• Clinical Research •

Systemic comorbidities, seasonal onset, and antihypertensive medication use in primary angle-closure disease subtypes

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Abstract

● **AIM:** To investigate clinical characteristics, comorbidities, seasonal onset, and antihypertensive medication use among acute primary angle-closure (APAC), chronic primary angle-closure glaucoma (CPACG), and primary angle-closure suspect (PACS) patients.

● **METHODS:** A retrospective cross-sectional study of 484 Chinese patients was conducted. Baseline demographics, hypertension and diabetes prevalence, antihypertensive medication use, and seasonal onset patterns were compared across primary angle-closure disease (PACD) subtypes. Seasonal variation was assessed using the von Mises distribution, with subgroup analyses stratified by systemic conditions and medication use.

● **RESULTS:** CPACG patients were older (median 71 *vs* 67y in APAC, $P<0.001$) with higher hypertension (47.74% *vs* 31.16%, $P=0.003$) and diabetes prevalence (20.60% *vs* 10.05%, $P=0.014$). Multivariate analysis showed hypertension [odds ratio (OR)=1.85] and diabetes (OR=2.00) were significant predictors of CPACG *vs* APAC. A modest but significant seasonal peak of APAC onset was identified in early June. Subgroup analyses revealed significant shifts in seasonal patterns according to hypertension ($P=0.023$), diabetes ($P<0.001$), and calcium channel blocker (CCB) use ($P=0.025$). Angiotensin-converting enzyme inhibitors (ACEIs) use was absent in APAC patients but present in CPACG and PACS groups; CCB use was highest in APAC patients, though differences were not statistically significant.

● **CONCLUSION:** Vascular and metabolic comorbidities are more prevalent in CPACG than APAC, suggesting their role in CPACG pathogenesis. The early-summer peak in disease onset points to possible environmental triggers. Seasonal variation in APAC onset appears to be influenced by systemic vascular conditions and antihypertensive medication use, supporting a multifactorial interaction between environmental, systemic, and pharmacologic factors in APAC.

● **KEYWORDS:** primary angle-closure glaucoma; acute primary angle-closure; chronic primary angle-closure glaucoma; hypertension; diabetes mellitus; antihypertensive medications

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INTRODUCTION

Glaucoma represents a group of disorders primarily characterized by damage to retinal ganglion cells and the optic nerve, often presenting clinically with decreased visual acuity, progressive visual field loss, and elevated intraocular pressure (IOP)[1]. Primary glaucoma can be classified into primary open angle glaucoma (POAG) and primary angle-closure glaucoma (PACG) based on the anatomical structure of the anterior chamber angle. PACG is more prevalent in Asia, particularly in China and Singapore[2]. The primary anatomical risk factor for PACG is angle closure, defined by the apposition of the trabecular meshwork and the peripheral iris. In the early stages of angle closure, gonioscopic examination revealing closure of multiple quadrants of the anterior chamber angle leads to a diagnosis of primary angle-closure suspect (PACS). PACS may progress to primary angle closure (PAC) when peripheral anterior synechiae (PAS) develop or when IOP rises, thereby increasing the risk of PACG[3]. Acute primary angle-closure (APAC) can occur at any stage of angle-closure disease and is characterized by sudden-onset ocular or periorbital pain, headache, nausea, and/or vomiting, accompanied by

a significant rise in IOP. In contrast, chronic angle-closure disease often manifests with insidious clinical features and gradual progression.

Hypertension is the most prevalent chronic non-communicable disease globally, characterized by elevated systemic arterial pressure. In its advanced stages, hypertension frequently affects vital organs, including the heart, brain, kidneys, and eyes, contributing to significant disability and mortality, thereby imposing a substantial social and economic burden[4]. Notably, increasing evidence suggests a close association between hypertension and glaucoma. However, evidence specifically addressing hypertension and primary angle-closure diseases (PACDs) is still limited, and further investigations are warranted to clarify this relationship. IOP is closely linked to systemic blood pressure (BP)[5]. Elevated BP may increase capillary pressure in the ciliary body and episcleral venous pressure, potentially disrupting aqueous humor dynamics. Horwitz *et al*[6] reported that, after adjusting for age and sex, hypertensive patients treated with antihypertensive medications had a significantly higher risk of developing glaucoma compared to non-hypertensive individuals (relative risk 1.31; $P<0.0001$). This finding aligns with other studies suggesting a close association between hypertension and glaucoma[7-9]. Large BP fluctuations, particularly nocturnal hypotension, are associated with reduced ocular perfusion pressure and decreased optic nerve head blood flow. These hemodynamic changes may cause ischemia and hypoxia of the optic nerve head, accelerating glaucomatous progression[10-11]. Jammal *et al*[12] observed that glaucoma patients with lower mean arterial pressure and diastolic BP experienced faster retinal nerve fiber layer thinning, even at similar IOP levels.

The relationship between antihypertensive therapy and glaucoma remains controversial. Horwitz *et al*[6] found that antihypertensive treatment, particularly with angiotensin-converting enzyme inhibitors (ACEIs), delayed the onset of glaucoma. This concentration of angiotensin-converting enzyme (ACE) in eyes with glaucoma is higher than in non-glaucomatous eyes[13]. Moreover, ACEIs have been shown to lower IOP and exhibit protective effects against glaucoma[14]. However, other research reported no significant impact of ACEIs or angiotensin receptor blockers (ARBs) on glaucoma risk[8,15-16], or even an increased risk[8,17-18]. Müskens *et al*[19] found that calcium channel blocker (CCB) use was associated with a 1.8-fold increased risk of open angle glaucoma [95% confidence interval (CI), 1.04–3.2; $P=0.037$). Two Meta-analyses further supported an association between CCB use and higher glaucoma prevalence[16,20].

Additionally, studies have explored potential associations between diabetes and POAG or PACG. Some investigations reported a positive correlation[21-22]. However, Tielsch *et al*[23], in a large-scale screening study, demonstrated that while a history of diabetes was positively correlated with increased IOP, there was no evidence supporting a direct association with POAG. Similar findings were reported in other studies[24-25]. Selection bias might explain discrepancies between clinic-based and population-based studies, as diabetes patients often undergo regular ophthalmologic examinations, increasing the likelihood of glaucoma diagnosis[23].

Emerging evidence suggests a seasonal pattern in the onset of acute PACG, with higher incidence in summer and winter. A retrospective study reported peak attacks in June–July for men and November for women, indicating possible environmental influences on disease onset[26]. Interestingly, BP also shows seasonal variation, typically rising in colder months. This has been linked to sympathetic activation and potential involvement of the renin-angiotensin-aldosterone system (RAAS). Cold exposure increases plasma norepinephrine and may activate RAAS, while heat stress can similarly stimulate RAAS through altered renal perfusion and catecholamine release[27]. These responses may disrupt ocular perfusion and aqueous humor dynamics, potentially precipitating angle-closure events in anatomically predisposed eyes such as PACS. Currently, the literature lacks consistent conclusions regarding the association between antihypertensive medication use, diabetes prevalence, and glaucoma. Moreover, there are no independent studies analyzing the characteristics of hypertension or diabetes comorbidities and antihypertensive drug usage in different primary angle-closure subtypes, including PACS, APAC, and chronic primary angle-closure glaucoma (CPACG).

PARTICIPANTS AND METHODS

Ethical Approval This retrospective, single-center, observational cross-sectional study was approved by the Institutional Review Board of Peking University People's Hospital (Beijing, China, No.2024PHB193-001) and adhered to the principles of the Declaration of Helsinki. Informed consent was obtained from all participants or their legal guardians, where applicable, prior to their inclusion in the study.

Study Design We recruited 484 patients diagnosed with primary angle-closure spectrum disorders (PACS, APAC, CPACG) at the glaucoma clinics of Peking University People's Hospital from August 2022 through January 2025.

Definitions of Subtypes Four subgroups of angle closure was defined based on International Society for Geographical and Epidemiological Ophthalmology criteria. PACS was defined as narrow angles with gonioscopic evidence of at least 180° of non-visibility of the pigmented posterior trabecular meshwork in the primary position, IOP≤21 mm Hg, and no evidence of glaucomatous optic neuropathy or PAS. PAC was characterized

Table 1 Baseline demographic and clinical characteristics of patients with different primary angle-closure subtypes

Parameters	Total (*n*=484)	Acute primary angle-closure (*n*=199)	Chronic primary angle-closure glaucoma (*n*=199)	Primary angle-closure suspect (*n*=86)	Statistic	*P*
Age, y, M (Q_1, Q_3)	69.00 (63.00, 75.00)	67.00 (63.00, 72.00)	71.00 (64.50, 78.00)	70.00 (65.25, 74.75)	χ^2=18.81[a]	<0.001
Sex, *n* (%)					χ^2=1.52	0.467
Male	133 (27.48)	57 (28.93)	57 (28.64)	19 (22.09)		
Female	351 (72.52)	142 (71.36)	142 (71.36)	67 (77.91)		
Hypertension, *n* (%)	191 (39.46)	62 (31.16)[b]	95 (47.74)[b]	34 (39.53)	χ^2=11.45	0.003
Diabetes mellitus, *n* (%)	75 (15.50)	20 (10.05)[b]	41 (20.60)[b]	14 (16.28)	χ^2=8.51	0.014

[a]Kruskal-Wallis test, χ^2: Chi-square test; M: Median, Q_1: 1st quartile, Q_3: 3rd quartile. [b]Indicates a statistically significant difference between the acute primary angle-closure and chronic primary angle-closure glaucoma groups.

by angle narrowing with PAS, elevated IOP>21 mm Hg, or both, without glaucomatous optic neuropathy. CPACG was defined as PAC without prior symptoms or signs of acute attack (*e.g.*, glaukomflecken, keratic precipitates, or iris atrophy) but with glaucomatous optic neuropathy or visual field defects. APAC was defined by the presence of at least two of the following symptoms: ocular or periorbital pain, nausea or vomiting, and a history of intermittent visual blurring with halos; concurrent IOP>28 mm Hg; the angle closure was diagnosed by gonioscopy or imaging devices; and at least three of the following signs: conjunctival hyperemia, corneal epithelial edema, mid-dilated nonreactive pupil, and shallow anterior chamber.

Exclusion criteria included patients with secondary glaucoma (*e.g.*, neovascular or uveitic glaucoma), non-glaucomatous ocular diseases, and systemic conditions or therapies affecting visual field assessment.

Data Collection Hypertension and diabetes status were confirmed through medical records. For hypertensive patients, antihypertensive medication use was recorded, specifically ACEIs, ARBs, and CCBs.

For APAC cases with acute attack onset dates between February 2023 and January 2025, the exact date of onset was recorded. To enable seasonal analysis, onset dates were normalized to a 365-day scale and transformed into angular data (0°–360°), where each calendar year was treated as a circular unit. Seasonal variation was evaluated by applying the von Mises distribution to estimate the mean direction (μ) and concentration parameter (κ), and to identify peak onset timing with corresponding 95%CI. The mean resultant vector length (R) was calculated to quantify the strength of seasonal clustering. The Watson's U^2 test was used to assess the significance of seasonal clustering within groups, while the Mardia-Watson-Wheeler test was applied to compare differences in seasonal distributions between subgroups. Analyses of medication effects were restricted to patients with diagnosed hypertension to reduce confounding by indication.

Descriptive statistics included means±standard deviations (SDs) for continuous variables and percentages for categorical variables. Normality of data was assessed using the Shapiro-Wilk test and histograms. Group comparisons were performed using analysis of variance (ANOVA) or Chi-square (χ^2) tests for baseline characteristics and prevalence of hypertension or diabetes. Logistic regression models were applied to estimate the odds ratios (ORs) for CPACG compared to APAC. A forest plot was used to visualize the effects of different factors and their interactions on CPACG and APAC risk. The proportions of patients using ACEIs, ARBs, and CCBs were calculated and compared across groups using χ^2 tests. A two-sided P value <0.05 was considered statistically significant. Data analyses were performed using SPSS version 27.0 (IBM Inc., Armonk, NY, USA).

RESULTS

Baseline Characteristics A total of 484 Chinese patients were included in the study. Table 1 presents the baseline demographic and clinical characteristics across the three primary angle-closure subtypes. The median age differed significantly among groups (P<0.001). Patients with CPACG had the highest median age of 71y (Q_1–Q_3: 64.50–78.00), followed by PACS at 70y (65.25–74.75), and APAC patients at 67y (63.00–72.00).

Across all subtypes, females predominated, comprising over 70% in each group. The female-to-male ratios were similar across groups (approximately 7:3), and no statistically significant difference in sex distribution was observed (P=0.467).

The prevalence of hypertension and diabetes mellitus varied significantly among groups. Hypertension was more prevalent in CPACG patients (47.74%) than in APAC patients (31.16%), with a statistically significant difference (P=0.003). Similarly, diabetes mellitus was more common in the CPACG group (20.60%) compared to the APAC group (10.05%; P=0.014).

Monthly Variation in Incidence In applying the von Mises distribution, data from each calendar year were normalized to a 365-day scale and then transformed into angles ranging from 0° to 360°. We visualized the timing of APAC attacks using a rose diagram (Figure 1), where each petal represented a standardized month, corresponding to an angle of 30°

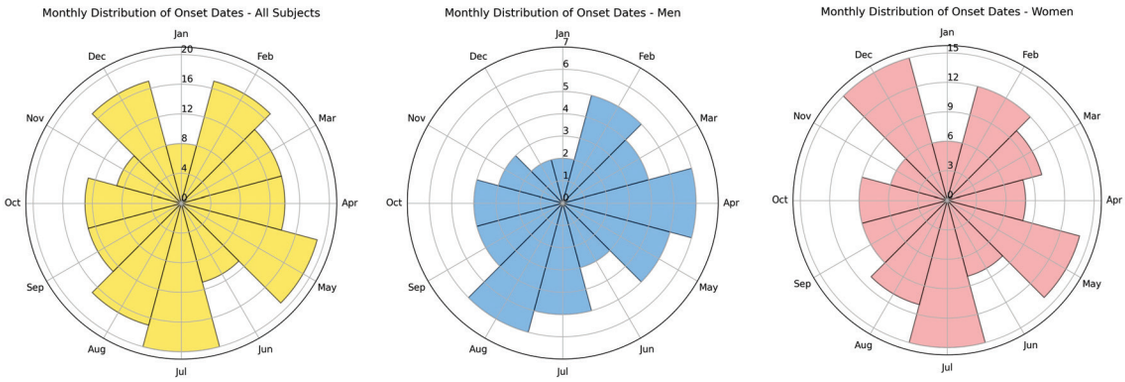

Figure 1 Rose plots illustrating the distribution of APAC onset dates along with the corresponding von Mises distribution probability density functions Onset dates from each calendar year were normalized to 365d and then converted into angles ranging from 0° to 360°, arranged in a clockwise direction. Each petal represents a standardized month corresponding to 30° (360°/12) and reflects the relative frequency of APAC onset during that month. The panels display data for all cases combined, male cases, and female cases separately. APAC: Acute primary angle-closure.

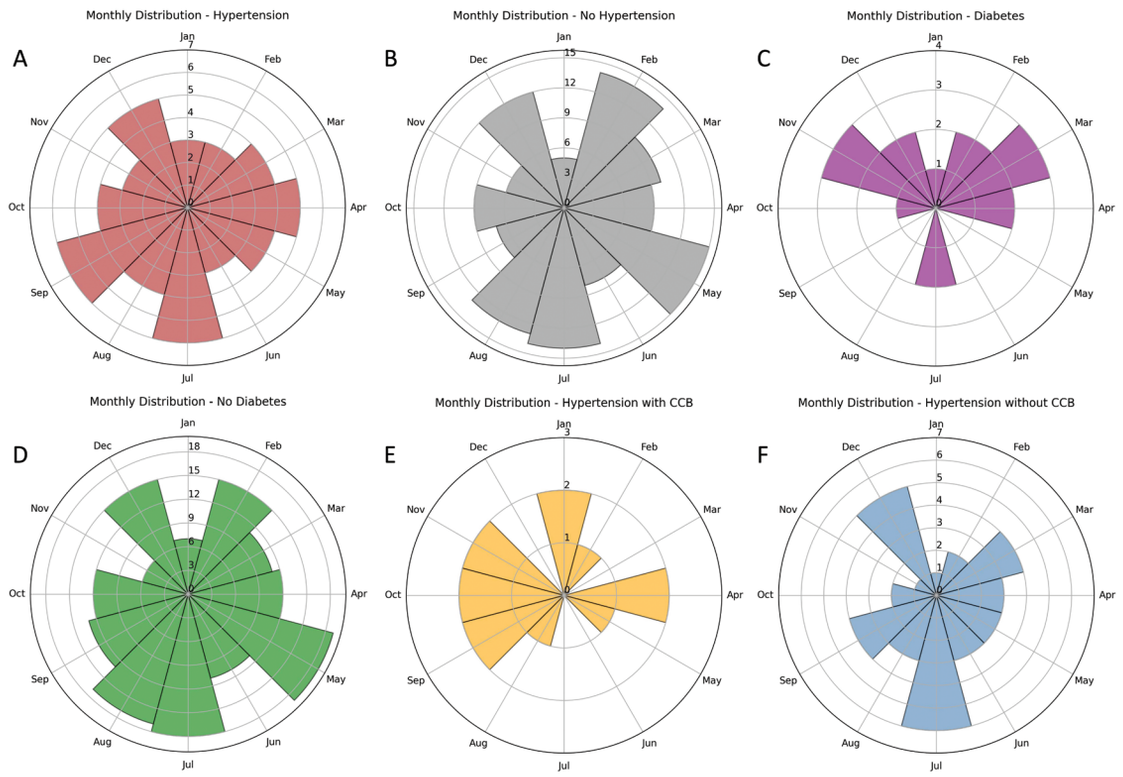

Figure 2 Seasonal distribution of APAC onset across systemic subgroups Rose plots illustrate the monthly distribution of APAC onset in different subgroups. A: Patients with hypertension; B: Patients without hypertension; C: Patients with diabetes mellitus; D: Patients without diabetes mellitus; E: Hypertensive patients using CCBs; F: Hypertensive patients not using CCBs. Each sector represents the number of cases occurring in a given month, arranged clockwise from January to December. Analyses of CCB use were restricted to patients with diagnosed hypertension to minimize confounding by indication. Differences in seasonal distribution were evaluated using circular statistical methods. APAC: Acute primary angle-closure; CCBs: Calcium-channel blockers.

(360°/12). For the combined sample, the estimated peak onset occurred on June 6 (95%CI, May 6 to July 6), with a mean direction of μ_0=155.78°. Among men, the estimated peak was on June 3, with μ_0=152.51° (95%CI, May 3 to July 3), while in women, the peak occurred on June 8 with μ_0=157.98° (95%CI, May 10 to July 10). All three peaks were statistically significant (Watson U^2=25.689, P=0.005 for the combined group; U^2=8.673, P=0.005 for men; U^2=23.566, P=0.005 for women), though their effect sizes were modest, as reflected by the mean resultant vector lengths (R=0.077, κ=0.155 for the combined group; R=0.065, κ=0.220 for men; R=0.109, κ=0.129 for women; Table 2).

Subgroup analyses based on systemic conditions revealed variations in seasonal patterns (Figure 2). Among patients with hypertension, the estimated peak occurred in early August (μ_0=209.34°, 95%CI, July 2 to August 30), whereas in those

Table 2 Circular statistical analysis of seasonal onset of APAC according to systemic conditions and antihypertensive medication use

Parameters	*n*	*R*	*κ*	Peak (μ_0°)	Date of peak	95%CI	Test statistic	*P*
Total	172	0.077	0.155	155.78	Jun 6	May 6–Jul 6	U^2=25.689	0.005
Sex								
Male	49	0.065	0.220	152.51	Jun 3	May 3–Jul 3	U^2=8.673	0.005
Female	123	0.109	0.129	157.98	Jun 8	May 10–Jul 10	U^2=23.566	0.005
Male *vs* female	-	-	-	-	-	-	*W*=4.385	0.036
Hypertension								
HTN (+)	50	0.053	0.107	209.34	Aug 1	Jul 2–Aug 30	U^2=8.215	0.032
HTN (–)	122	0.097	0.196	145.37	May 27	Apr 26–Jun 26	U^2=19.296	0.012
HTN *vs* non-HTN	-	-	-	-	-	-	*W*=5.200	0.023
Diabetes mellitus								
DM (+)	16	0.360	0.772	25.28	Jan 25	Dec 26–Feb 25	U^2=4.705	0.125
DM (–)	156	0.113	0.227	170.94	Jun 22	May 22–Jul 22	U^2=9.127	0.136
DM *vs* non-DM	-	-	-	-	-	-	*W*=16.275	<0.001
CCB use								
CCB (+)	13	0.232	0.154	316.94	Nov 17	Oct 17–Dec 17	U^2=10.698	0.280
CCB (–)	37	0.123	0.249	171.03	Jun 22	May 22–Jul 22	U^2=16.847	0.057
CCB *vs* non-CCB	-	-	-	-	-	-	*W*=5.048	0.025

APAC: Acute primary angle-closure; CI: Confidence interval; *R*: Mean resultant vector length; *κ*: Concentration parameter; *μ*: Mean direction; U^2: Watson's U^2 statistic; *W*: Mardia-Watson-Wheeler test statistic; HTN: Hypertension; DM: Diabetes mellitus; CCB: Calcium channel blocker.

Table 3 Univariate and multivariate logistic regression analysis results for differentiation between CPACG and APAC

Parameters	Single factor logistic analysis					Multi factor logistic analysis				
	β	SE	*Z*	*P*	OR (95%CI)	*β*	SE	*Z*	*P*	OR (95%CI)
Sex										
Male					Reference					
Female	0.00	0.22	0.00	1.000	1.00 (0.65–1.54)					
Hypertension										
No					Reference					Reference
Yes	0.70	0.21	3.36	<0.001	2.44 (1.34–3.04)	0.61	0.21	2.88	0.004	1.85 (1.22–2.81)
Diabetes mellitus										
No					Reference					Reference
Yes	0.84	0.29	2.87	0.004	2.32 (1.31–4.13)	0.69	0.30	2.30	0.021	2.00 (1.11–3.60)

CPACG: Chronic primary angle-closure glaucoma; APAC: Acute primary angle-closure; OR: Odds ratio; CI: Confidence interval; SE: Standard error.

without hypertension, the peak was observed in late May (μ_0=145.37°, 95%CI, April 26 to June 26). The difference in seasonal distribution between these groups was statistically significant (*W*=5.200, *P*=0.023). Similarly, patients with diabetes mellitus showed a distinct peak in late January (μ_0=25.28°, 95%CI, December 26 to February 25), while those without diabetes exhibited a peak in late June (μ_0=170.94°, 95%CI, May 22 to July 22). The difference between these groups was also significant (*W*=16.275, *P*<0.001).

To further evaluate the potential influence of antihypertensive medications, analyses were restricted to patients with diagnosed hypertension. Within this subgroup, patients using CCBs demonstrated a peak onset in late November (μ_0=316.94°, 95%CI, October 17 to December 17), whereas non-users showed a peak in mid-June (μ_0=171.03°, 95%CI, May 22 to July 22). A significant difference in seasonal distribution was observed between the two groups (*W*=5.048, *P*=0.025; Table 2).

Logistic Regression Analysis In the univariate logistic regression analysis, hypertension was significantly associated with an increased likelihood of CPACG compared to APAC (OR=2.44, 95%CI: 1.34–3.04, *P*<0.001; Table 3). Similarly, diabetes mellitus was also significantly associated with higher odds of CPACG (OR=2.32, 95%CI: 1.31–4.13, *P*=0.004). Sex was not a significant predictor of CPACG in the univariate model (OR=1.00, 95%CI: 0.65–1.54, *P*=1.000).

In the multivariate logistic regression analysis, after adjusting for potential confounders, both hypertension and diabetes remained statistically significant predictors. Patients with hypertension had 1.85 times higher odds of CPACG than those

Table 4 Distribution of antihypertensive medication use among patients with different primary angle-closure subtypes *n* (%)

Parameters	Total (*n*=106)	Acute primary angle-closure (*n*=31)	Chronic primary angle-closure glaucoma (*n*=56)	Primary angle-closure suspect (*n*=19)	Statistic	*P*
ACEIs	5 (4.72)	0	4 (7.14)	1 (5.26)	-	0.385[a]
ARBs	58 (54.72)	14 (45.16)	35 (62.50)	9 (47.37)	χ^2=2.93	0.232
CCBs	68 (64.15)	22 (70.97)	34 (60.71)	12 (63.16)	χ^2=0.92	0.631
Monotherapy	25 (24.51)	5 (16.67)	17 (31.48)	3 (16.67)	χ^2=3.01	0.222
Combination therapy	26 (24.53)	5 (16.13)	17 (30.36)	4 (21.05)		

[a]Fisher exact. ACEIs: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; CCBs: Calcium channel blockers.

without hypertension (OR=1.85, 95%CI: 1.22–2.81, *P*=0.004), and those with diabetes had 2.00 times higher odds (OR=2.00, 95%CI: 1.11–3.60, *P*=0.021). Sex remained non-significant in the multivariate model.

Antihypertensive Medication Use Table 4 presents the distribution of antihypertensive medication use across the different angle-closure subtypes. There were no statistically significant differences in the use of ACEIs, ARBs, or CCBs among the APAC, CPACG, and PACS groups. Notably, ACEIs were not used in any APAC patients, while their use was observed in both CPACG and PACS groups, although the difference was not statistically significant (*P*=0.385, Fisher's exact test). ARBs were used more frequently in CPACG patients (62.50%) compared to APAC (45.16%) and PACS (47.37%), but again without statistical significance (*P*=0.232). CCB use was relatively common across all groups, with the highest proportion in APAC patients (70.97%), though this difference was not significant (*P*=0.631).

Regarding treatment patterns, no significant differences were found in the distribution of monotherapy and combination therapy among the three groups (χ^2=3.01, *P*=0.222). Monotherapy was used in 16.67%, 31.48%, and 16.67% of APAC, CPACG, and PACS patients, respectively, while combination therapy was observed in 16.13%, 30.36%, and 21.05% of patients in the corresponding groups.

DISCUSSION

Our study found that CPACG and APAC exhibit distinct clinical characteristics and systemic associations. CPACG patients had the highest median age (71y) among the three groups, compared with 67y in APAC and 70y in PACS. CPACG patients also showed a markedly higher prevalence of hypertension (47.74%) and diabetes mellitus (20.60%) compared to APAC patients (31.16% and 10.05%, respectively). These findings suggest stronger vascular and neuropathological links in CPACG, potentially reflecting the impact of chronic systemic vascular dysregulation over a prolonged disease course.

Our findings align with previous studies indicating that PACDs primarily affects older populations and is more prevalent in women[28]. Notably, our study revealed that the onset age of CPACG was higher than that of APAC, likely due to the more insidious clinical course of CPACG, often leading to delayed diagnosis in its early stages.

Prior studies have demonstrated the critical role of vascular endothelium in ocular blood flow regulation, suggesting that endothelial dysfunction may precipitate ischemia and dysregulation[29]. In glaucoma patients with hypertension, reduced ability to maintain retinal blood flow during ocular perfusion pressure fluctuations has been linked to increased susceptibility to glaucomatous optic nerve damage[30]. In our multivariate logistic regression, hypertension was associated with 1.85-fold higher odds of CPACG compared to APAC (*P*=0.004), even after adjusting for confounders. This association is unlikely to be explained solely by age-related increases in hypertension prevalence, and may instead reflect chronic ocular blood flow dysregulation during the prolonged course of CPACG.

Vascular dysregulation has also been reported in both diabetes and glaucoma, with upregulation of nitric oxide (NO) as a potential shared mechanism[31-32]. Additionally, diabetes and glaucoma share pathological pathways for optic nerve and retinal damage, including glial cell dysfunction and impaired retrograde axonal transport[33-34]. Animal models of diabetes and glaucoma have demonstrated that dysfunction of glial cells, key non-neuronal cells supporting central nervous system neurons, can exacerbate apoptosis through neuroinflammatory pathways[35]. In our study, diabetes prevalence was 20.60% in CPACG, 10.05% in APAC, and 16.28% in PACS, with diabetes doubling the odds of CPACG versus APAC in the multivariate model (OR=2.00, *P*=0.021). Compared with age-matched general population data (20%–27%)[36], CPACG patients had similar diabetes prevalence, indicating that diabetes is not disproportionately overrepresented in this group relative to the background population risk. However, the significantly higher prevalence of diabetes in CPACG than in APAC within our cohort suggests that diabetes may influence disease trajectory—predisposing anatomically susceptible eyes toward a chronic course rather than an acute presentation. This association may be mediated by diabetes-related microvascular dysfunction, impaired ocular perfusion regulation, and glial

cell pathology, which are more likely to contribute to insidious optic nerve injury and progressive angle closure than to trigger abrupt acute attacks.

APAC represents an ophthalmic emergency characterized by sudden anterior chamber angle closure and a rapid increase in IOP, necessitating prompt treatment to minimize optic nerve damage and vision loss. Various mechanisms contribute to angle closure in APAC, including pupillary block, anteriorly positioned peripheral iris, anteriorly rotated ciliary body, and plateau iris configuration, with some cases involving multiple mechanisms simultaneously[37]. However, the understanding of APAC triggers remains limited due to a lack of prospective data and appropriate animal models.

Interestingly, our seasonal analysis revealed a modest but statistically significant clustering of APAC onset in early June (combined peak: June 6, 95%CI: May 6–July 6), consistent with our observation that APAC peaks in summer. This pattern aligns with prior reports of increased APAC incidence during warm months[26,38].

From a pathophysiological perspective, these seasonal variations may be mediated through dynamic changes in the ciliary body and anterior chamber angle. Environmental factors such as ambient temperature, humidity, and atmospheric pressure can influence autonomic tone, vascular permeability, and choroidal blood flow[27,38-39]. Increased choroidal vascular permeability and expansion may lead to anterior displacement of the lens–iris diaphragm, narrowing the anterior chamber angle and predisposing susceptible individuals to angle closure. Nevertheless, the modest effect size in our cohort (R=0.077) suggests these environmental factors are more likely facilitators than primary causes of acute attacks.

Our seasonal analysis showed that patients with diabetes exhibited a distinct temporal pattern, with a peak in late January, in contrast to the late June peak observed in non-diabetic individuals. This winter predominance may be related to diabetes-associated microvascular dysfunction, impaired endothelial responsiveness, and altered autonomic regulation, which could increase susceptibility to ocular hemodynamics under colder environmental conditions. Conversely, hypertensive patients may exhibit altered vascular reactivity and delayed adaptive responses to heat stress, contributing to the observed shift toward later summer peaks.

Antihypertensive medications may further modulate these mechanisms by directly or indirectly affecting iris and ciliary body perfusion and aqueous humor dynamics. In addition to their systemic hemodynamic effects, increasing evidence suggests that the renin-angiotensin-aldosterone system (RAAS) is locally expressed within ocular tissues, including the trabecular meshwork, ciliary body, and iris, where it plays an important role in regulating aqueous humor dynamics, vascular tone, and inflammatory responses[40]. ACE catalyzes the conversion of angiotensin (Ang) I to Ang II, which exerts vasoconstrictive, pro-inflammatory, and pro-fibrotic effects *via* angiotensin II type 1 receptor (AT1R). Experimental studies have shown that Ang II can promote trabecular meshwork fibrosis, oxidative stress, and inflammation, thereby impairing aqueous outflow and contributing to IOP elevation, whereas ACEIs and ARBs may counteract these effects[41-43]. CCBs are known to induce systemic and ocular vasodilation, which may increase choroidal blood volume and promote anterior rotation of the ciliary body, thereby contributing to angle narrowing in anatomically predisposed eyes[44]. Furthermore, vasodilatory effects may alter episcleral venous pressure and aqueous humor outflow resistance. These mechanisms provide a plausible explanation for the distinct seasonal pattern observed among CCB users in our study. However, given the limited sample size and the presence of combination antihypertensive therapy in clinical practice, these findings should be interpreted with caution.

In the present study, the distribution of antihypertensive medications, including ACEIs, ARBs, and CCBs, did not differ significantly among APAC, CPACG, and PACS groups, and no differences were observed in monotherapy or combination therapy patterns, indicating broadly comparable treatment profiles across subtypes. Although ACEIs were not used in APAC patients and ARBs were numerically more frequent in CPACG, these differences were not statistically significant. CCBs were commonly used across all groups.

Recent studies have examined the epidemiology and triggers of APAC, particularly during the COVID-19 Omicron outbreak, highlighting the potential role of infection-related factors[45]. Others have focused on treatment strategies, such as laser peripheral iridotomy[46]. However, these investigations have largely centered on external triggers or management strategies of APAC, with limited attention to the heterogeneity among PACDs or their systemic associations. In contrast, our study provides several novel insights. We performed a comparative analysis across multiple PACDs subtypes within a single cohort, enabling a more comprehensive characterization of the disease spectrum. In addition, we incorporated systemic conditions, including hypertension and diabetes mellitus, and further evaluated the seasonal patterns of APAC and the use of antihypertensive medications (ACEIs, ARBs, and CCBs). Collectively, these findings extend current knowledge by offering a more integrated understanding of angle-closure disease, with potential implications for individualized management.

This study has several limitations. First, reliance on self-reported hypertension and diabetes histories may have introduced information bias, though this risk was minimized by corroborating data with prior medical records. Second,

the small sample sizes for specific medication groups limit generalizability and statistical power. Larger studies and controlled experiments are needed to explore the potential impact of the RAAS on APAC.

In conclusion, our study demonstrates that vascular and metabolic comorbidities, specifically hypertension and diabetes, are significantly more prevalent in CPACG patients compared to those with APAC. Furthermore, although antihypertensive medication use was not differentially distributed across subtypes, its association with shifts in seasonal onset patterns highlights a potential modulatory role in disease timing. These findings underscore the complex interaction among systemic vascular conditions, pharmacologic exposures, and environmental factors in the pathogenesis of PACD.

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