

Acute primary angle closure during the Omicron outbreak

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INTRODUCTION

Acute primary angle-closure (APAC) glaucoma^[1] is an urgent ophthalmic condition characterized by a rapid increase in intraocular pressure (IOP) and is more common in Asians with shorter eye axial length (AL). The coronavirus disease-19 (COVID-19) can affect almost every organ of the body^[2-3], including the eyes^[4]. Limited studies have investigated the impact of COVID-19 on APAC, mostly relying on individual case reports^[5-7] due to much lower incidence of APAC in Caucasians. Therefore, there is still a lack of research with larger sample size on the relationship between COVID-19 and APAC.

On December 7, 2022, the Chinese government announced the end of the two-year-long zero-COVID policy^[8]. However, the relaxation of restrictions resulted in new outbreaks in various cities, including Shenzhen, primarily caused by the SARS-CoV-2 Omicron lineages BA.5.2 and BF.7^[9-10]. The Omicron infection in China was concentrated within a window period of approximately two months, during which a significant portion of the population was infected^[11]. This unique timeframe presents an ideal opportunity to investigate the association between Omicron and APAC. With a population of more than 17 million, Shenzhen, as the first city to implement China's reform and opening-up policy, predominantly consists of migrants from other cities, making it a suitable location for observing this trend.

This study aims to explore the incidence, clinical characteristics, and demographic features of APAC during this specific outbreak period in relation to Omicron in Shenzhen. Additionally, we intend to examine the correlation between systemic symptoms and ocular manifestations in APAC patients infected with Omicron.

SUBJECTS AND METHODS

Ethical Approval This study was approved by the Institutional

Abstract

• **AIM:** To investigate Omicron's impact on clinical presentation of acute primary angle closure (APAC) in China.

• **METHODS:** A consecutive case series with historical controls was conducted at Shenzhen Eye Hospital, the largest specialized hospital in Shenzhen, China. Medical records from a two-month period during the Omicron pandemic (December 1, 2022, to January 31, 2023) were compared with records from two control groups (12/2018–1/2019 and 12/2021–1/2022) before pandemic. Patients with APAC were included, and the prevalence of APAC and demographic characteristics in Omicron-infected and non-infected patients were compared.

• **RESULTS:** Seventy-one (23.43%) out of 303 patients were diagnosed with APAC in the pandemic cohort, which was 2.98 and 2.61 times higher than that in control cohorts (7.87% in 2019, 8.96% in 2022, $P < 0.001$). The pandemic cohort has significantly higher Omicron-infected rate (78.87% vs 0 vs 0; $P < 0.001$), lower proportion of glaucoma history (16.90% vs 42.86% vs 41.67%, $P = 0.005$), higher surgical rate (95.77% vs 83.33% vs 78.57%, $P = 0.024$), higher total medical costs and larger pupil diameter (5.63 ± 0.15 vs 4.68 ± 0.15 vs 4.69 ± 0.22 mm, $P < 0.01$). In 83% Omicron-infected patients, ocular symptoms appeared within 3d after systemic symptoms onset. In multivariate analysis, Omicron infection ($P < 0.001$) was the only independent predictor of pupil diameter.

• **CONCLUSION:** In the Omicron epidemic in China, there is an increase of prevalence and severity of APAC, particularly focusing on the first 3d following infection.

• **KEYWORDS:** Omicron; acute primary angle closure; ocular symptoms

Review Board of Shenzhen Eye Hospital (Shenzhen, China, No.2023KYPJ054). All data were anonymized prior to the analysis. The research conformed to the principles of the Declaration of Helsinki and its later amendments. Informed consent was waived following the institutional review board protocol.

This retrospective cohort study included APAC patients who sought evaluation and treatment at Shenzhen Eye Hospital in China from December 1, 2022, to January 31, 2023. Shenzhen Eye Hospital, the sole tertiary specialized hospital in Shenzhen with a population of over seventeen million people, provides round-the-clock ophthalmic emergency services. The historical control groups consisted of all APAC patients who sought treatment during the corresponding two-month period in the previous year (December 1, 2021, to January 31, 2022) and the year before COVID-19 (December 1, 2018, to January 31, 2019). APAC was defined based on the following criteria: 1) at least two of the following symptoms: eyeball pain, nausea, vomiting, or both; history of intermittent visual blurring; 2) IOP exceeding 21 mm Hg with at least three of the following signs: conjunctival congestion, corneal edema, moderate pupil dilation, and shallow anterior chamber; 3) gonioscopy revealing angle closure^[12-13]. Patients with chronic symptomatic visual loss or ocular hypertension lasting over 30d were excluded, as the onset of their condition should have predated the pandemic. Cases where both eyes experienced the aforementioned changes during the two-month enrollment period are defined as bilateral APAC. Patients receiving medical care, upon confirmation of APAC are initially recommended for systemic and local drug-based conservative treatment. If conservative treatment fails to control IOP, surgical treatment including laser iridectomy, anterior chamber puncture, phacoemulsification cataract surgery with or without goniosynechialysis, and trabeculectomy is considered.

Detailed demographic and preoperative data were collected by reviewing electronic health records. The primary outcomes of the study were the proportion of APAC patients and the proportion of APAC patients with Omicron infection in the three cohorts. The proportion of APAC patients refers to the proportion of APAC patients among the total number of patients seeking medical attention in the hospital's emergency department during the respective time frames. Secondary outcomes included the surgical rate, medical expenses in the three cohorts, patients' pupil size, visual acuity (VA), IOP, and AL at presentation. Pupil size was determined through ultrasound biomicroscope (UBM) examination, while AL was measured using the IOL Master (Carl Zeiss Meditec, Jena, Germany). The total medical expenses are computed by aggregating the expenses associated with outpatient services

and inpatient services incurred from the onset of APAC. Patients were classified as having Omicron infection if they tested positive for the virus by polymerase chain reaction within 24h. Patients tested positive will be scheduled for treatment at the isolation clinic established in the hospital.

Snellen VA measurements were converted to the logarithm of the minimum angle of resolution (logMAR). Hand motion and counting fingers were converted to logMAR values of 2.3 and 2.0, respectively, based on previous studies^[14-15]. Continuous variables between three cohorts were compared using one-way ANOVA test or Kruskal-Wallis test. Chi-square test or Fisher's exact test was used for comparing categorical variables. A *P*-value of less than 0.05 was considered statistically significant. All data were analyzed using SPSS 27.0 Software (SPSS Inc., Chicago, IL, USA).

RESULTS

During the two-month period of the Omicron outbreak in 2023, a total of 303 patients visited the emergency department of the hospital, compared to 356 patients and 268 patients in the corresponding control period of 2019 and 2022. The proportion of APAC patients in the 2023 cohort was 2.98 times and 2.61 times higher than that in the control years (*P*<0.001). Out of a total of 303 patients during the 2023 pandemic period, 71 (23.43%) sought treatment for APAC, compared to 28 (7.87%) patients in the corresponding 2019 control periods and 24 (8.96%) patients in the corresponding 2022 control periods. In the 2023 cohort, 56 patients (78.87%) patients were diagnosed with Omicron infection, while all patients in the 2019 and 2022 cohorts were not infected with Omicron, and only one patient (3.57%) in 2019 cohort have recent upper respiratory symptoms. The difference in the proportion of Omicron-infected patients between the three cohorts was statistically significant (*P*<0.001).

Patient Demographics Between Cohorts The demographic characteristics and presenting ocular characteristics of the three cohorts were shown in the proportion heat map in Figure 1. Table 1 provides an overview of the demographic characteristics of the three cohorts. The mean±SD ages of the three APAC cohorts were 61.60±2.31y, 63.80±1.69y, and 63.20±1.09y, respectively, with no significant differences among the three cohorts. Regarding gender, all three cohorts showed a clear trend of more female patients than male patients. The male-to-female ratios in the three groups were 6/22, 6/18, and 11/60, respectively, with no significant differences in gender distribution among the cohorts. In terms of residence, compared to 2019 period (before the pandemic) and the 2022 period (during the pandemic), there was a significant increase in the proportion of patients from outside the local area during the Omicron outbreak in 2023, following the relaxation of containment policies. All included

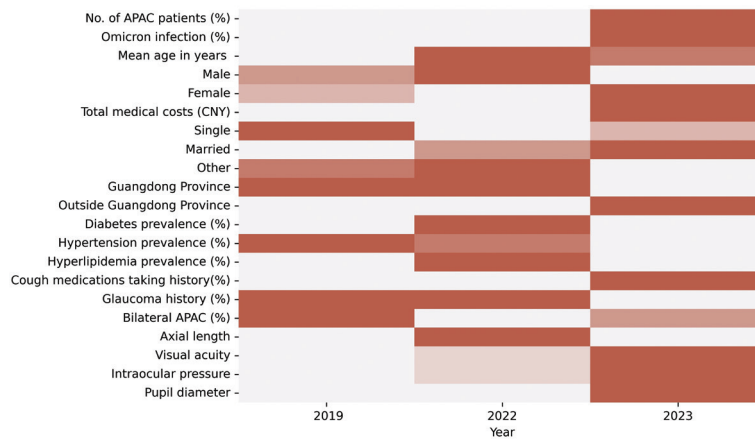


Figure 1 The proportion heatmap of patients diagnosed with acute primary angle closure in each cohort. Darker colors represent higher proportion; APAC: Acute primary angle.

Table 1 Demographic characteristics of patients with APAC seeking treatment in three cohorts

Parameters	2019 (Dec 1, 2018 to Jan 31, 2019)	2022 (Dec 1, 2021 to Jan 31, 2022)	2023 (Dec 1, 2022 to Jan 31, 2023)	P1	P2	P3
No. of APAC patients (%)	28/356 (7.87)	24/268 (8.96)	71/303 (23.43)	0.63 ^b	<0.001 ^{b,d}	<0.001 ^{b,d}
Age (y, mean±SD)	61.60±2.31	63.80±1.69	63.20±1.09	0.78 ^a	0.90 ^a	0.91 ^a
Sex, n (%)				0.76 ^b	0.48 ^b	0.29 ^b
Male	6 (21.43)	6 (25.00)	11 (15.49)			
Female	22 (78.57)	18 (75.00)	60 (84.51)			
Race	Asia	Asia	Asia			
Total medical costs ² (CNY)	346 161	348 000	1 114 000			
Marital status, n (%)				0.90 ^c	0.75 ^c	0.70 ^c
Single	2 (7.14)	1 (4.17)	4 (5.63)			
Married	25 (89.29)	22 (91.67)	66 (92.96)			
Other	1 (3.57)	1 (4.17)	1 (1.41)			
Systemic diseases, n (%)						
Diabetes	4 (14.29)	6 (25.00)	9 (12.68)	0.48 ^c	1.00 ^c	0.20 ^b
Hypertension	10 (35.71)	8 (33.33)	17 (23.94)	0.86 ^b	0.24 ^b	0.37 ^b
Location of permanent residence, n (%)				0.97 ^b	0.07 ^b	0.08 ^b
Guangdong Province	15 (53.57)	13 (54.17)	24 (33.80)			
Outside Guangdong Province	13 (46.43)	11 (45.83)	47 (66.20)			
Glaucoma history ¹ , n (%)	12 (42.86)	10 (41.67)	12 (16.90)	0.93 ^b	0.01 ^{b,d}	0.01 ^{b,d}
Omicron infection, n (%)	0	0	56 (78.87)	-	<0.001 ^{c,d}	<0.001 ^{c,d}
Cough medications taking history, n (%)	1 (3.57)	0	17 (23.94)	1.00 ^c	<0.001 ^{c,d}	<0.001 ^{c,d}

APAC: Acute primary angle closure glaucoma. P1: 2019 vs 2022 cohort; P2: 2019 vs 2023 cohort; P3: 2022 vs 2023 cohort. ¹Patients with any type of diagnosed glaucoma and those with a family history of the condition; ²Expenses associated with outpatient services and inpatient services. ^aMann-Whitney U test; ^bChi-square test; ^cFisher's exact test; ^dStatistically significant.

patients were Asian. The percentage of non-local (reside in Shenzhen but originate from other cities) patients increased from 46.43% in 2019 and 45.83% in 2022 to 66.20% in 2023, although this difference was not statistically significant. There are no significant differences in race, gender, age, marital status, prevalence of systemic diseases (diabetes, hypertension) between cohorts.

APAC Characteristics between Cohorts Table 2 provides an overview of presenting ocular characteristics of APAC patients

in three cohorts. In the three cohorts, the proportion of patients with a history of glaucoma in the 2023 cohort (16.90%) was significantly lower than in the 2019 (42.86%) and 2022 cohort (41.67%, $P=0.005$). During the pandemic, the rate of bilateral APAC was 9.86% (7 out of 71 patients), comparable to 10.71% (3 out of 28) and 8.33% (2 out of 24) in the control periods ($P=0.96$). There were no significant differences between the three cohorts in terms of VA (1.43 ± 0.11 vs 1.45 ± 1.23 vs 1.51 ± 0.09), IOP (42.74 ± 1.24 vs 43.06 ± 1.46

Table 2 Presenting ocular characteristics of patients with APAC seeking treatment in three cohorts

Parameters	2019 (Dec 1, 2018 to Jan 31, 2019)	2022 (Dec 1, 2021 to Jan 31, 2022)	2023 (Dec 1, 2022 to Jan 31, 2023)	P
Bilateral APAC ¹ , n (%)	3 (10.71)	2 (8.33)	7 (9.86)	0.96 ^c
Axial length (mm, mean±SD)	22.38±0.39	22.62±0.60	22.36±0.72	0.24 ^a
Visual acuity (mean±SD)	1.43±0.11	1.45±1.23	1.51± 0.09	0.84 ^b
Intraocular pressure (mm Hg, mean±SD)	42.74±1.24	43.06±1.46	43.80±0.91	0.86 ^b
Pupil diameter (mm, mean±SD)	4.68±0.15	4.69±0.22	5.63±0.15	<0.01 ^{b,d}
Treatment, n (%)				
Medical treatment	28 (100.00)	24 (100.00)	71 (100.00)	
2% pilocarpine	28 (100.00)	24 (100.00)	71 (100.00)	
1% brinzolamide	25 (89.29)	23 (95.83)	67 (94.37)	
0.15% brimonidine tartrate	26 (92.86)	24 (100.00)	70 (98.59)	
0.5% timolol	23 (82.14)	21 (77.77)	62 (87.32)	
20% mannitol intravenous infusion	20 (71.43)	18 (75.00)	58 (81.69)	
Laser periiridectomy	4 (14.29)	4 (16.67)	5 (7.04)	
Anterior chamber puncture	2 (7.14)	2 (8.33)	5 (7.04)	
Phacoemulsification cataract surgery with or without goniosynechialysis	16 (57.14)	18 (75.00)	66 (92.96)	
Trabeculectomy	2 (7.14)	0	2 (2.82)	

APAC: Acute primary angle closure. ¹Both eyes present with APAC symptoms at the time of diagnosis. ^aOne-way ANOVA test; ^bKruskal-Wallis test; ^cFisher’s exact test; ^dStatistically significant.

vs 43.80±0.91 mm Hg), and AL (22.38±0.39 vs 22.62±0.60 vs 22.36±0.72 mm, P=0.84, 0.86, 0.24). However, the pupil diameter at presentation during the pandemic (5.63±0.15 mm) was significantly larger than that in the 2019 (4.68±0.15 mm) and 2022 (4.69±0.22 mm) control period (P<0.01).

During the initial phase of medical treatment, all patients received 2% pilocarpine eye drops. Subsequently, among the cohorts of 2018, 2022, and 2023, the number of cases exhibiting a favorable response to pilocarpine treatment (pupillary constriction to 3 mm or below) were 17 (60.7%), 14 (58.3%), and 31 (43.7%) respectively. A total of 68 out of 71 patients (95.77%) underwent surgical treatment in the 2023 cohort. The specific surgical methods are detailed in Table 2. The surgical rate in the 2023 cohort was significantly higher than that in the 2022 and 2019 cohort (95.77% vs 83.33% vs 78.57%, P=0.024). Regarding medical expenses, the total medical expenses (both medical and surgical treatments) in the 2023 cohort were dramatically higher than those in the 2022 cohort and 2019 cohort (CNY 1 114 000 vs 348 000 vs 346 161). After undergoing surgical or medical treatment, all patients from both cohorts consistently maintained IOP within or below 25 mm Hg for a follow-up period of three months (15.59±3.12 vs 16.00±2.43 vs 16.74±2.92 mm Hg).

APAC Patients with Omicron Infection Among the 71 patients in the 2023 cohort, 56 patients (78.87%) were diagnosed with Omicron infection. Another 2 patients did not undergo polymerase chain reaction testing. The remaining 13 patients tested negative for Omicron, with 4 having recovered from a recent Omicron infection.

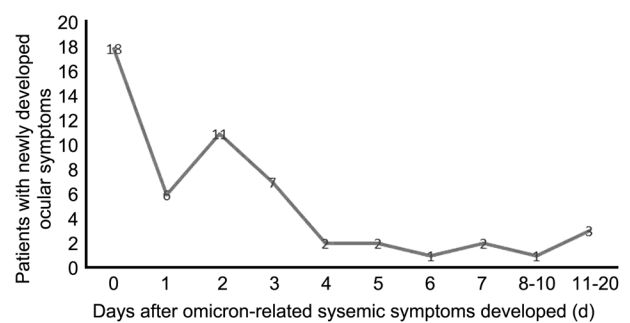


Figure 2 The temporal relationship between systemic symptoms and ocular symptoms in Omicron-infected APAC patients The trend reveals that for the infected patients with systemic symptoms, ocular symptoms occurred on the same day or after the onset of systemic symptoms, ranging 0–20d after systemic symptoms onset. The majority of patients experienced ocular symptoms within 3d of the onset of systemic symptoms. APAC: Acute primary angle closure.

For the 53 infected patients with systemic symptoms, ocular symptoms occurred on the same day or after the onset of systemic symptoms, with an average time of 7d (range 0–20d) after the onset of systemic symptoms. Ocular symptoms manifested on the same day as the onset of systemic symptoms in 18 out of 53 patients, and within 3d in 44 out of 53 patients (Figure 2). The primary symptoms reported by these 53 patients were fever in 37 patients (18 of whom had a temperature of 38.5°C or higher), impersistent cough in 33 patients, cough with sputum expectoration in 21 patients, muscle aches in 12 patients, headaches in 12 patients, and other symptoms such as sore throat, abdominal pain, asthenia, and nasal discharge or congestion. Thirteen

Table 3 Characteristics of Omicron-infected APAC patients with or without cough medicine taking history

Parameters	Cough medicine taking history	No cough medicine taking history	P
No. of APAC patients (eyes)	17 (18)	36 (39)	
Male gender (%)	2 (11.8)	5 (13.9)	1 ^c
Age (y), mean±SD	61.00±2.43	62.78±1.48	0.52 ^b
Axial length, mean±SD, mm	22.46±0.16	22.20±0.12	0.25 ^b
Visual acuity, mean±SD	1.60±0.17	1.46±0.13	0.52 ^a
Intraocular pressure, mm Hg	42.51±1.68	43.84±1.38	0.57 ^b
Pupil diameter, mm	5.67±0.26	5.82±0.23	0.78 ^a

APAC: Acute primary angle closure. ^aMann-Whitney *U* test; ^b*t* tests; ^cFisher's exact test.

patients did not take any medication, 17 took cough medicine (containing anticholinergic and epinephrine), 33 took aspirin or acetaminophen, 4 took antibiotics, and 11 took traditional Chinese medicine. Only one patient used the prone position to relieve pneumonia during the course. Among the 17 patients who took cough medications, 8 reported experiencing ocular discomfort prior to taking the cough medications, 7 indicated that the onset of ocular discomfort and cough medication intake occurred simultaneously, and 2 patients could not recall the timing.

Since cough medicine contains certain anticholinergic and mydriatic effects, a comparison was made between two subgroups of Omicron-infected patients, one group taking cough medicine and the other not taking cough medicine. Table 3 presents a comparison of the characteristics between these two groups, showing no significant differences in terms of gender, age, VA, IOP, and pupil size. A multivariate logistic regression analysis, including age, gender, IOP, AL, time to presentation, history of taking cough medicine, and Omicron infection, was conducted to identify demographic and ocular predictors of pupil diameter at presentation. The analysis revealed that Omicron infection ($P < 0.001$) was the only factor predictive of pupil diameter, while history of taking cough medicine, age, gender, IOP, AL, and time to presentation were not significant predictors.

DISCUSSION

In this study, our aim was to assess the demographic and presenting characteristics of patients with APAC during the Omicron pandemic. Our findings revealed a significant increase in the proportion of APAC patients during the Omicron outbreak period (2023) compared to the same periods before the pandemic (2019) and during the pandemic (2022). Majority of the APAC patients in 2023 were infected with Omicron, while no infections were reported in the 2019 and 2022 cohort. Additionally, we observed a notable rise in the rate of surgery and total medical costs in the 2023 pandemic cohort. Remarkably, the 2023 pandemic cohort exhibited a significantly larger pupil diameter, which was found to be solely associated with Omicron infection, not influenced by

factors such as age, gender, AL, year of onset, or medication history as determined through multiple regression analysis. Furthermore, in most omicron-infected patients with APAC, ocular symptoms appeared within 3d after the onset of systemic symptoms.

The substantial increase in the proportion of APAC patients in the pandemic cohort compared to the control cohorts suggests that the Omicron pandemic may have contributed to the rise in APAC incidence. Several scholars^[5-7,16] have also reported cases of APAC associated with COVID-19, which aligns with our study's findings. Previous research has indicated that the risk factors for Omicron-associated APAC primarily stem from the mydriatic effects of systemic therapeutic drugs^[17], prone positioning^[18] leading to impaired aqueous humor drainage, increased IOP, and hyponatremia^[19]. In our study, we discovered that the pupils of patients in the 2023 cohort were significantly larger than those in the control cohorts. Pupil dilation can cause iris relaxation, resulting in decreased anterior chamber depth and shallowing of the anterior chamber angle^[20]. This obstruction of aqueous humor drainage can eventually lead to increased IOP^[21]. Among the Omicron-associated APAC patients in our study, only one patient used prone position to relieve pneumonia, and there was no significant difference in pupil size between subgroups treated with systemic medications or not. This suggests that factors other than position and medication may cause pupil enlargement and subsequent IOP elevation. Multivariate analysis revealed that Omicron infection was the only predictive factor associated with pupil diameter. Similarly, studies^[22-24] have demonstrated impaired pupil responses in patients recovering from COVID-19, with significantly higher photopic and scotopic pupil diameters compared to healthy controls. This change may be linked to autonomic dysfunction^[25]. On the other hand, SARS-CoV-2 cell entry depends on angiotensin-converting enzyme 2 (ACE-2) receptor^[26-27], which is expressed in the non-pigmented epithelial cells of the ciliary body^[28-29]. This could be a possible reason for the increased incidence of APAC in patients following Omicron infection. However, whether pupil dilation is the cause or the result of APAC

attacks remains unclear, and further validation to confirm the relationship between pupil diameter and COVID-19 is needed in conjunction with basic research. Furthermore, we observed a high proportion of bilateral APAC cases in the 2023 cohort, with 7 cases (9.86%). This elevated proportion may be attributed to the definition used for bilateral APAC in our study, where patients experiencing bilateral APAC either simultaneously or sequentially during the two-month enrollment period were classified as bilateral APAC. Another plausible explanation could be the limited medical access and travel restrictions during the pandemic, potentially resulting in underrepresentation of patients with mild to moderate glaucoma attacks who did not seek medical care, thus leading to an inflated proportion of bilateral APAC cases in this cohort. Although a correlation exists between Omicron infection and an increase in APAC cases, the causal relationship between the two remains unclear. In terms of the relationship between the onset of systemic symptoms and ocular symptoms in Omicron-infected patients with APAC, we found that in more than one-third of patients, ocular symptoms coincided with the onset of systemic symptoms, and in most patients, they appeared within 3d after the onset of systemic symptoms. These findings suggest that APAC may be secondary to Omicron. Consequently, clinicians should consider the potential association between Omicron infection and APAC when evaluating infected patients, and screen high-risk patients to rule out APAC.

The study's findings regarding a higher surgical rate and increased medical expenses in the 2023 pandemic cohort suggest that the COVID-19 pandemic may significantly impact the severity of APAC and healthcare costs. The significantly higher medical expenses in the pandemic cohort can be attributed to the larger number of APAC cases and higher surgical rate during the pandemic, underscoring the importance of preparedness for pandemics and other public health emergencies. We also found that the proportion of patients with a history of glaucoma in the 2023 cohort was significantly lower than in the control cohort. The possible reason for this phenomenon is that during the Omicron period, individuals with milder cases of glaucoma were less likely to seek treatment at hospital emergencies^[30].

One limitation of our study is that it exclusively focused on patients who received treatment in an acute care setting. Therefore, we cannot draw definitive conclusions regarding the broader population-level significance of this difference. Additionally, in the 2019 cohort, Omicron screening was not a routine practice, even though the Omicron variant was not identified until late 2019, and despite conducting a retrospective assessment of patients for systemic symptoms, especially fever and cough, we cannot rule out the possibility

of missing asymptomatic COVID-19 infections. Meanwhile, our study is limited by its retrospective design and single-center approach, which precluded the inclusion of patients from diverse racial backgrounds. Consequently, there is a need for large-scale epidemiological studies to further validate the association between APAC and Omicron infection.

In conclusion, our study offers valuable insights into the characteristics and demographics of APAC patients during the Omicron pandemic. The findings suggest that Omicron has significantly affected the occurrence and severity of APAC cases, as well as contribute to increased healthcare costs. The observed trend shift may be associated with pupil dilation, highlighting the need for further research into the underlying mechanisms behind pupil dilation in these patients. The implications of this study's findings are of great importance to healthcare providers and clinicians, emphasizing the necessity for preparedness in public health emergencies and the significance of early detection and treatment of APAC in Omicron-infected patients.

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