to the non-COVID-19 group, along with a significantly higher proportion of moderate/severe corneal edema (47.5% vs. 37.22%, p=0.008). In addition, axial length was greater in the COVID-19 group, while anterior chamber depth showed no significant difference between groups; however, there were no notable differences in time from AAC onset to presentation (p=0.129), as shown in Fig. 3.

Discussion

Our results show a significant association between daily activity factors pertaining to COVID-19 post-infection and the occurrence of AAC. After the end of zero-COVID-19 control measure, AAC cases nearly tripled during post-TOC-1 compared to the same months in TOC-2021 and TOC-2020. Individuals with comorbid AAC and COVID-19 exhibited higher water intake, poorer sleep quality, and prolonged exposure to dark environments. Over half received antipyretic analgesic. Additionally, we observed a heightened risk of blindness in COVID-19 patients, characterized by elevated IOP, worse UDVA, and more severe corneal edema.

SARS-CoV-2, the causative agent of COVID-19, belongs to the beta-coronavirus family and utilizes angiotensin-converting enzyme 2 (ACE2) as its receptor for cellular entry [11]. ACE2 receptors are widely distributed in many organs including the eyes [12]. Animal studies suggest a potential link between COVID-19 and ocular manifestations such as conjunctivitis, uveitis, and optic neuritis [13]. Some studies have noted an increase in AAC cases after the end of zero-COVID-19 control measure [7, 14, 15]. However, these were small-sample, single-center studies that merely reported this phenomenon without further exploring potential reasons. During the pandemic, the number of patients seeking care at ophthalmology clinics significantly decreased, altering treatment patterns for related diseases [16-18]. This decline can be attributed to patients' fears about COVID-19, the closure of some clinics, and restrictions from control measures; these factors may partially explain the increase in AAC cases after lockdowns were lifted.

However, our questionnaire survey found that over half of the AAC patients were co-infected with this virus during P-TOC, leading to daily activity changes like taking antipyretics and analgesics or increasing water intake. Previous studies have shown that individuals at a heightened risk of contracting COVID-19 exhibited alterations during the pandemic, including increased screens time and longer sleep duration, but poorer sleep quality [19, 20]. Additionally, AAC can be triggered by certain medications, specific light exposure, and excessive water intake [21]. Therefore, daily activities changes due to COVID-19 may also contribute to more AAC cases.

First, certain medications can act as triggers. Sulfamides like topiramate and acetazolamide may increase ciliochoroidal effusions, pushing the lens-iris diaphragm forward and causing angle closure. Anticholinergic and adrenergic agents can lead to pupillary blockage in susceptible patients [22–25]. Telephone follow-up revealed that most AAC patients with COVID-19 infection used antipyretics and analgesics such as Paracetamol, Pseudoephedrine Hydrochloride, Dextromethorphan Hydrobromide, Chlorphenamine Maleate Tablets and cold

Table 2 The self-reported daily activity changes and the clinical characteristics of acute angle closure comorbidity with COVID-19 or
non-COVID-19 after relaxing the zero-COVID-19 policy (Dec 7, 2022, to Jan 17, 2023)

	COVID-19 group	non-COVID-19	P value
Number of acute angle closure cases	474	270	/
Affected eye, N (%)	520	309	/
Bilateral	46 (9.7%)	39 (14.44%)	
Unilateral	428 (90.3%)	231 (85.56)	
Age (mean \pm SD), years	65.97±8.62	66.14±8.91	0.794
Gender, N (% female)	387(81.65)	217(80.37)	0.669
History of COVID-19 vaccination, N (% Yes)	282(59.49)	225(83.33)	< 0.001
Self-reported of water intake			
Increase	177	6	< 0.001
Unchange	297	264	
Self-reported of sleep state			
Better	31	12	< 0.001
Unchange	210	247	
Worse	233	11	
Self-reported of the time of eye use in dark environm	ent		
Increase	70	5	< 0.001
Unchange	310	264	
Reduce	94	1	
Antipyretic analgesic drug			
Yes	279	1	< 0.001
No	195	269	
Anti-anxiety-depression drug			
Yes	12	0	0.008
No	462	270	
IOP at presentation, mmHg (mean \pm SD)	40.75 ± 16.58	35.26±17.21	0.001
UDVA at presentation (LogMAR)	1.47±0.83	1.29 ± 0.82	0.016
Axial length, mm	22.42 ± 0.89	22.26 ± 0.94	0.034
Anterior chamber depth, mm	1.85 ± 0.37	1.84 ± 0.39	0.883
Slit lamp exam-corneal edema			
no/mild corneal edema	273 (52.50%)	194 (62.78%)	0.008
moderate/severe corneal edema	247 (47.50%)	115 (37.22%)	

COVID-19 group=Coronavirus Disease 2019 group (Definite-COVID-19+Suspected-COVID-19); SD=Standard Deviation; IOP=Intraocular pressure; UDVA=Uncorrected distance visual acuity



Fig. 3 The proportion of new-onset acute angle closure patients at different time points from symptom onset to presentation between the COVID-19 group and non-COVID-19 group following the relaxation of zero-COVID-19 policy. The bias line represents the COVID-19 group, and the grey line represents the Non-COVID-19 group. AAC=acute angle closure; COVID-19=Coronavirus Disease 2019

medications containing alpha-1 adrenergic receptor agonists or anticholinergics. Additionally, adjuvant therapies like anti-allergic nasal drops, intranasal phenylephrine for epistaxis treatment, and oral decongestants could also precipitate AAC [26-28]. Our study primarily involved middle-aged and elderly Asians predisposed to shallow anterior chamber; this may explain the drug effects observed. Secondly, COVID-19 infection can cause fever and electrolyte imbalances; hyponatremia is common among these patients and linked to high mortality rates. It can elevate IOP by creating an osmotic pressure difference between aqueous humor and the blood vessels, leading to shallower anterior chamber or even angle closure [29]. Thirdly, individuals infected with COVID-19 may consume more water, or use electronic devices to pass time in dark environment, or assume prone positions due to poor ventilation assistance [5], as identified through our telephone survey; these factors could further accelerate AAC development in those already prone to narrow-angles.

Most acute angle closure cases occur in patients unaware of their narrow-angle, especially among Asians, Who are three times more likely to experience AAC than Caucasians. In Singapore [29] and Hong Kong [30], the crude incidence rate of AAC were 12.2 and 10.4 per 100,000 people annually for those over 30 years old, while European regions reported an average incidence rate ranging from 2.0 to 4.1 cases per 100,000 people per year [31, 32]. The reasons for this disparity remain debated but may relate to racial differences in anterior chamber and angle anatomy [33, 34]. We observed a widespread surge in AAC admissions post-lockdown due to new outbreaks in China, unlike trends observed in Europe and America. Our study found that most AAC patients were females over 60 years old-consistent with previous studies highlighting both age-related susceptibility and female predominance [35, 36].

AAC patients with COVID-19 showed higher IOP, potentially leading to more severe optic nerve damage and visual field losses. Morrison et al. [37]. demonstrated that the most prominent axonal change associated with increased IOP is axon loss. Assessment of optic nerve cross-sections revealed an increase in degenerated axons and a decrease in axonal counts [38]. We also observed greater corneal edema in the COVID-19 group, likely due to elevated IOP leading to lower corneal endothelial cell density. This reduction disrupts the barrier integrity and pump function of corneal endothelial cells [39, 40]. While some studies indicated that delayed treatment for AAC in COVID-19 patients may worsen eye symptoms [41], we found no difference in time from symptom onset to presentation between the COVID-19 and non-COVID-19 groups. This could be attributed to extensive preparations by Chinese authorities for managing COVID-19 spread after relaxing zero-COVID-19 policies, along with heightened public awareness about the virus. This study highlights the potential worse prognosis and increased burden on individuals and society when AAC coexists with COVID-19, urging both practitioners and the public to prioritize eye health during long-term management of COVID-19 infection.

Our study has certain limitations. First, it is a retrospective analysis without data on daily activity changes in non-AAC COVID-19 patients. Consequently, we are unable to address the question of "causality or reverse causality". Second, the lack of nationwide coverage of the digital ophthalmology system prevented us from obtaining accurate incidence rates for AAC patients with COVID-19. This limitation also hindered our ability to gather comprehensive information on total AAC cases and population size in the region. Additionally, our study did not include patient follow-up for prognosis evaluation purposes. Nevertheless, our analysis offers an unprecedented look at daily activity patterns related to COVID-19 among AAC patients post-infection and provides clinical data from a large sample of newly diagnosed AAC patients during lockdown and post-lockdown periods amid this pandemic.

Conclusion

This study investigates the link between AAC occurrence, and daily activity factors related to COVID-19, while also noting a correlation between COVID-19 infection and AAC severity. This relationship highlights the need to consider daily activity changes as modifiable risk factor in managing AAC-susceptible patients with COVID-19. Moreover, early recognition of AAC in active COVID-19 cases can help reduce blindness associated with AAC.

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Author contributions

YB L and XJ W conceived the study. XJ W, AJ T, SD Z, B Q, LJ Z, XJ P, P L, XQ C, L Y, SP H, JB W, JG Y, XH W, P Y, YX Y, WZ Z, ZY W, JT Z, CQ L, JH L, YH J, ZX C, ZX D, SY X, C Y and YB L contributed to the study's design, the acquisition of data, or the data analysis and interpretation. XJ W drafted the manuscript, and AJ T, SD Z, B Q, LJ Z, XJ P, P L, XQ C, L Y, SP H, JB W, JG Y, XH W, P Y, YX Y, WZ Z, ZY W, JT Z, CQ L, JH L, YH J, ZX C, ZX D, SY X, C Y, HY Z, N C and YB L provided critical revisions.

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Data availability

The datasets for the analysis of the current study are readily available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study followed the tenets of the Declaration of Helsinki and was approved by the Ethics committee of the Eye Hospital of Wenzhou Medical University Institutional Review Board (2023 Science Ethic No.13). Patient informed consent was waived for this retrospective non-interventional study in accordance with Chinese regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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