• **Clinical Research** •

Modular surgical approach for angle-closure glaucoma secondary to nanophthalmos

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Abstract

● **AIM:** To explore and summarize outcomes of a modular surgical approach for the personalized management of angle-closure glaucoma (ACG) secondary to nanophthalmos.

● **METHODS:** This was a retrospective interventional case series involving consecutive patients with nanophthalmos and ACG. All patients were treated with a modular surgical approach tailored to their specific disease characteristics, which included the following surgical combinations: Procedure I [phacoemulsification (phaco)+goniosynechialysis (GSL)], Procedure II [Procedure I +irido-zonulo-hyaloid-vitrectomy (IZHV)], Procedure III [phaco +IZHV+Ahmed glaucoma valve (AGV) implantation], and Procedure IV (Procedure III+scleral window creation).

● **RESULTS:** A total of 92 eyes from 62 patients were enrolled, with a median age of 52 (range: 23-72)y and a median axial length of 19.89 (range: 14.84-20.99) mm. According to the patients' distinct clinical characteristics, 14, 26, 22, and 30 eyes underwent Procedures I, II, III, and IV, respectively. The median follow-up duration was 13 (range: 12-36)mo. At the final follow-up visit, all patients achieved a sustained intraocular pressure (IOP) below 21 mm Hg without the administration of anti-glaucoma medications. Postoperative complications included malignant glaucoma (MG, 9 eyes), uveal effusion (UE, 5 eyes), suprachoroidal hemorrhage (1 eye), fibrin membrane formation (4 eyes), uveitis (1 eye), macular edema (1 eye), and impaired corrected distance visual acuity (CDVA, 6 eyes). Univariate analysis revealed that younger age was associated with a higher risk of MG (OR: 1.06, P=0.04), UE (OR: 1.07, P=0.046), and impaired CDVA (OR: 1.11, P=0.02).

● **CONCLUSION:** The modular surgical approach yields favorable and consistent clinical prognoses, while reducing the incidence of complications, in the challenging clinical scenario of ACG secondary to nanophthalmos.

● **KEYWORDS:** nanophthalmos; angle-closure glaucoma; irido-zonulo-hyaloid-vitrectomy; malignant glaucoma; uveal effusion

INTRODUCTION

Nanophthalmos, a variant of microphthalmos, results from halted eye development in early embryogenesis. The estimated birth prevalence of microphthalmos ranges from 0.2 to 1.7 per 10 000 births worldwide and 0.9 in China[1]. Nanophthalmos is a relatively rare eye disorder identified by an axial length (AL) at least 2 standard deviations (SD) below the age mean (*i.e.*,<21/20.5/20 mm) without ocular malformations[2-4]. The condition exhibits distinctive anatomical traits, such as a shallow anterior chamber, narrow angle, high lens-to-eye volume ratio, and thickened sclera[5-6], contributing to a heightened risk of angle-closure glaucoma (ACG)[7].

Managing ACG secondary to nanophthalmos poses a perpetual challenge. Traditional surgical approaches, including lens extraction, filtration surgery, surgical iridectomy, sclerectomy, sclerotomy, and vortex decompression have demonstrated effectiveness in some instances[6]. However, these procedures in such eyes often lead to compromised visual outcomes due to the high occurrence of severe intraoperative and postoperative complications, such as uveal effusion (UE), effusive retinal detachment, uveitis, malignant glaucoma (MG), and suprachoroidal hemorrhage[8-9]. Consequently, the decision to proceed with surgeries is frequently postponed,

rendering patients in this category more susceptible to presenting with extensive synechia angle closure and/or advanced glaucomatous optic neuropathy, further complicating their management. In cases where surgery becomes inevitable, the primary objective shifts to complication prevention, a formidable task, particularly in eyes with extremely short AL[10]. Despite the introduction of numerous surgical strategies aimed at mitigating complications in these eyes[4,9-13], none have consistently shown success.

Based on previous studies and our clinical experiences, effectively addressing ACG secondary to nanophthalmos relies on managing abnormalities within the ciliary body-zonules-crystalline lens-hyaloid-anterior vitreous complex (CZLHV)[14] and angle closure while also preventing MG, UE and suprachoroidal hemorrhage. In order to achieve this goal, we've devised a modular surgical approach tailored to the specific challenges presented by each individual. This approach comprises several key components: phacoemulsification (phaco) to alleviate anterior segment crowding, irido-zonulo-hyaloid-vitrectomy (IZHV) to mitigate MG, goniosynechialysis (GSL) or Ahmed glaucoma valve (AGV) implantation for intraocular pressure (IOP) management, and scleral windows to prevent UE. We adeptly combined these components according to each patient's distinct clinical profile, a process honed over the past 10y and solidified in the recent 5y through our vast clinical experience and thorough comprehension of related complications[15-16].

Ideally, evaluation of alternative strategies for disease management is based on randomized clinical trials; however, conducting such studies in these challenging cases is often impractical due to the complex and rare nature of the conditions. Particularly, our experience has substantiated the heightened risk associated with traditional alternative treatments. This study aims to outline the outcomes of our personalized modular surgical approach in these complex cases with varying clinical characteristics. By doing so, we seek to validate the effectiveness of our individualized therapy, with the overarching goal of reducing the incidence of severe complications while consistently achieving surgical success. Ultimately, this research represents a potential advancement in the surgical management of these challenging cases.

PARTICIPANTS AND METHODS

Ethical Approval This study protocol was reviewed and approved by the Ethics Committee of Beijing Tongren Eye Center (approval number TREC2023-KY014). Informed consent was obtained from each patient.

This was a retrospective consecutive case series. Totally 92 eyes of 62 patients with ACG secondary to nanophthalmos underwent the modular surgical approach by the same experienced surgeon (Fan ZG) between October 2020 and June 2023 at Beijing Tongren Eye Center. Nanophthalmos was defined as a small but morphologically normal eye, with AL at least 2 SD below the population mean (*i.e.*, <21 mm). ACG was diagnosed in the presence of these 3 criteria: 1) peripheral anterior synechiae (PAS) in association with elevated pretreatment IOP>21 mm Hg; 2) gonioscopy revealing >180° of iridotrabecular contact (includes both appositional and synechial closures); 3) glaucomatous optic nerve damage and visual field loss. Patients meeting any of the following criteria were excluded: prior intraocular surgery, history of intraocular inflammation, trauma, other congenital malformation, complex microphthalmos, relative anterior microphthalmos, posterior microphthalmos, presence of additional ocular pathology like chorioretinal coloboma, retinitis pigmentosa or foveal schisis.

The clinical records of each patient were scrutinized, and the subsequent preoperative characteristics were compiled: demographic information, history of ocular disease, treatment history, assessment of corrected distance visual acuity (CDVA) utilizing the 5 m Standard Logarithmic (5SL) Visual Acuity Chart, which was then converted to the logarithm of the minimum angle of resolution (logMAR) for analysis, IOP measurement using the Goldmann applanation tonometer, anterior chamber depth (ACD) and AL measurement *via* IOL master (v.5, Carl-Zeiss Meditec, Dublin, CA, USA), visual field measured with Humphrey perimetry (Carl Zeiss Meditec, Dublin, CA, USA), examination of anterior segment findings through slit-lamp examination and gonioscopic examination with indentation, evaluation of posterior segment findings including assessment of vertical cup-to-disc ratio (VCDR), B-scan ultrasonography.

All patients underwent a composite set of the modular surgical approach tailored to their clinical presentations and intraoperative conditions, subsequently being classified into four groups. Patients with acute ACG or chronic ACG with angle adhesion ≤180° and early-stage visual field defects (mean defect ≥-6.0 dB) underwent phacoemulsification (phaco), intraocular lens (IOL) implantation, and GSL (Procedure I). In cases with positive vitreous pressure (under stable perfusion pressure conditions, the anterior chamber becomes shallow or even collapse) during surgery, additional IZHV was performed (Procedure II). Eyes exhibiting chronic ACG with angle adhesion >180° and moderate to advanced stage visual field defects (mean defect less than -6.0 dB, or poor vision precluding reliable visual field testing) underwent phaco, IOL implantation, IZHV in combination with AGV (Procedure III). In addition, for those with AL less than 18 mm or preoperative evidence of UE, such as ciliochoroidal effusion, choroidal effusion, ciliochoroidal detachment, and choroidal detachment (identified through B-scan or ultrasound biomicroscopy examination), Procedure III together with sclerotomy under a

superficial scleral flap (scleral window) was implemented as a prophylactic or therapeutic measure for UE (Procedure IV). Postoperative data, including IOP and complications, such as MG, UE, suprachoroidal hemorrhage, fibrin membrane formation, uveitis, macular edema and compromised CDVA (a decline of more than two lines on the visual acuity chart or a decrease to hand movement, light perception, or no light perception), were gathered on the first day, first week, and first month after the surgery, with subsequent intervals of 3 or 6mo thereafter. Complications were further classified as early-stage (within 3mo) and late-stage (after 3mo) complications.

Surgical Procedures Aligned with the surgical plan for the four groups, we detailed the specific modular surgical approach as follows: Modular surgical design 1: managing basic nanophthalmos diathesis (anterior segment crowding) through lens removal. In instances where the preoperative IOP was equal to or exceeded 40 mm Hg, a regimen of maximum anti-glaucoma medications was prescribed. If this approach proved ineffective, an anterior-chamber (AC) paracentesis was meticulously conducted in a gradual and stepwise manner to reduce preoperative IOPs to the lowest feasible levels, as outlined in previous studies[17]. A 2.2 mm clear temporal corneal incision was then created. In selected cases with notably opaque or edematous cornea, suspected zonulopathy, or white/brown cataracts, 0.2 mL of indocyanine green (ICG) was injected to paint the anterior capsule under ophthalmic viscoelastic device (OVD, DisCoVisc, Alcon Laboratories, Inc., USA). Subsequently, a standardized procedure involving phaco and IOL implantation was carried out. Phaco chop was performed with "Slow Phaco" settings. This procedure employed low IOP settings (30 mm Hg or 5-10 mm Hg higher than the preoperative IOP in cases with an initial IOP exceeding 30 mm Hg), low flow (30 mL/min), and low vacuum (450 mm Hg) parameters, utilizing the Alcon Centurion® Vision System and Active Sentry® Handpiece (Alcon Laboratories, Inc., USA). Note the presence of zonulopathy in elderly patients with nanophthalmos where particular attention was used to hold the fragments up without pressure on the capsule and zonule. Furthermore, to maintain consistent space and pressure within AC, OVD was injected prior to the withdraw of phaco or I/A probe. A single-piece foldable IOL with an appropriate IOL power [the maximum diopter IOL available in China is 36 diopter (D)] was implanted with loops placed at 3-9 position. The incision was slightly enlarged to ease the passing of thickened optics.

Modular surgical design 2: management of the potential MG through IZHV. Preferably utilizing 23G vitrector from Centurion, we performed a peripheral iridectomy through either a superior or inferior clear corneal incision. The diameter of the iris opening was carefully maintained at around 1-1.5 mm to enable the 23G vitrector to cut posteriorly through the zonule, hyaloid, and anterior vitreous under direct microscopic visualization. Further 23G vitrectomy at 5000 rpm was carried out in the anterior vitreous cavity briefly *via* the IZHV route to facilitate complete drainage of trapped aqueous inside the vitreous and reduce the volume of the vitreous (Figure 1). It is recommended not to excessively reduce the vitreous volume at once, and the extent of vitrectomy should be considered appropriate when the surgeon senses a balance of pressure in the anterior and posterior segments. We suggest placing the IZHV at the 11-1 or 5-7 o'clock area, necessitating the placement of IOL haptics at 3 and 9 o'clock. A bimanual I/A procedure was carried out using the 23G vitrector in cutter-off mode to clear any residual viscoelastic substance within the AC. Injecting 1 mg of triamcinolone acetonide (TA, 40 mg/mL) into the vitreous cavity *via* the IZHV route was employed to confirm the successful establishment of the IZHV route and aid in managing postoperative inflammation. It is important to note that the IOL power should be adjusted slightly toward the over-power spectrum (adding 0.5 to 1.0 D based on the results of the IOL master). This adjustment compensates for the restoration of the IOL-iris diaphragm through IZHV, causing the IOL-capsule complex to sit slightly backward.

Modular surgical design 3: management of the closed angle and glaucomatous optic neuropathy with either AGV or GSL. For patients underwent GSL, Carbachol (Bausch & Lomb Freida Pharmaceutical Co. LTD, Shandong Province, China) was used for pupil miosis and subsequently a viscoelastic-assisted blunt GSL under direct vision through intraoperative gonioscopy was accomplished to reopen the angle. GSL was performed for all clock hours that could be separated bluntly. For areas with dense peripheral anterior synechiae (PAS), forced separation was not attempted to avoid exacerbating intraocular inflammation due to bleeding. For patients underwent AGV implantation, a limbus-based conjunctival flap was made 8 mm posterior to the limbus in the superotemporal quadrant between rectus muscles. The device (Ahmed glaucoma drainage implant, model FP7; New World Medical Inc., CA, USA) was primed with 2 to 3 mL of balanced salt solution and was gently inserted into the sub-Tenon space. The plate was secured to the sclera 8 to 10 mm posterior to the limbus using 6-0 silk suture. And then, a rectangular scleral limbal-based flap of approximately 4×4 mm^2 was made. A 3-4 mm intrascleral tunnel was made between the front edge of the disc and the scleral flap using a 20-G blade. AC entry under the scleral flap was made with a 23-G needle to create a track parallel to the iris with the track beginning 1 to 2 mm posterior to the limbus. The tube was trimmed with an anterior-facing bevel with an estimated intracameral length
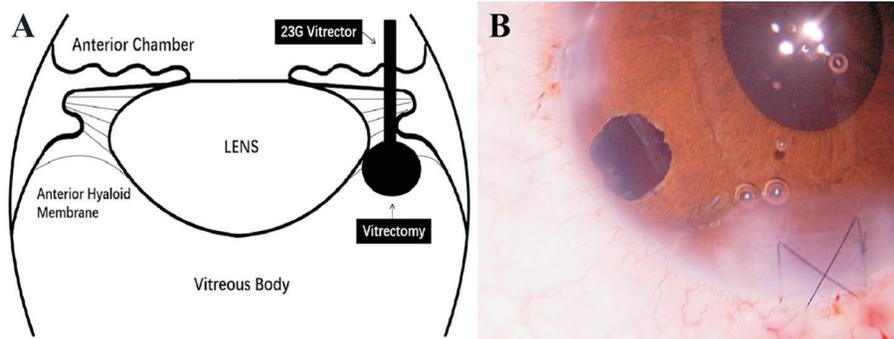
Figure 1 Irido-zonulo-hyaloid-vitrectomy (IZHV) diagram (A) and postoperative slit-lamp photography (B) The anterior chamber (AC) deepened immediately after IZHV, which indicated the complete drainage of trapped aqueous inside vitreous.

of 2 mm. The tube was passed through the intrascleral tunnel and the scleral track under the flap into the AC, positioned parallel to and close to the iris to minimize the risk of corneal endothelial loss. The starting part of the tube before entering the intrascleral tunnel was secured to the sclera with a 6-0 silk suture. The tube was covered by the previously created scleral flap, which was sutured with 10-0 nylon suture. Selectively, if concerning excessive early postoperative filtration, the tube can be ligated with absorbable adjustable restrictive sutures (8-0 Vicryl®) by creating two slipknots and left a longer suture end outside the conjunctiva. The suture would be released if the postoperative IOP exceeds 21 mm Hg with a stable AC. If the IOP remains within the normal range, the knots will still gradually loosen after approximately two weeks as the suture degrades and will be fully absorbed within 4 to 6wk, which helps prevent excessive aqueous humor filtration and shallow AC in the early postoperative period. The conjunctiva and Tenon's capsule were then interlocked with 8-0 Vicryl®. Appropriate OVD (DisCoVisc, Alcon Laboratories, Inc., USA) was further injected in the AC to prevent shallow AC after AGV implantation.

Modular surgical design 4: prophylactic or therapeutic management for UE by perioperatively anti-inflammatory treatment and scleral windows. One week before the surgical procedure, we administered systemic prednisone at a dosage of 1 mg/kg once daily and applied topical prednisolone acetate (Pred Forte, Prednisolone Acetate Ophthalmic Suspension) every 2h for 3-7d to proactively manage inflammatory response. Scleral window was performed under a triangular superficial scleral flap 5-6 mm from the limbus in the inferotemporal quadrant between the rectus muscles, measuring 3 to 4 mm in width. To expose the underlying choroid and establish the scleral window, a 1.5 mm×1.5 mm deep scleral flap was excised. The superficial scleral flap was then loosely sutured with a single 10-0 nylon suture at the flap tip to maintain a loose approximation at its original position. Finally, a parabulbar injection of 20 mg TA was administered to mitigate inflammation post-surgery.

Represent photographs of our surgical procedure was shown in Figure 2 and Video 1 (supplementary; the complete surgical procedures of the case in Figure 2, AL=15.42 mm, Procedure IV).

Post-operatively, antibiotic eyedrops 4 times daily were prescribed for 2wk. Additionally, systemic prednisone at 1 mg/kg, *q.d.* and topical prednisolone acetate ophthalmic suspension (Pred Forte) *q.2h.* were prescribed for 7d and tapered down according to the inflammation in each eye[16,18].

Additional Strategies Frequently Utilized in Challenging Situations In cases with extremely shallow AC, the iris hook placed under the primary corneal incision was frequently employed to prevent iris prolapse during capsulorhexis and phaco, and was removed after IOL implantation. Pupil conglutination or atresia was addressed by using OVD, blunt needles, and radial cutting of the pupil margin with capsular scissors. When necessary, the pupil was enlarged with 4-5 elastic iris hooks, especially note the one with sub-incisional placement which helped prevent prolapse of iris. Iris hooks should be placed in a stepwise fashion, enlarging the pupil while separating posterior synechia of the iris. In cases where the AC remained extremely shallow despite attempts with OVD, continuous circular capsulorhexis (CCC) was created with 23G Seibel capsulorhexis forceps from MST (with viewport, sharp tip, curved, MST SKU: DFH-0030) or discission needle (Video 1, supplementary). In situations involving zonulopathy, lifting the nucleus without tension on the capsular bag and zonule, along with low infusion parameter settings during phaco, was crucial to avoid iatrogenic zonular injury.

Statistical Analysis All statistical analyses were conducted using SPSS version 25 (SPSS, Inc., Chicago, IL, USA). The normality of variables was assessed using the Shapiro-Wilk test. Continuous variables with a normal distribution were expressed as mean±SD, while non-normally distributed data were presented as median (Q1, Q3). Chi-square test was employed for examining characteristics in different surgical procedures, gender, and surgical eye. Comparison
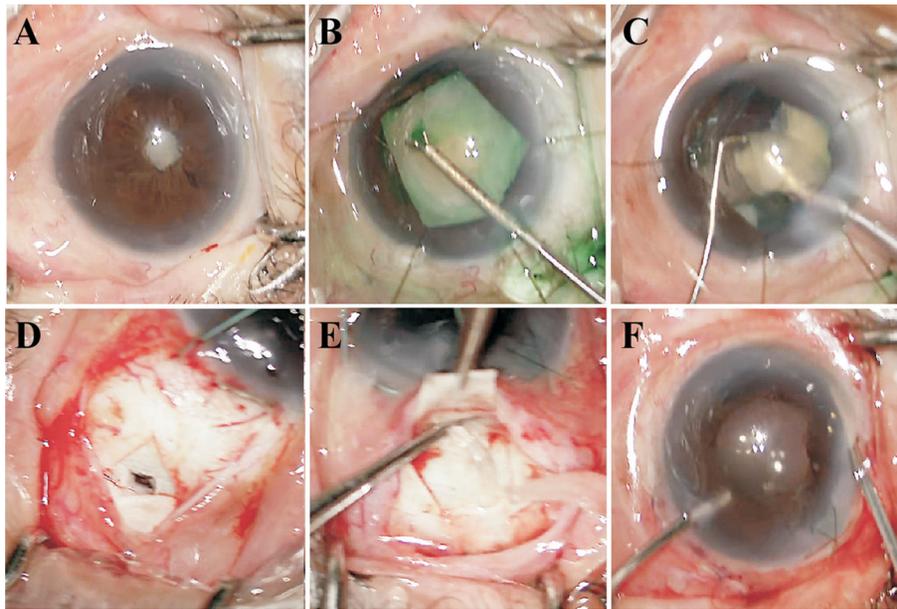
Figure 2 Represent photographs of our surgical procedures in a case of nanophthalmos with advanced glaucoma (axial length=15.42 mm, Procedure IV) A: Preoperative photographs showing the miosis and posterior synechia of the iris; B: Enlarge the pupil with elastic iris hooks, especially note the one with sub-incisional placement; C: Phaco lens extraction; D: Ahmed glaucoma Valve (AGV) implantation in a modified fashion in the superotemporal quadrant; E: Scleral window under a superficial scleral flap in the inferotemporal quadrant; F: Irido-zonulo-hyaloid-vitrectomy (IZHV) with a 23G vitrector.

of continuous data in normal distribution utilized one-way analysis of variance (ANOVA), and for non-normally distributed data, the Kruskal-Wallis test was applied. The IOP and CDVA at the final visit were contrasted with their preoperative counterparts using the paired-samples t-test for normally distributed data and the Wilcoxon signed-rank test for non-normally distributed data. Fisher's exact test was utilized to compare differences in complications between two groups. Univariate logistic regression analyses were utilized to identify factors associated with postoperative MG, UE and compromised CDVA. Multivariable logistic regression was further modeled with factors having a P value less than 0.2. A significance level of $P<0.05$ was considered statistically significant.

RESULTS

This study included 92 ACG eyes secondary to nanophthalmos from 62 patients, with a median age of 52 (range: 23-72)y. Among these patients, 51 (82%) were females. The demographic data and baseline characteristics of demographics are summarized in Table 1. The median AL for all eyes was 19.89 (17.38, 20.62) mm, ranging from 14.84 to 20.99 mm, and the median ACD was 1.87 (1.47, 2.20) mm. Follow-up duration ranged from 12 to 36mo, with a median of 19mo. At the final follow-up, the median IOP decreased from 21 (17, 36) mm Hg with a median of 3 (0, 4) medications preoperatively to 14 (12, 16) mm Hg postoperatively ($P<0.001$), and IOPs in all patients were maintained below 21 mm Hg without the need for anti-glaucoma medications. The median CDVA of patients

was significantly improved from 0.70 (0.40, 1.66) logMAR preoperatively to 0.65 (0.30, 1.08) logMAR postoperatively ($P<0.001$). The complete success rate was 77%.

Surgical procedures I, II, III, and IV were performed on 14, 26, 22, and 30 eyes, respectively. Patients in Procedure IV were the youngest ($P=0.001$) and had the shortest AL ($P<0.001$). They also had the highest number of preoperative anti-glaucoma medications ($P=0.01$), the poorest preoperative CDVA ($P<0.001$), and the most compromised postoperative CDVA ($P<0.001$). Additionally, ACG eyes in procedure II had a shorter AL than those in procedure I ($P=0.003$), and no significant difference in preoperative demographic and clinical characteristic was observed between Groups II and III. At the final follow-up, a significant reduction in IOP (all $P<0.001$) and an improvement in postoperative CDVA (all $P<0.001$) were all observed in each group. There were no significant differences in postoperative IOP ($P=0.60$) among groups.

Postoperative complications were identified in 18 eyes of 16 patients, and the details of complications in each group with different surgical procedures were listed in Tables 2 and 3. Across all subjects, early-stage complications included MG (9 eyes, 10%), UE (5 eyes, 5%), and suprachoroidal hemorrhage (1 eye, 1%). All of these complications occurred within the first postoperative month. Specifically, in each group, 2 (14%), 1 (4%), 3 (14%), and 3 (10%) eyes experienced MG; 0, 0, 3 (14%), and 2 (7%) eyes had UE; and 0, 0, 0, and 1 (3%) eye had suprachoroidal hemorrhage, respectively. While no significant statistical differences were observed in

Table 1 Summary of demographics and clinical characteristics of 92 eyes in 62 patients with angle-closure glaucoma secondary to nanophthalmos

Characteristics	Surgery procedure				P^a	P^b	P^c	Total (n=92)	P
	I (n=14)	II (n=26)	III (n=22)	IV (n=30)					
Gender[d] (male/female)	1/13	5/21	5/17	7/23	0.31	0.77	0.96	18/74	0.62
Eye[d] (right/left)	9/5	13/13	9/13	16/14	0.39	0.53	0.38	47/45	0.58
Age (y)	62.50 (56, 68.50)	54.50 (49, 61.50)	50 (39, 61.75)	40 (31.75, 54.50)	0.73	0.30	0.07	52 (38, 63)	0.001
AL (mm)	20.73 (20.48, 20.95)	20.26 (19.9, 20.68)	19.83 (18.87, 20.5)	16.81 (15.92, 17.59)	0.003	0.12	<0.001	19.89 (17.38, 20.62)	<0.001
ACD (mm)	1.99 (1.76, 2.13)	1.84 (1.43, 2.13)	2.09 (1.48, 2.34)	1.70 (1.25, 2.35)	0.27	0.14	0.24	1.87 (1.47, 2.20)	0.41
Pre-medications (n)	1 (0, 3)	2 (0, 4)	3 (0, 4)	4 (3, 4)	0.36	0.24	0.29	3 (0, 4)	0.01
Pre-IOP (mm Hg)	20 (12, 30)	20 (16, 32)	22 (18, 32)	29 (18, 39)	0.77	0.20	0.48	21 (17, 36)	0.17
Post-IOP[e] (mm Hg)	15 (12, 16)	14 (13, 16)	13 (12, 15)	14 (13, 16)	0.86	0.24	0.34	14 (12, 16)	0.60
Pre-CDVA (logMAR)	0.52 (0.14, 1.00)	0.51 (0.22, 0.87)	0.65 (0.43, 1.43)	1.61 (0.93, 2.30)	0.79	0.25	0.01	0.70 (0.40, 1.66)	<0.001
Post-CDVA[e] (logMAR)	0.31 (0, 0.57)	0.40 (0.10, 0.70)	0.56 (0.14, 1.08)	1.2 (0.73, 2,00)	0.43	0.15	0.01	0.65 (0.30, 1.08)	<0.001
Follow-up (mo)	15 (12, 17)	31 (21, 35)	22 (12, 33)	13 (12, 22)	0.001	0.14	0.06	19 (12, 31)	0.001

P: Difference between four groups (Kruskal-Wallis test); [a]P: Difference between I and II (Mann-Whitney U test); [b]P: Difference between II and III (Mann-Whitney U test); [c]P: Difference between III and IV (Mann-Whitney U test); [d]Differences in the eye and gender of each group were compared by Chi-square test; [e]Difference between Pre-IOP and Post-IOP (P<0.001) or Pre-CDVA and Post-CDVA (P<0.001). All data are presented as median (Q1, Q3) in for clarity. AL: Axial length; ACD: Anterior chamber depth; CDVA: Corrected distance visual acuity; IOP: Intraocular pressure; Pre-medications: Preoperative anti-glaucoma medications; Pre-IOP: Preoperative IOP; Pre-CDVA: Preoperative CDVA; Post-IOP: Postoperative IOP recorded at the final follow-up; Post-CDVA: Postoperative CDVA recorded at the final follow-up. Surgery Procedure I: Phaco+GSL; Surgery Procedure II: I+IZHV; Surgery Procedure III: Phaco+IZHV+AGV; Surgery Procedure IV: III+scleral window; Phaco: Phacoemulsification; GSL: Goniosynechialysis; IZHV: Irido-zonulo-hyaloid-vitrectomy; AGV: Ahmed glaucoma valve.

Table 2 Summary of postoperative complications in different surgery procedures

Postoperative complications	Surgery procedure					P^a	P^b	P^c
	I (n=14)	II (n=26)	III (n=22)	IV (n=30)	Total (n=92)			
Early-stage Complications, n (%)								
MG	2 (14)	1 (4)	3 (14)	3 (10)	9 (10)	0.28	0.32	0.69
UE	0	0	3 (14)	2 (7)	5 (5)	-	0.09	0.64
Suprachoroidal hemorrhage	0	0	0	1 (3)	1 (1)	-	-	1
Total	2 (14)	1 (4)	6 (27)	6 (20)	15 (16)			
Late-stage complications, n (%)								
Fibrin membrane	0	0	1 (5)	3 (10)	4 (4)	-	0.46	0.63
Uveitis	0	1 (4)	0	0	1 (1)	1	1	-
Macular edeme	0	0	1 (5)	0	1 (1)	-	0.46	0.42
Compromised CDVA	0	1 (4)	2 (9)	3 (10)	6 (7)	1	0.59	1

[a]P: Difference between I and II (Fisher's exact test); [b]P: Difference between II and III (Fisher's exact test); [c]P: Difference between III and IV (Fisher's exact test). Compromised CDVA, a decline of more than two lines on the visual acuity chart or a decrease to hand movement, light perception, or no light perception; Early-stage: Within 3mo; Late-stage: After 3mo; MG: Malignant glaucoma; UE: Uveal effusion; CDVA: Corrected distance visual acuity; Surgery Procedure I: Phaco+GSL; Surgery Procedure II: I+IZHV; Surgery Procedure III: Phaco+IZHV+AGV; Surgery Procedure IV: III+scleral window; Phaco: Phacoemulsification; GSL: Goniosynechialysis; IZHV: Irido-zonulo-hyaloid-vitrectomy; AGV: Ahmed glaucoma valve.

each postoperative complication among the four groups with different surgical procedures due to the relatively low incidence in each group. All these eyes underwent subsequent surgeries to address the complications, with all MG cases recovering after further IZHV, all eyes with UE recovering after additional full-thickness sclerotomy or scleral windows surgery. The eye affected by suprachoroidal hemorrhage experienced a decline in vision from light perception to no light perception. Late-stage complications beyond 3mo included fibrin membrane formation (4 eyes, 4%), uveitis (1 eye, 1%), macular edema (1 eye, 1%), and compromised CDVA (6 eyes, 7%). All eyes with intraocular exudate membrane were advanced glaucoma cases and underwent surgery for removal, resulting in improved visual acuity. Additionally, the eye that developed uveitis and the eye with macular edema after 1y recovered after receiving the dexamethasone intravitreal implant (OZURDEX®), but with compromised CDVA. During the follow-up period, none of the patients experienced corneal endothelial decompensation as a complication.

In the entire study population, univariate and multivariable models were constructed to identify risk factors for postoperative MG, UE and compromised CDVA. Among all

Table 3 Details of clinical characteristics of 18 eyes in 16 nanophthalmos with postoperative complications

No.	Surgery procedure	Age (y)	Gender	Eye	AL (mm)	Early-stage complications	Late-stage complications
1	I	44	M	L	20.06	MG	
2	II	32	F	L	20.79	MG	Uveitis, Compromised CDVA
2	I	32	F	R	20.74	MG	
3	III	51	M	R	16.15	UE	Compromised CDVA
4	III	61	F	L	19.85	MG	Fibrin membrane
5	III	56	F	R	20.99	UE	
6	III	41	F	L	18.50	MG	
7	III	49	F	L	20.26	MG	
8	III	34	M	R	17.45		Macular edeme, Compromised CDVA
9	III	31	F	R	18.09	UE	
10	IV	32	F	R	16.81	UE	Compromised CDVA
10	IV	32	F	L	16.45	Suprachoroidal hemorrhage	Compromised CDVA
11	IV	29	M	R	19.31	UE	Compromised CDVA
12	IV	50	F	R	15.84		Fibrin membrane
13	IV	31	F	R	15.32	MG	Fibrin membrane
14	IV	40	M	R	16.86	MG	
15	IV	65	F	R	16.60		Fibrin membrane
16	IV	36	F	L	17.54	MG	

AL: Axial length; M: Male; F: Female; L: Left; R: Right; MG: Malignant glaucoma; UE: Uveal effusion; CDVA: Corrected distance visual acuity; Surgery Procedure I: Phaco+GSL; Surgery Procedure II: I+IZHV; Surgery Procedure III: Phaco+IZHV+AGV; Surgery Procedure IV: III+scleral window; Phaco: Phacoemulsification; GSL: Goniosynechialysis; IZHV: Irido-zonulo-hyaloid-vitrectomy; AGV: Ahmed glaucoma valve.

clinical characteristics, only younger age was significantly associated with a higher risk of MG [odds ratio (OR): 1.06, 95%CI=1.004 to 1.12, P=0.04], UE (OR: 1.07, 95%CI=1.001 to 1.15, P=0.046) and compromised CDVA (OR: 1.11, 95%CI=1.11 to 1.21, P=0.02). Additionally, the development of a fibrin membrane 3mo after surgery was associated with MG (OR: 7.62, 95%CI=1.09 to 53.49, P=0.04). The majority of eyes (4/6) with compromised CDVA were affected by UE (3 eyes) or suprachoroidal hemorrhage (1 eye), showing a significant correlation (OR: 84, 95%CI=9.29 to 759.40, P<0.001). The other two eyes were affected by uveitis and macular edema respectively.

DISCUSSION

In this study, we first introduced a modular surgical approach optionally incorporating phaco, IZHV, GSL/AGV, and scleral windows to tailor the treatment for ACG secondary to nanophthalmos. This approach was developed by comprehensively considering the diverse disease processes and clinical features, taking into account the associated risks for specific complications based on previous studies and our clinical experiences. Following this sequence of surgeries in our case series, IOPs in all patients were maintained below 21 mm Hg without the need for anti-glaucoma medications at the final follow-up visit. Moreover, the occurrence of complications leading to visual deterioration was 7% (6 eyes), which is notably lower than the rates reported in prior studies (65%-87%)[19-20].

The removal of the lens in eyes with ACG secondary to nanophthalmos serves to reduce AC crowding and facilitate the opening of the angle, thereby alleviating obstruction of the filtration meshwork and establishing reconstruction of aqueous outflow[10-11,21]. However, the AC might not deepen when encountering MG, which is the most frequently complication with an incidence of 20%-38% in previous literatures[5,19], especially in eyes with a shorter AL undergoing phaco[10]. The pathophysiology of MG in nanophthalmos is intricate and not fully understood. Contributing factors include the abnormal permeability of the anterior hyaloids, expansion of the choroid, and the presence of thickened and structurally abnormal sclera[5,7,22-23]. These collectively lead to increased vitreous pressure, resulting in the anterior displacement of CZLHV. Intraoperatively, the positive vitreous pressure can be detected when maintaining the AC becomes difficult together with an increased IOP as we encountered in eyes underwent Procedure II, despite that we had already optimized the phaco settings to reduce the risk of misdirecting fluid into vitreous. IZHV, which could directly and effectively create a communication passage through the CZLHV and then balance the pressures of the anterior and posterior segments, was the standard solution in this circumstance as we implemented in Procedure II, III and IV. Consequently, the incidence of MG in our study was low (9 eyes, 10%). While IZHV does not provide an absolute guarantee against MG. In our study, among the preoperative characteristics, we observed that

younger age was associated with the development of MG. This might be attributed to the denser vitreous fibers and larger vitreous volume in younger patients, conducting more pressure from choroidal expansion and create a predisposed higher positive vitreous pressure, which could also be a possible pathogenic factor for the presentation of severe ACG at a younger age, as suggested in our previous study[24]. Meanwhile, severe postoperative inflammation presented as fibrin membrane formation after 3mo was found to be related to the occurrence of MG in our study. Inflammation induced the formation of fibrin membranes, which might be invisible in the early stage after surgery, potentially closing the passage created by IZHV on the CZLHV, still lead to aqueous fluid misdirection. In such circumstances, immediate additional IZHV or YAG laser to reopen the passage can be effective, and we did discern the presence of a membrane during these procedures. For cases with severe inflammation, IZHV is more effective than YAG since it can reopen the passage, further reduce the volume of vitreous, and drain the inflammation directly. This was evident in our patients with MG, as eyes that didn't recover from YAG treatment improved after IZHV. This also emphasizes the benefits of aggressive anti-inflammatory treatment[18], as implemented in patients undergoing IZHV in our study. Although further study is warranted to elucidate the pathogenesis of MG, the positive vitreous pressure initially posed by the short eyes or secondary to the misdirection of aqueous humor caused by the abnormality in CZLHV (such as zonulopathy)[25-26] or inflammation appears to be the key mechanism for this complication.

Other studies have also recommended pars plana vitrectomy to address this issue; however, it cannot ensure comprehensive communication between the anterior and posterior segments. Some surgeons may opt to debulk more vitreous during pars plana vitrectomy to prevent MG, but excessive debulking of core vitreous may raise the risk of UE by diminishing the supportive effect of vitreous on the choroid and retina, creating space for choroidal expansion. Additionally, due to the challenges in determining the position of the pars plana in nanophthalmic eyes, retinal tears may result from pars plana vitrectomy[27-28]. Given these considerations, IZHV should be the standard prophylactic and therapeutic approach for MG in nanophthalmos. In our initial practice, we performed a relatively extensive anterior vitrectomy in a few young patients with higher positive vitreous pressure. However, two of them experienced severe UE after surgery. These further underscores the importance of exercising caution to prevent excessive debulking of the core vitreous in such cases. When MG is initiated, the immediate implementation of IZHV can interrupt the progression into a vicious circle and promptly restore visual acuity, thereby no decline in CDVA from MG was

observed in our patients. Hence, adopting a graded incremental approach to debulk vitreous through several rounds of IZHV could be a more secure option in cases with high risk of UE.

Unlike MG, UE poses a potential catastrophic complication, occasionally accompanied by suprachoroidal hemorrhage when it occurs suddenly and dramatically, leading to the rupture of choroidal vessels and causing severe visual impairment or even complete vision loss. This was evident in our study, where 67% eyes exhibited compromised vision due to UE, despite that all cases of UE recovered after additional scleral windows or vortex decompression. In nanophthalmos eyes, UE may develop spontaneously or after an uncomplicated anterior segment surgery such as cataract surgery. Different theories regarding the pathophysiology of UE have been speculated, including vortex vein compression, choroidal permeability changes, and decreased scleral permeability[29]. Although the precise mechanism for UE remains unclear, effective prevention and management rely on maintaining a delicate balance of pressure between the vitreous and the suprachoroidal space.

In our study, almost all eyes with AL less than 18 mm or pre-operative evidence of UE, which indicate a higher pressure in the suprachoroidal space, underwent prophylactic scleral windows to minimize the risk of UE during and after surgery[30]. This may explain why the incidence of UE in Group IV was not higher than that in Group III. Still, we only found younger age was associated with postoperative UE, possibly because younger individuals are more likely to have a more complex pathogenesis leading to early onset and faster progression. In our clinic, younger patients may also exhibit more anxiety about vision loss, a psychological factor suggested by previous studies as contributing to the risk of glaucoma progression[31-33] and UE development[34]. Additionally, eyes with higher preoperative IOP and thick, curved scleral vessels observed (Figure 3) during surgery may have a higher risk of UE and may benefit from prophylactic scleral windows. However, for these specific cases, only prophylactic scleral windows might not be enough, the risk of UE is still high as the vitreous pressure decreased by vitreous debulking through IZHV and AGV. Thus, we employed various techniques to address this challenge. These techniques included graded incremental approach to debulk vitreous during IZHV guided by the injection of TA to ensure the successful establishment of the passage without excessive debulking, and ligating the tube of AGV with absorbable adjustable restrictive sutures to prevent hypotony. With these preventive approaches, the incidence of UE was relatively low in our study (5 eyes, 5%). Notably, a 32-year-old patient with all the aforementioned risk factors experienced suprachoroidal hemorrhage five days after the surgical procedure, resulting in
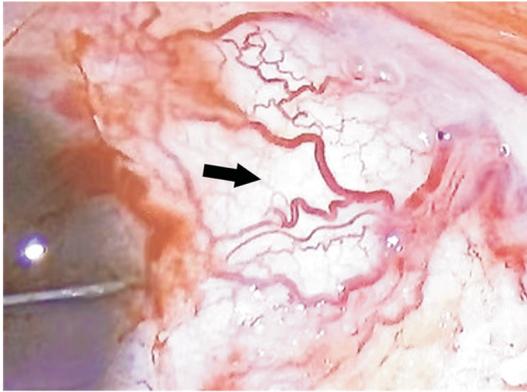
Figure 3 Curved scleral vessels (black arrow) observed in a case of nanophthalmos (axial length=17.15 mm, Procedure IV) during surgery Surgery Procedure IV: Phaco+IZHV+AGV+scleral window; Phaco: Phacoemulsification; IZHV: Irido-zonulo-hyaloid-vitrectomy; AGV: Ahmed glaucoma valve.

the loss of preoperative light perception in her left eye. Despite a more meticulous prevention strategy, she, still anxious about potential vision loss, encountered UE in her right eye two weeks after the same procedure, which fortunately recovered after more extensive scleral windows without any deterioration in visual acuity. This underscores the need for continued efforts to identify high-risk patients preoperatively and modify surgical strategies to avoid such disastrous complications. We suggest that general anesthesia and perioperative psychotherapy could be additional options for patients with severe anxiety.

Regarding the surgical details of the scleral window, various techniques have been employed in previous studies. Given that eyes with UE often exhibit ciliary effusion and detachment first[35], implying that UE may initiate peripherally and progress posteriorly, we positioned the scleral window at 6 mm from the limbus (or even 5 mm in eyes with AL<15 mm). We utilized a triangular and side-based superficial scleral flap, aligning the flap tip with a needle gently to prevent direct contact and adhesion between the scleral window and Tenon's capsule. In cases with concomitant AGV in the superior temporal quadrant, inferior two-quadrant windows were the typical choice in our cases. Additional windows in the superior nasal quadrant and more extensive scleral window in 2-4 quadrants might be considered as options to treat subsequent UE. In patients with Procedure IV requiring a second sclerostomy, partial healing of the initial scleral window was observed, which may account for the occurrence of UE in these cases. However, given the short interval since the original surgery, the flap could still be reopened with relative ease. The exact timeline of healing at the sclerostomy site remains unclear, as we have not had the opportunity to assess long-term healing outcomes. However, the absence of UE beyond one month postoperatively suggests that the early postoperative period

is the critical window for UE development. This highlights both the necessity and effectiveness of our surgical design—combining perioperative anti-inflammatory treatment with the creation of scleral windows—in preventing uveal effusion during this vulnerable stage.

When addressing closed-angle and glaucomatous optic neuropathy in nanophthalmic eyes, it's important to note that these eyes have a narrower anterior segment compared to primary angle-closure glaucoma (PACG)[5], and synechial angle closure is prone to persist after surgery. Therefore, GSL is a crucial surgical procedure that involves stripping peripheral anterior synechiae from the angle wall to restore trabecular function. GSL alone is often sufficient for ensuring adequate trabecular function in cases of acute ACG and chronic ACG with angle adhesion ≤180° and without or with early stage glaucomatous optic neuropathy. For patients with significant angle adhesion who were already in advanced stages of glaucoma, it was eventually essential to resort to filtration surgery to maintain IOP within the desired low teens, as recommended by others[36]. Here, we consider AGV to be a reasonable choice that may serve as an alternative to trabeculectomy. This preference is based on the fact that the AC is adequately deepened after lens extraction and IZHV to accommodate the tube. Additionally, in nanophthalmic eyes, the conjunctiva is often too thick to form a functional bleb in the context of trabeculectomy. It's noteworthy that, despite having a shorter AL, nanophthalmic eyes do not exhibit a significant reduction in orbital volume, providing ample space for AGV implantation. Although AGV incorporates a valve to prevent hypotony, ligating the tube of AGV with absorbable adjustable restrictive sutures was recommended in cases with high risks for UE, such as young patients with extremely short eyes. Although placing the tube into the sulcus may offer better protection for the corneal endothelium, it increases technical difficulty, especially in nanophthalmic eyes with a very narrow sulcus and large, thick ciliary processes. Improper technique may lead to damage of the capsular bag or bleeding from the ciliary processes. The absence of corneal endothelial decompensation during the follow-up period supports the safety of AC tube implantation. However, sulcus tube insertion remains a viable alternative, depending on specific factors such as poor preoperative endothelial status, severe PAS, and the surgeon's preference.

Several limitations in this study should be considered. First, it was a retrospective, non-comparative case series. However, the outcomes of this surgical modular approach in this study provide insights that could potentially optimize personalized surgical treatment for these challenging cases. For instance, with younger patients, a more preventive approach should be considered to mitigate the risk of MG and UE. Second,

although this modular approach has been firmly established in our clinical practice over the past 5y, ongoing minor adjustments continue to evolve based on accumulated clinical experience. We firmly believe that the surgeon's judgment and experience in managing challenging and complex cases are indispensable in clinical practice. This holds true even when standard protocols are applied in randomized controlled trials assessing surgical outcomes. And we believe these individualized approaches have played a significant role in achieving successful IOP control with fewer severe complications in this study. This subjectivity implies that our results may not be universally applicable to other practitioners or patient populations. Third, the precision in documenting complications such as UE may not be exhaustive. Minor peripheral effusions may have been overlooked, and cases with early-stage shallow AC, effectively treatable with pharmacotherapy and YAG laser, were not categorized as MG in our study. Nevertheless, the strength of this study lies in its large sample size for a rare and complex disease, our specific and extensive experience in this field may offer significant value for the management of these challenging cases.

Above all, the modular surgical approach involving phaco, IZHV, AGV, and scleral windows, customized with individualized surgical designs, is both theoretically and practically safe and effective for managing ACG secondary to nanophthalmos. With specific surgical details evolved in our clinical practice, this approach could potentially serve as a standard surgical suite for ACG secondary to nanophthalmos. However, further evidence-based clinical studies, designed with a thorough understanding of the underlying pathogenesis, are still necessary to refine the management of these refractory and challenging cases.

REFERENCES

1 Guo CC, Zhao ZN, Chen DH, *et al*. Detection of clinically relevant genetic variants in Chinese patients with nanophthalmos by trio-based whole-genome sequencing study. *Invest Ophthalmol Vis Sci* 2019;60(8):2904-2913.

2 Foster PJ, Broadway DC, Hayat S, *et al*. Refractive error, axial length and anterior chamber depth of the eye in British adults: the EPIC-Norfolk Eye Study. *Br J Ophthalmol* 2010;94(7):827-830.

3 Tay T, Smith JE, Berman Y, *et al*. Nanophthalmos in a Melanesian population. *Clinical Exper Ophthalmology* 2007;35(4):348-354.

4 Rajendrababu S, Shroff S, Uduman MS, *et al*. Clinical spectrum and treatment outcomes of patients with nanophthalmos. *Eye (Lond)* 2021;35(3):825-830.

5 Guo CC, Zhao ZN, Zhang DD, *et al*. Anterior segment features in nanophthalmos with secondary chronic angle closure glaucoma: an ultrasound biomicroscopy study. *Invest Ophthalmol Vis Sci* 2019;60(6):2248-2256.

6 Lu Q, He WW, Lu Y, *et al*. Morphological features of anterior segment: factors influencing intraocular pressure after cataract surgery in nanophthalmos. *Eye Vis (Lond)* 2020;7(1):47.

7 Quigley HA, Friedman DS, Congdon NG. Possible mechanisms of primary angle-closure and malignant glaucoma. *J Glaucoma* 2003;12(2):167-180.

8 Ally N, Ismail S, Alli HD. Prevalence of complications in eyes with nanophthalmos or microphthalmos: protocol for a systematic review and meta-analysis. *Syst Rev* 2022;11(1):25.

9 Jung KI, Yang JW, Lee YC, *et al*. Cataract surgery in eyes with nanophthalmos and relative anterior microphthalmos. *Am J Ophthalmol* 2012;153(6):1161-1168.e1.

10 Yosar JC, Zagora SL, Grigg JR. Cataract surgery in short eyes, including nanophthalmos: visual outcomes, complications and refractive results. *Clin Ophthalmol* 2021;15:4543-4551.

11 He MY, Feng JR, Zhang L. Treatment of nanophthalmos cataracts: surgery and complications. *Semin Ophthalmol* 2022;37(7-8):849-855.

12 Rajendrababu S, Babu N, Sinha S, *et al*. A randomized controlled trial comparing outcomes of cataract surgery in nanophthalmos with and without prophylactic sclerostomy. *Am J Ophthalmol* 2017;183:125-133.

13 Steijns D, Bijlsma WR, Van der Lelij A. Cataract surgery in patients with nanophthalmos. *Ophthalmology* 2013;120(2):266-270.

14 Yu X, Fan Z, Shi Y. Surgical strategy of angle closure glaucoma secondary to lens subluxation. *Ophthalmology (China)* 2023;32(5):363-368.

15 Shi Y, Oatts J, Tian JX, *et al*. Low-dose transscleral cyclophotocoagulation with subsequent phacoemulsification in the treatment of prolonged acute primary angle closure. *Br J Ophthalmol* 2023;107(2):221-226.

16 Yu XW, Zhao ZN, Zhang DD, *et al*. Anterior vitrectomy, phacoemulsification cataract extraction and irido-zonulo-hyaloid-vitrectomy in protracted acute angle closure crisis. *Int Ophthalmol* 2021;41(9):3087-3097.

17 Carnahan MC, Platt LW. Serial paracenteses in the management of acute elevations of intraocular pressure. *Ophthalmology* 2002;109(9):1604-1606.

18 Yu XW, Zhang M, Zhao HX, *et al*. Nanophthalmos-Associated MYRF gene mutation facilitates intraocular inflammation in mice. *Int Immunopharmacol* 2024;137:112519.

19 Yalvac IS, Satana B, Ozkan G, *et al*. Management of glaucoma in patients with nanophthalmos. *Eye* (*Lond*) 2008;22(6):838-843.

20 Singh OS, Belcher CD, Simmons RJ. Nanophthalmic eyes and neodymium-YAG laser iridectomies. *Arch Ophthalmol* 1987;105(4):455-456.

21 Hoffman RS, Vasavada AR, Allen QB, *et al*. Cataract surgery in the small eye. *J Cataract Refract Surg* 2015;41(11):2565-2575.

22 Jin SW, Caprioli J. Long-term treatment outcomes for malignant glaucoma. *Ophthalmol Glaucoma* 2024;7(3):282-289.

23 Sharma A, Sii F, Shah P, *et al*. Vitrectomy-phacoemulsification-vitrectomy for the management of aqueous misdirection syndromes in phakic eyes. *Ophthalmology* 2006;113(11):1968-1973.

24 Shi Y, Tian JX, Han Y, *et al*. Pathogenic role of the vitreous in angle-closure glaucoma with autosomal recessive bestrophinopathy: a case report. *BMC Ophthalmol* 2020;20(1):271.

25 Grzybowski A, Kanclerz P. Acute and chronic fluid misdirection syndrome: pathophysiology and treatment. *Graefes Arch Clin Exp Ophthalmol* 2018;256(1):135-154.

26 Sadeghi R, Momeni A, Fakhraie G, *et al*. Management of malignant glaucoma. *J Curr Ophthalmol* 2022;34(4):389-397.

27 Zhang Z, Zhang S, Jiang X, *et al*. Combined 23-G pars plana vitrectomy and lensectomy in the management of glaucoma associated with nanophthalmos. *Ophthalmic Res* 2018;59(1):37-44.

28 Ohkita T, Emi K, Toyoda E, *et al*. Efficacy of vitreous surgery for uveal effusion syndrome. *Nippon Ganka Gakkai Zasshi* 2008;112(5):472-475.

29 Özdek Ş, Yalınbaş Yeter D, Özmen MC, *et al*. Treatment of nanophthalmos-related uveal effusion with two- *vs*. four-quadrant partial-thickness sclerectomy and sclerotomy surgery. *Turk J Ophthalmol* 2022;52(1):37-44.

30 Yang N, Jin SY, Ma LL, *et al*. The pathogenesis and treatment of complications in nanophthalmos. *J Ophthalmol* 2020;2020(1):6578750.

31 Shin DY, Jung KI, Park HYL, *et al*. The effect of anxiety and depression on progression of glaucoma. *Sci Rep* 2021;11:1769.

32 Zhang DD, Fan ZG, Gao XB, *et al*. Illness uncertainty, anxiety and depression in Chinese patients with glaucoma or cataract. *Sci Rep* 2018;8:11671.

33 Zhang DD, Sun NN, Guo CC, *et al*. Psychological stress induces moderate pathology in the ganglion cell layer in mice. *Mol Vis* 2022;28:451-459.

34 Sesar A, Sesar AP, Jurisic D, *et al*. Unraveling the puzzle of central serous chorioretinopathy: exploring psychological factors and pathophysiological mechanisms. *Med Sci Monit* 2023;29:e941216.

35 Shen ZJ, Shen L, Wang H. Clinical characteristics and surgical treatment of idiopathic uveal effusion syndrome. *Int J Ophthalmol* 2022;15(4):604-608.

36 Razeghinejad MR, Myers JS. Contemporary approach to the diagnosis and management of primary angle-closure disease. *Surv Ophthalmol* 2018;63(6):754-768.