frontiers | Research Topics

Update on glaucoma research: from basic science to clinical practice

Edited by
Alessio Martucci, Maria Dolores Pinazo-Duran and Carlo Nucci

Published in
Frontiers in Medicine

ISSN 1664-8714
ISBN 978-2-8325-6107-2
DOI 10.3389/978-2-8325-6107-2

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Update on glaucoma research: from basic science to clinical practice

Topic editors

Alessio Martucci — University of Rome Tor Vergata, Italy

Maria Dolores Pinazo-Duran — Ophthalmic Research Unit "Santiago Grisolia", Foundation for the Promotion of Health and Biomedical Research of the Valencian Community, Spain

Carlo Nucci — University of Rome Tor Vergata, Italy

Citation

Martucci, A., Pinazo-Duran, M. D., Nucci, C., eds. (2025). *Update on glaucoma research: from basic science to clinical practice*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-6107-2

Table of contents

frontiers | Frontiers in Medicine

TYPE Editorial
PUBLISHED 27 February 2025
DOI 10.3389/fmed.2025.1572755

OPEN ACCESS

EDITED AND REVIEWED BY
Jodhbir Mehta,
Singapore National Eye Center, Singapore

*CORRESPONDENCE
Alessio Martucci
✉ alessio.martucci@live.it

RECEIVED 07 February 2025
ACCEPTED 17 February 2025
PUBLISHED 27 February 2025

CITATION
Martucci A, Pinazo-Duran MD and Nucci C (2025) Editorial: Update on glaucoma research: from basic science to clinical practice. *Front. Med.* 12:1572755. doi: 10.3389/fmed.2025.1572755

Editorial: Update on glaucoma research: from basic science to clinical practice

Alessio Martucci[1]*, Maria Dolores Pinazo-Duran[2] and Carlo Nucci[1]

[1]Ophthalmology Unit, Department of Experimental Medicine, University of Rome "Tor Vergata", Rome, Italy, [2]Ophthalmic Research Unit "Santiago Grisolia", Foundation for the Promotion of Health and Biomedical Research of the Valencian Community, Valencia, Spain

KEYWORDS

glaucoma, MIGS, tonometry, quality of life (QoL), microRNA (miRNA), acid uric levels, limbal stem cell deficiency (LSCD), blood pressure variability (BPV)

Editorial on the Research Topic
Update on glaucoma research: from basic science to clinical practice

Glaucoma remains one of the leading causes of irreversible blindness worldwide. As an insidious disease often asymptomatic in its early stages, it poses unique challenges for timely diagnosis and treatment. This Research Topic sheds light on various aspects of glaucoma, ranging from factors leading to delayed diagnosis, innovations in intraocular pressure (IOP) measurement, the role of systemic health, neurodegenerative aspects and novel treatment approaches (1, 2).

In this context, a qualitative study by Liu et al. exploring factors associated with delayed ophthalmological consultation in primary glaucoma patients identified four major barriers: subtle onset of symptoms, insufficient patient awareness, perceived challenges in accessing care, and inadequate support systems. These findings underscore the urgent need for improved public health initiatives, patient education, and streamlined referral pathways to encourage early detection and prevent irreversible vision loss. Healthcare professionals should prioritize educating at-risk populations and integrating community-based screening programs to effectively address these barriers (Liu et al.).

Accurate IOP measurement is also critical to glaucoma management. In a comparative study between the Goldmann Applanation Tonometry and the SUOER SW-500 Rebound Tonometer, Chaung et al. revealed that the latter provides comparable readings within the normal IOP range but may underestimate elevated pressures. While rebound tonometry offers advantages such as portability and disposable probes to minimize infection risk, clinicians should remain cautious when relying solely on this method in patients with high IOP. Future research should explore the refinement of non-contact tonometry techniques to improve precision and reliability (Chaung et al.).

Novel biomarkers also offer a promising avenue for improving glaucoma diagnosis, prognosis, and treatment response assessment. By identifying molecular, genetic, and biochemical markers associated with glaucomatous neurodegeneration, clinicians may be able to detect the disease earlier, differentiate subtypes, and personalize treatment strategies. Biomarkers found in the aqueous humor, tear film, blood, and even imaging-based parameters could provide valuable insights into disease mechanisms and therapeutic targets (3).

In this context, given the neuroprotective role of uric acid (UA) in neurodegenerative diseases, its relationship with glaucoma has been the subject of investigation.

A meta-analysis of multiple studies authored by Mohammadi et al. revealed that while glaucoma patients tend to have slightly higher serum UA levels than controls, the difference is not statistically significant. While these findings do not establish UA as a definitive biomarker for glaucoma, further longitudinal research is necessary to elucidate its potential role in the pathogenesis of the disease (Mohammadi et al.).

In a recent molecular research Yu et al. also identified apoptosis-related microRNAs (miRNAs) as potential biomarkers in glaucoma. Elevated levels of hsa-miR-193a-5p and hsa-miR-222-3p in aqueous humor and lens capsules suggest their involvement in glaucoma pathophysiology. The downregulation of PTEN, a key regulatory gene, further supports their role in retinal ganglion cell apoptosis. These findings pave the way for novel diagnostic and therapeutic strategies leveraging miRNA modulation (Yu et al.).

Evaluating local and systemic aspects is essential for comprehensive glaucoma management, as they may impact treatment response, disease progression, and overall patient outcomes. A multidisciplinary approach integrating ophthalmology, cardiology, neurology, and internal medicine may help optimize glaucoma care and preserve visual function.

As the incidence of glaucoma rises globally, patients require prolonged medical therapy and multiple surgeries, increasing the risk of systemic and local adverse events such as limbal stem cell deficiency (LSCD) risk.

In glaucoma, LSCD can be associated with multiple limbal surgeries, bullous keratopathy, mitomycin C, 5-fluorouracil, and preservatives in topical treatments. Using confocal microscopy and optical coherence tomography Nakakura et al. have demonstrated limbal epithelial thinning in glaucoma patients using topical medications.

Vascular dysregulation, systemic hypertension, hypotension, diabetes, obstructive sleep apnea, and neurodegenerative disorders have also all been implicated in the pathophysiology of glaucoma (4–6).

In this regard, a large population-based cohort study by Lee et al. examined the impact of visit-to-visit blood pressure variability (BPV) on the risk of open-angle glaucoma (OAG) in normotensive individuals. While BPV was not associated with an increased overall risk of OAG, younger individuals (<60 years) with high systolic BPV had a significantly higher risk of developing the disease. These findings highlight the need for a more nuanced approach to monitoring cardiovascular and ocular health, particularly in younger patients (Lee et al.).

Furthermore, glaucoma not only affects visual function but also has a significant impact on the psychological wellbeing of patients. A study by Kopilaš and Kopilaš assessing quality of life (QOL) and psychological distress in glaucoma patients demonstrated strong correlations between disease progression, decreased visual acuity, and increased anxiety and depression.

Although observational studies have suggested a link between glaucoma and psychiatric conditions such as depression, insomnia, and schizophrenia, a Mendelian Randomization study by Zhang et al. and a study of anxiety in glaucoma by Lin et al. found no causal relationship between these conditions. These results indicate that psychiatric conditions in glaucoma patients are more likely to be due to modifiable factors rather than genetic predisposition.

The chronic nature of glaucoma, coupled with the gradual loss of vision, underscores the importance of holistic patient care. This highlights the need for targeted psychological support and intervention strategies rather than attributing mental health challenges to inherent disease risk. Mental health support should be integrated into routine glaucoma management to improve overall patient outcomes (Kopilaš and Kopilaš; Zhang et al.; Lin et al.).

Advancements in surgical techniques, such as Micro-invasive glaucoma surgery (MIGS), have improved the safety profile of glaucoma surgery, offering less invasive options with faster recovery times. Nevertheless, the selection of the appropriate surgical approach requires careful evaluation of patient-specific factors to optimize outcomes and minimize complications.

A recent retrospective study evaluated cases of ocular hypertension following EyeCee One preloaded intraocular lens (IOL) implantation. The findings indicated a significant increase in IOP in a subset of patients, emphasizing the importance of careful postoperative monitoring, especially in individuals with a history of glaucoma. González-Martín-Moro et al. suggest that clinicians should remain vigilant about potential IOP fluctuations and consider alternative IOL options where necessary.

MIGS has gained traction as a safer alternative to traditional surgery. A retrospective study by Hajduga-Szewczyk et al. evaluating iStent implantation in conjunction with cataract surgery demonstrated significant reductions in IOP and reliance on topical medications. However, patients with higher preoperative IOP showed limited benefit, suggesting that single iStent implantation may be insufficient in uncontrolled glaucoma cases. Further research to optimize MIGS techniques is warranted (Hajduga-Szewczyk et al.).

Recent advancements in glaucoma research highlight the multifaceted nature of the disease, spanning early detection, systemic influences, mental health considerations, and evolving treatment modalities. A concerted effort to improve patient education, refine diagnostic tools, integrate psychological support, and expand surgical options will be critical to mitigating the global burden of glaucoma. In the future, interdisciplinary collaboration among ophthalmologists, primary care physicians, mental health professionals, and researchers will be essential in developing a comprehensive, patient-centered approach to glaucoma care.

Author contributions

AM: Conceptualization, Writing – original draft, Writing – review & editing. MP-D: Writing – original draft, Writing – review & editing, Conceptualization. CN: Writing – original draft, Writing – review & editing, Conceptualization.

Acknowledgments

We sincerely appreciate the valuable contributions of the Authors to this Research Topic and acknowledge their efforts.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Martucci A, Cesareo M, Toschi N, Garaci FG, Bagetta G, Nucci C. Brain networks reorganization and functional disability in glaucoma. *Prog Brain Res.* (2020) 257:65–76. doi: 10.1016/bs.pbr.2020.07.007

2. Martucci A, Nucci C, Pinazo-Durán MD. Editorial: New perspectives in glaucoma pathophysiology, diagnosis, and treatment. *Front Med.* (2023) 10:1200427. doi: 10.3389/fmed.2023.1200427

3. Pinazo-Durán MD, Zanón-Moreno V, García–Villanueva C, Martucci A, Peris-Martínez C, Vila-Arteaga J, et al. Biochemical–molecular–genetic biomarkers in the tear film, aqueous humor, and blood of primary open-angle glaucoma patients. *Front Med.* (2023) 10:1157773. doi: 10.3389/fmed.2023.1157773

4. Nucci C, Martucci A, Mancino R, Cerulli L. Glaucoma progression associated with Leber's hereditary optic neuropathy. *Int Ophthalmol.* (2013) 33:75–7. doi: 10.1007/s10792-012-9623-4

5. Nucci C, Martucci A, Martorana A, Sancesario GM, Cerulli L. Glaucoma progression associated with altered cerebral spinal fluid levels of amyloid beta and tau proteins. *Clin Exp Ophthalmol.* (2011) 39:279–81. doi: 10.1111/j.1442-9071.2010.02452.x

6. Cesareo M, Giannini C, Martucci A, Di Marino M, Pocobelli G, Aiello F, et al. Links between obstructive sleep apnea and glaucoma neurodegeneration. *Progr Brain Res.* (2020) 257:19–36. doi: 10.1016/bs.pbr.2020.07.010

frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 06 July 2023
DOI 10.3389/fmed.2023.1161568

OPEN ACCESS

EDITED BY
Yong Tao,
Capital Medical University, China

REVIEWED BY
Siqi Xiong,
Central South University, China
Katarzyna Krysik,
Wojewódzki Szpital Specjalistyczny nr 5
Sosnowiec, Poland

*CORRESPONDENCE
Shunsuke Nakakura
✉ shunsukenakakura@yahoo.co.jp

RECEIVED 08 February 2023
ACCEPTED 14 June 2023
PUBLISHED 06 July 2023

CITATION
Nakakura S, Maruoka S, Chikama T, Nagata Y, Terao E, Ueda K, Dote S and Oogi S (2023) Case report: Medical treatment for limbal epithelial stem cell deficiency in patients treated for glaucoma.
Front. Med. 10:1161568.
doi: 10.3389/fmed.2023.1161568

Case report: Medical treatment for limbal epithelial stem cell deficiency in patients treated for glaucoma

Shunsuke Nakakura[1]*, Sachiko Maruoka[1,2], Taiichiro Chikama[3], Yuki Nagata[1], Etsuko Terao[1], Kanae Ueda[1], Saki Dote[1] and Satomi Oogi[1]

[1]Department of Ophthalmology, Saneikai Tsukazaki Hospital, Himeji, Japan, [2]Ikuno Eye Clinic, Osaka, Japan, [3]Department of Ophthalmology and Visual Sciences, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan

Limbal epithelial stem cell deficiency (LSCD) is an abnormal corneal epithelial lesion with several causes. The patient was diagnosed using fluorescein staining. Bullous keratopathy, multiple surgeries, and drug-related damage can cause LSCD in glaucoma patients. We evaluated the medical treatment course for LSCD in patients with glaucoma. We retrospectively reviewed the electronic medical records of patients diagnosed with LSCD and investigated their background, course of treatment, and classification stages of LSCD before and after treatment. The global consensus classification system (stages IA–C, IIA–B, and III) proposed by Deng et al. (Cornea 2020) was used. Seven patients (two males) and eight eyes were studied. The median age of the patients was 82 years, and the mean duration of glaucoma treatment was 8 years. The patients had open-angle glaucoma (four eyes), exfoliation glaucoma (one eye), neovascular glaucoma (one eye), normal tension glaucoma (one eye), and uveitic glaucoma (one eye). Stage classifications at diagnosis were stage IA in four eyes and stages IC, IIA, IIB, and III in one eye each. All treatments were carried out with dry eye drops, steroid eye drops, and antibiotics. The mean duration of treatment was 1.4 years. The classifications at the time of the final visit were normal corneal epithelium (three eyes), stage IA (two eyes), IIA (one eye), and III (two eyes). Three eyes (37%) improved by more than one stage and one eye deteriorated by more than one stage. LSCD is long-lasting and difficult to treat in a short period; thus, it requires careful medical attention.

KEYWORDS

glaucoma, limbal epithelial stem cell deficiency, cornea, anti-glaucoma, topical

1. Introduction

Limbal epithelial stem cells (LSCs) exist in the basal epithelium of the limbus between the transparent cornea and the opaque sclera. The normal limbus and LSCs act as a barrier against invasion of the conjunctival epithelium onto the corneal surface. (1) Most LSCs live in the superior and inferior corneal limbus (niche) called the palisades of Vogt. (2) Damage to the LSCs by many factors leads to LSC deficiency (LSCD), which leads to abnormal instability of the corneal epithelium. LSCD involves the replacement of the normal corneal epithelium with the conjunctival epithelium, recurrent corneal epithelium defects, neovascularization, inflammation, and scaring

(1). These problems lead to decreases in visual acuity and ocular discomfort. The representative causes of LSCD are chemical injury, Steve-Johnson's syndrome, allergic ocular surface diseases, contact lens wear, and chronic lid disease (1). Related causes of glaucoma include multiple surgeries involving the limbus (2), bullous keratopathy (3), mitomycin C (4), 5-fluorouracil (5), and preservertives (6). Recently, glaucoma has become the leading cause of irreversible blindness in the world (7) and the number of newly diagnosed cases is increasing (estimated 111.8 million individuals in 2040) (8). Glaucoma patients will have long-term and multiple uses of anti-glaucoma medications and may have several glaucoma surgeries throughout life due to increased life expectancy, which may increase the incidence of LSCD. Previously, confocal microscopy and impression cytology showed how topical glaucoma medications induced limbal modification due to increased inflammatory responses (9). Confocal microscopy and anterior segment optic coherence tomography showed thinning of the limbal epithelium thickness in patients with glaucoma who used topical glaucoma medications (10, 11). Some reports suggested LSCD was induced by glaucoma surgery (2, 5, 12), repairs with amniotic membrane transplantation, or conjunctival limbal autografts (5). LSCD induced by soft contact lens wear was shown to be resolved by cessation of contact lens wear and topical corticosteroids, artificial tears, and antibiotics (13, 14). However, the effects of medical treatments for LSCD in glaucoma patients remain unknown. In this case series, we present an analysis of eight eyes with LSCD in glaucoma patients who were treated medically.

2. Case description

This retrospective cross-sectional comparative study was approved by the Institutional Review Board of Lanikai Tsukazaki Hospital (IRB No. 221019) and performed in accordance with the tenets of the Declaration of Helsinki. Information from the electronic database of the Department of Ophthalmology, Samika Tsukazaki Hospital, was collected between August 2021 and March 2022. Our electronic medical records for the past 10 years were reviewed according to the diagnosis of "limbal epithelial stem cell deficiency" and "glaucoma." The inclusion criteria were as follows: (1) minimal follow-up period of 1 month, (2) previous or ongoing treatment for LSCD, (3) existing slit-lamp photography before and after treatment, and (4) use of topical anti-glaucoma medications for more than 1 year. After eliminating two patients (one without clear photography and one who used glaucoma drugs for only 2 months), eight eyes of seven patients with both LSCD and glaucoma treatment were evaluated. We used the latest global consensus classification system for LSCD (1). The classifications were based on the extent of corneal and limbal involvement; that is, whether the visual axis or central 5 mm of the cornea was affected (stages I or II and III) and whether more than 50% of the LSCs were intact (A: <50%, B: ≥50 and < 100%, and C: 100%). In stage III, the entire corneal surface is affected. All the regimens for topical glaucoma medication were carried out by SN, and the various regimen for LSCD was performed by SM or TC. Staging of LSCD using slit lamp photography at both the initial diagnosis and the final visit was performed by SN and SM. The patient backgrounds are shown in Table 1. Among the eight eyes of seven patients, the median age of the two male patients was 82 years (range: 70–87 years), and the median duration of glaucoma medical treatment was 8 years (range: 6–15 years). The glaucoma types were primary open-angle glaucoma (four eyes), exfoliation glaucoma (one eye), normal tension glaucoma (one eye), neovascular glaucoma (one eye), and uveitic glaucoma (one eye). Only two eyes had previously undergone glaucoma surgery. The LSCD classifications at the initial diagnosis and the final visit are shown in Table 2 and Figure 1 (upper panel and lower panel,

TABLE 1 Patient backgrounds.

Patient	Eye	Sex	Age	Glaucoma type	Estimated duration of glaucoma eye drop (years)	Other ophthalmic diseases	Previous glaucoma surgery	Visual acuity at diagnosis (logMAR)	Visual acuity at final visit (logMAR)	Endothelial cell densities (cells/mm^2)
1	R	F	73	NVG	9	Proliferative diabetic retinopathy and blepharitis	–	0	0	1,347
2	L	F	70	POAG	6	Ptosis	–	0.5	0.19	2,572
3	R	M	87	POAG	12	–	–	0	0.1	1,316
4	L	F	83	NTG	15	Trichiasis	–	0.5	0.12	2,371
5	L	M	82	Uveitic glaucoma	7	Cytomegalovirus uveitis and ptosis	Trabeculectomy with MMC, needling with MMC	0.1	0.7	746
6	R	F	82	Exfoliation glaucoma	9	Macula hole	Ahmed implant	1.9	1.8	1,167
7	R	F	71	POAG	7	–	–	0.1	0	1859
	L			POAG	7	–	–	−0.2	−0.2	2,245

NVG, neovascular glaucoma; POAG, primary open angle glaucoma; NTG, normal tension glaucoma; MMC, mitomycin C.

TABLE 2 Changes of stages in limbal epithelial stem cells deficiency with treatment and the treatment regime.

Patient	Eye	Staging of LSCD at initial diagnosis	Staging of LSCD at final visit	Improvement (↑)/no change (→)/ aggravation (↓)	Duration of treatment for LSCD (years)	Regime for LSCD	Use of topical glaucoma eye drops during the treatment of LSCD
1	R	IA	0	↑	2	2% rebamipide, 0.3% ofloxacin ophthalmic ointment, artificial tears eye drop	Latanoprost/Carteolol Fixed Combination
2	L	IIB	0	↑	1.3	3% diquafosol sodium, 0.1% fluorometholone, artificial tears eye drop	Tafluprost
3	R	IA	IA	→	1.3	0.3% ofloxacin ophthalmic ointment	Tafluprost
4	L	IA	0	↑	1.5	0.1% fluorometholone	Brimonidine/brinzolamide fixed combination
5	L	IC	III	↓	1	0.1% betamethasone, 0.3% ofloxacin ophthalmic ointment	Dorzolamide/Timolol Fixed Combination
6	R	III	III	→	0.75	0.1% fluorometholone	Tafluprost + Dorzolamide/ Timolol Fixed Combination
7	R	IIA	IIA	→	2	0.1% fluorometholone, 1.5% levofloxacin	–
	L	IA	IA	→	2	0.1% fluorometholone, 1.5% levofloxacin	–

LSCD: limbal epithelial stem cells deficiency.

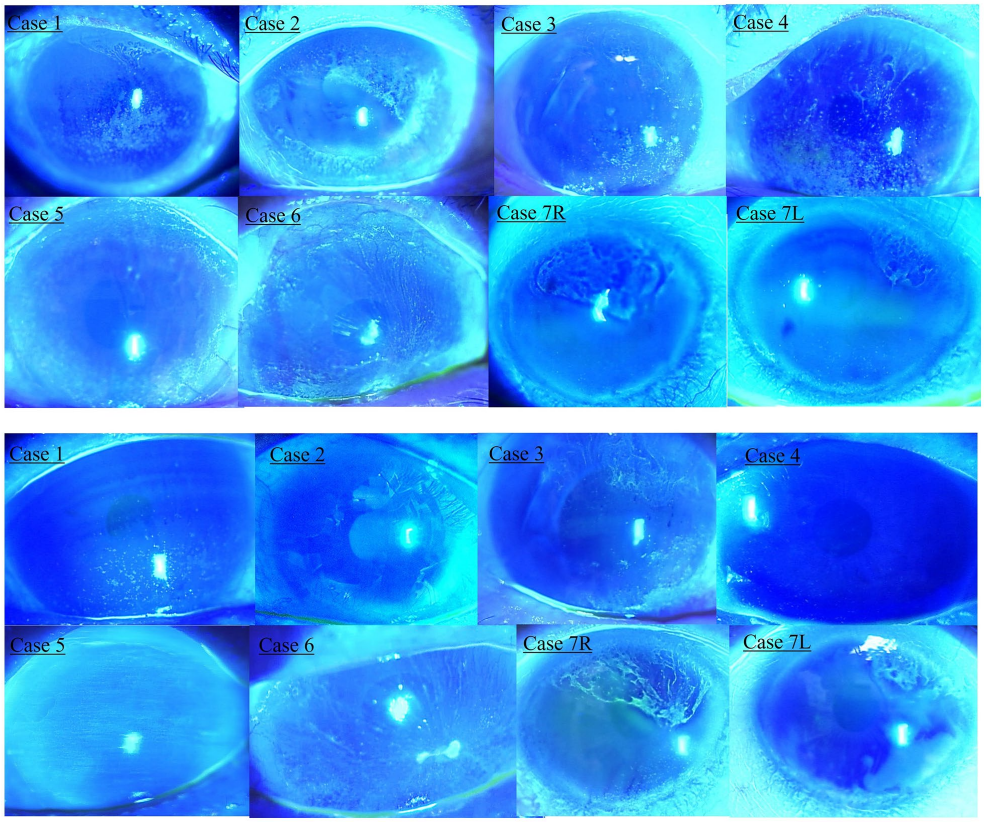

FIGURE 1
Slit lamp photography of limbal epithelial stem cell deficiency (LSCD) at the initial diagnosis and final visit. Upper panel shows LSCD photography at the initial diagnosis. Lower panel shows LSCD photography at the final visit.

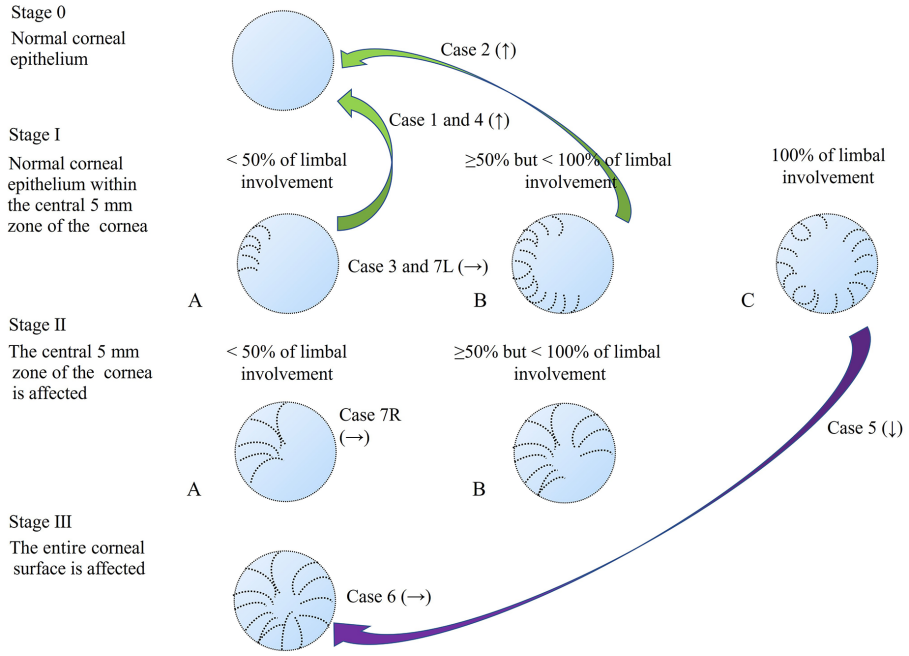

FIGURE 2
Staging of LSCD1 and changes in staging after treatment. The green arrow shows the improvement (↑) in the stage with the case number. The purple arrow indicates the aggravation (↓) of the stage with the number of cases. No change (→) showed with the case number.

respectively). The median treatment duration for LSCD was 1.4 years (range: 0.75–2 years). Treatment regimens mostly consisted of topical dry eye drops, low-concentrate corticosteroids, topical antibiotics, and ointment. The frequency of topical eye drops and ointments use depended on the LSCD situation. At the initial diagnosis of LSCD, the number of eyes in each stage was IA (four eyes), IC (one eye), IIA (one eye), IIB (one eye), and III (one eye). At the final visit, the number of eyes in each stage was as follows:0, normal corneal epithelium (three eyes); IA (two eyes); IIA (one eye); and III (two eyes). Three eyes (37%) showed more than one category of improvement, and one eye (12%) showed aggravation in more than one category (Figure 2). Visual acuity (logomark) did not improve significantly after treatment ($p = 0.828$, paired t-test). Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this article.

3. Discussion

The current study is the first to analyze the medical treatment outcomes of LSCD in patients who had been treated for glaucoma. Our results showed that some eyes improved (37%) and only one eye (12%) worsened despite relatively longer treatment. A previous medical treatment study for LSCD in patients with contact lens wearers was over a mean follow-up of 15 months (range, 4–60 months) (14). All eyes achieved a stable cornea and the function and niche of LSCs or both were reversible (14). Additionally, another study on contact lens-induced LSCD showed that 16 eyes recovered medically, but two eyes needed surgical intervention (13). Contact lens users were relatively younger and were not exposed to the toxicity of topical medications compared to glaucoma patients. Glaucoma medications induce inflammation, dry eye, tear film instability, and meibomian gland dysfunction (15, 16). These medications cannot be stopped because they are required to prevent high intraocular pressure. Therefore, recovery from LSCD in glaucoma patients will be more difficult and will require longer time periods than soft contact lens users who develop LSCD. A total of 63% of the patients in our study maintained the same stage or deteriorated despite medical treatment. In these patients, the function and niche of LSCs or both may become irreversible due to structural changes caused by long-term exposure to drugs. In our cases, two eyes (25%) underwent glaucoma surgery. Case 5, who underwent trabeculectomy with mitomycin C and needling with mitomycin C, was the only patient who experienced worsened LSCD (stage IC to III). This was probably due to 7 years of glaucoma medications, filtering surgery with mitomycin C, and ongoing bullous keratopathy (endothelial cell density 746 cells/mm2), which led to aggregate LSCD. Three eyes [stage IA (two eyes) and stage IIB (one eye)] recovered completely to stage 0 after more than 1 year of treatment. The other four eyes maintained the same stage after 9 months to 2 years of treatment. It is difficult to discontinue glaucoma medications because of the need to prevent glaucoma progression. This affects recovery from the LSCD. Topical antiglaucoma medication was discontinued only in case 7; however, the stage did not change before and after treatment for LSCD. The purpose of medical therapy is to: (1) stop traumatic or toxic insults to the limbus, and (2) optimize the ocular surface environment by improving the tear film, controlling inflammation, and promoting differentiation of the healthy epithelium (14). In the current study, we used corticosteroids in six of eight patients to decrease inflammation. Artificial tear eye drops and 3% diquafosol sodium are also useful for stabilizing the tear film (17). Rebamipide 2% can modify epithelial cell function, improve tear stability, and suppress

inflammation (18). Additionally, ofloxacin ointment is useful for tear lipid layer treatment, which contributes to tear stability (19). When medical therapy proves ineffective, which unfortunately happens frequently, surgical intervention should be considered (20). In such cases, a sequential conjunctival epitheliectomy is often performed as the initial procedure. This is followed by the transplantation of lost limbal cells, typically achieved through either a conjunctival limbal autograft or a keratolimbal allograft (20).

4. Conclusion

LSCD is long-lasting and difficult to treat in a short period; thus, it requires careful medical attention.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by IRB of Tsukazaki Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this article.

Author contributions

SN, SM, and TC designed and supervised the study. SN and TC analyzed and interpreted the data and drafted the manuscript. Data collection was performed by SN, ET, YN, KU, SD, and SO. SN, SM, TC, YN, ET, KU, SD, and SO were responsible for data acquisition. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Deng SX, Borderie V, Chan CC, Dana R, Figueiredo FC, Gomes JAP, et al. Global consensus on definition, classification, diagnosis, and staging of limbal stem cell deficiency. *Cornea*. (2019) 38:364–75. doi: 10.1097/ICO.0000000000001820

2. Muthusamy K, Tuft SJ. Iatrogenic limbal stem cell deficiency following drainage surgery for glaucoma. *Can J Ophthalmol*. (2018) 53:574–9. doi: 10.1016/j.jcjo.2018.01.037

3. Uchino Y, Goto E, Takano Y, Dogru M, Shinozaki N, Shimmura S, et al. Long-standing bullous keratopathy is associated with peripheral conjunctivalization and limbal deficiency. *Ophthalmology*. (2006) 113:1098–101. doi: 10.1016/j.ophtha.2006.01.034

4. Sauder G, Jonas JB. Limbal stem cell deficiency after subconjunctival mitomycin C injection for trabeculectomy. *Am J Ophthalmol*. (2006) 141:1129–30. doi: 10.1016/j.ajo.2006.01.018

5. Pires RT, Chokshi A, Tseng SC. Amniotic membrane transplantation or conjunctival limbal autograft for limbal stem cell deficiency induced by 5-fluorouracil in glaucoma surgeries. *Cornea*. (2000) 19:284–7. doi: 10.1097/00003226-200005000-00005

6. Lin Z, He H, Zhou T, Liu X, Wang Y, He H, et al. A mouse model of limbal stem cell deficiency induced by topical medication with the preservative benzalkonium chloride. *Invest Ophthalmol Vis Sci*. (2013) 54:6314–25. doi: 10.1167/iovs.12-10725

7. World Glaucoma Association. Glaucoma information. Available at: https://www.glaucomapatients.org/basic/statistics/. (Accessed August 18, 2022).

8. Gedde SJ, Vinod K, Wright MM, Muir KW, Lind JT, Chen PP, et al. Primary open-angle glaucoma preferred practice pattern®. *Ophthalmology*. (2021) 128:P71–P150. doi: 10.1016/j.ophtha.2020.10.022

9. Mastropasqua R, Agnifili L, Fasanella V, Curcio C, Brescia L, Lanzini M, et al. Corneoscleral limbus in glaucoma patients: *in vivo* confocal microscopy and immunocytological study. *Invest Ophthalmol Vis Sci*. (2015) 56:2050–8. doi: 10.1167/iovs.14-15890

10. Güçlü H, Çınar AK, Çınar AC, Akaray İ, Şambel Aykutlu M, Sakallıoğlu AK, et al. Corneal epithelium and limbal region alterations due to glaucoma medications evaluated by anterior segment optic coherence tomography: a case-control study. *Cutan Ocul Toxicol*. (2021) 40:85–94. doi: 10.1080/15569527.2021.1902341

11. Chan EH, Chen L, Yu F, Deng SX. Epithelial thinning in limbal stem cell deficiency. *Am J Ophthalmol*. (2015) 160:669–677.e4. doi: 10.1016/j.ajo.2015.06.029

12. Sun Y, Yung M, Huang L, Tseng C, Deng SX. Limbal stem cell deficiency after glaucoma surgery. *Cornea*. (2020) 39:566–72. doi: 10.1097/ICO.0000000000002249

13. Jeng BH, Halfpenny CP, Meisler DM, Stock EL. Management of focal limbal stem cell deficiency associated with soft contact lens wear. *Cornea*. (2011) 30:18–23. doi: 10.1097/ICO.0b013e3181e2d0f5

14. Kim BY, Riaz KM, Bakhtiari P, Chan CC, Welder JD, Holland EJ, et al. Medically reversible limbal stem cell disease: clinical features and management strategies. *Ophthalmology*. (2014) 121:2053–8. doi: 10.1016/j.ophtha.2014.04.025

15. Fineide F, Lagali N, Adil MY, Arita R, Kolko M, Vehof J, et al. Topical glaucoma medications—clinical implications for the ocular surface. *Ocul Surf*. (2022) 26:19–49. doi: 10.1016/j.jtos.2022.07.007

16. Soriano D, Ferrandez B, Mateo A, Polo V, Garcia-Martin E. Meibomian gland changes in open-angle glaucoma users treated with topical medication. *Optom Vis Sci*. (2021) 98:1177–82. doi: 10.1097/OPX.0000000000001782

17. Park DH, Chung JK, Seo DR, Lee SJ. Clinical effects and safety of 3% diquafosol ophthalmic solution for patients with dry eye after cataract surgery: a randomized controlled trial. *Am J Ophthalmol*. (2016) 163:122–131.e2. doi: 10.1016/j.ajo.2015.12.002

18. Kashima T, Itakura H, Akiyama H, Kishi S. Rebamipide ophthalmic suspension for the treatment of dry eye syndrome: a critical appraisal. *Clin Ophthalmol*. (2014) 8:1003–10. doi: 10.2147/OPTH.S40798

19. Goto E, Dogru M, Fukagawa K, Uchino M, Matsumoto Y, Saiki M, et al. Successful tear lipid layer treatment for refractory dry eye in office workers by low-dose lipid application on the full-length eyelid margin. *Am J Ophthalmol*. (2006) 142:264–270.e1. doi: 10.1016/j.ajo.2006.03.022

20. Schwartz GS, Holland EJ. Iatrogenic limbal stem cell deficiency: when glaucoma management contributes to corneal disease. *J Glaucoma*. (2001) 10:443–5. doi: 10.1097/00061198-200112000-00001

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 17 July 2023
DOI 10.3389/fmed.2023.1161980

OPEN ACCESS

EDITED BY
Alessio Martucci,
University of Rome Tor Vergata, Italy

REVIEWED BY
Ning Fan,
Shenzhen Eye Hospital, China
Massimo Cesareo,
University of Rome Tor Vergata, Italy
Federico Carlucci,
Policlinico Tor Vergata, Italy,
in collaboration with reviewer MC

*CORRESPONDENCE
Wei Liu
✉ weiliu05@tmu.edu.cn

RECEIVED 09 February 2023
ACCEPTED 22 June 2023
PUBLISHED 17 July 2023

CITATION
Liu H, Chen C, Chen Z, Li Q, Li Q and Liu W (2023) Factors associated with delayed first ophthalmological consultation for primary glaucoma: a qualitative interview study. *Front. Med.* 10:1161980. doi: 10.3389/fmed.2023.1161980

Factors associated with delayed first ophthalmological consultation for primary glaucoma: a qualitative interview study

Hua Liu, Chen Chen, Zhuo Chen, Qian Li, Quan Li and Wei Liu*

Tianjin Key Laboratory of Retinal Functions and Diseases, Tianjin Branch of National Clinical Research Center for Ocular Disease, Eye Institute and School of Optometry, Tianjin Medical University Eye Hospital, Tianjin, China

Background: Glaucoma has an insidious onset with non-specific early symptoms, often leading patients to delay in seeking help. However, postponing the first ophthalmological consultation can result in delayed diagnosis and treatment, with adverse effects on vision. This study explored the factors associated with delayed first ophthalmological consultation in patients with primary glaucoma, with the overarching aim of informing measures to reduce delayed consultation and avoid the consequent adverse outcomes.

Methods: We adopted a phenomenological approach. Semi-structured interviews were conducted with patients admitted to a tertiary eye hospital in Tianjin, China, from January 2021 to April 2021. Data were analyzed by Colaizzi's seven-step method.

Results: We identified 46 patients with primary glaucoma who delayed their first ophthalmological consultation for various reasons. There were four major themes and 16 sub-themes. The major themes were as follows: (1) occult symptoms that are difficult to identify; (2) insufficient knowledge and understanding of glaucoma-related risks and harm; (3) perceived difficulties in accessing medical care; and (4) inadequate support system.

Conclusion: In order to avoid patient delay and consequent irreversible damage to the visual field in patients with primary glaucoma, it is essential that medical staff identify symptoms more effectively, change habitual medical behavior of the patients, adopt a medical union model, and promote the use of a social medical support system to address practical difficulties in delivering adequate care.

KEYWORDS

delayed consultation, glaucoma, medical care behavior, occult symptoms, visual field damage

Background

Glaucoma is the main cause of irreversible blindness globally, with pathological elevated intraocular pressure being the major risk factor. Elevated intraocular pressure levels and the intolerance of the optic nerve to this pressure lead to optic nerve atrophy and visual field defects (1). Glaucoma was estimated to have affected 79.6 million people worldwide in 2020, and this

number is anticipated to increase to 111.8 million in 2040 (2, 3), with Asia proposed to have the highest incidence (4).

Notably, approximately 50% of patients are not aware that they have glaucoma (5). Glaucoma poses a serious threat to vision, as its development is insidious and the early symptoms are atypical. Clinical manifestations of glaucoma overlap with those of few degenerative brain and digestive system diseases (6). In order to improve the early diagnosis and treatment of glaucoma, efforts have been made to construct predictive genetic risk models (7) and a glaucoma self-reporting system (8), and establish the relationship between the risk assessment of systemic diseases and glaucoma (9). Nevertheless, these approaches have been unable to significantly improve delays in first ophthalmological consultation for primary glaucoma.

In 1946, Pack and Gallo first described the concept of "patient delay," in which a patient delays seeking help. A delay of ≥3 months has been defined as an undue delay (10). Eissa et al. (11) divided the total delay into three stages: patient delay, diagnosis delay, and treatment delay. Prior et al. (12) divided the medical treatment delay into patient delay and healthcare provider delay. Patient delay refers to a delay in seeking care by the patient, while healthcare provider delay includes both detection delay and service delay. Detection delay refers to a delay in investigations by a healthcare professional to diagnose glaucoma. Service delay refers to a delay in referring the patient to a glaucoma specialist and a delay in glaucoma treatment.

A high proportion of patients with glaucoma experience irreversible damage to their vision due to a delay in their first ophthalmological consultation. Jones et al. (13) investigated 10,766 patients with glaucoma who attended a glaucoma clinic for the first time in Britain and Tanzania. Data from the British glaucoma clinic showed that 4.6% of patients already had severe visual field damage in one or both eyes. Data from Tanzania were even more alarming, with 44.7% of patients already having severe visual field damage in one or both eyes. Other epidemiological data from Africa showed that the proportion of glaucoma cases with delayed first ophthalmological consultation was as high as 50%; the degree of visual impairment in severe cases had already reached the level of blindness (14). Thus, as glaucoma is a chronic ophthalmic disease, early detection and treatment is crucial to retard progressive damage to the visual field, ensure patient quality of life, conserve medical resources, and reduce the burden of care imposed by the onset of blindness.

At present, factors associated with delays in first ophthalmological consultation in patients with glaucoma are unclear. Therefore, the objective of this study was to determine causes of first ophthalmological consultation delay by interviewing patients with glaucoma who had previously delayed their first ophthalmological consultation. Determination of the underlying factors for such delays would facilitate improvements in the early detection of glaucoma and reduce the incidence of consequent adverse outcomes.

Methods

Study participants

This study used a purposive sampling method, and the sample size was based on the principle of information saturation. Participants were selected from inpatients admitted to the glaucoma ward of a tertiary eye hospital in Tianjin, China, from January 2021 to April 2021. The inclusion criteria were as follows: intraocular pressure >21 mmHg; glaucomatous optic nerve changes and glaucomatous visual field defects in one or both eyes at the first ophthalmological visit; requirement for glaucoma treatment; and ability and willingness to express the full details of the process leading to the delay of their first ophthalmological consultation.

Research method

Theoretical basis

The theoretical basis for our investigation was that the first ophthalmological consultation delay can be caused by both patient delay and seeking care delay; this was supported by the results of our literature review (11, 12) (Figure 1). Thus, this theoretical basis was used to ensure that the interview content reached saturation.

Interview outline

Semi-structured interviews were used to collect data. A preliminary interview outline was formulated based on our study objective and literature review. We then consulted one qualitative research expert, two nursing master graduate students, two glaucoma experts, and one glaucoma ward nurse to revise the interview outline. Two glaucoma patients who met the inclusion criteria of this study were selected via a convenience sampling method for a pre-interview, which was performed to ensure that the interview questions were clear and understandable. The interview outline was subsequently finalized.

The interview questions were as follows: (1) "Do you know the disease from which you suffer? What is it?"; (2) "What troubles and difficulties did you encounter in the process of detecting symptoms, determining that you were sick, deciding to seek care, choosing a hospital, and starting treatment and monitoring?"; (3) "Please recall the influence of your work, economic state, and family life on your first ophthalmological consultation and medical treatment"; and (4) "Please recall the influence of your knowledge level and medical treatment attitude on first seeking ophthalmological consultation."

Data collection method

The interview was conducted in the glaucoma ward. Before starting the interview, the purpose of the study was explained to the patients. It was clarified that the interview recording was to be used only for medical research and that the research results would be summarized anonymously. After obtaining consent, the interview process, including non-linguistic expressions such as expression, tone, and gesture, were recorded. The interview process was based on the principle that patients fully expressed the details of their experience with delaying their first ophthalmological consultation. The interview was ended when no new information was procured.

Data analysis method

After the interview, Colaizzi's seven-step method (15) was used to analyze the data. Two researchers listened to the recordings after each interview was completed, to determine the degree of saturation of the data. After confirming data saturation, transcription personnel transcribed the recordings for consistency calibration. The text was carefully and repeatedly read and subsequently imported into

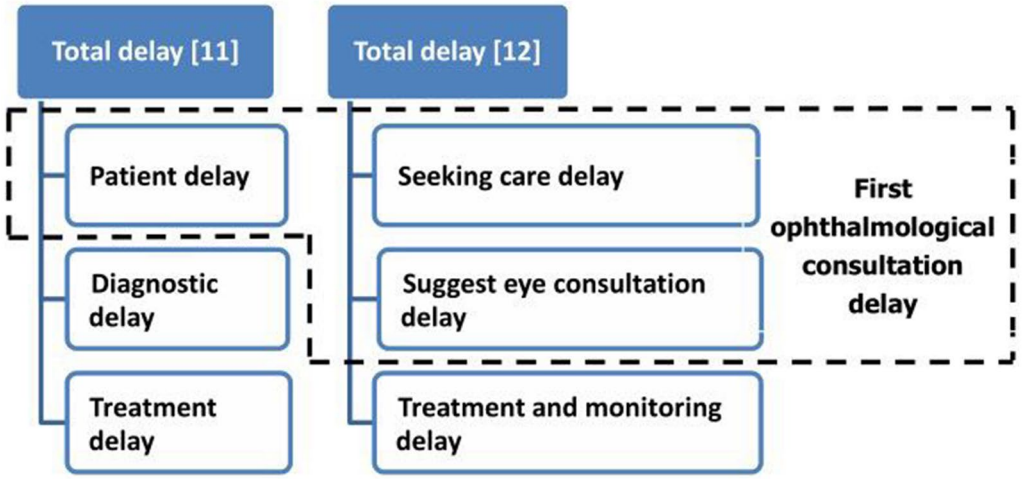

FIGURE 1
Theoretical basis of first ophthalmological consultation delay. The theoretical basis for our investigation was that the first ophthalmological consultation delay can be caused by both patient delay and seeking care delay.

Nvivo12[1] to identify significant statements, formulate meaning, cluster themes, develop exhaustive descriptions, and produce the fundamental structure.

Results

Forty-six patients with glaucoma, who delayed their first ophthalmological consultation and subsequently received glaucoma treatment, were enrolled in this study. There were 29 primary angle closure glaucoma (PACG) patients (11 males, 18 females) with a mean age of 64.07 ± 7.33. The delay time ranged from 3 to 24 months with a median of 7 (3, 14) months, and most of the caregivers were spouses (21/29, 72.41%). Among these 29 PACG patients, 10 were retired, 8 were unemployed and had pensions, and 11 were other professionals, covering multiple occupations. In terms of medical insurance, 27 patients had medical insurance and only 2 patients did not. The degree of visual field impairment from mild to severe was as follows: 5 patients with binocular paracentral scotoma (PS), 4 patients with monocular PS and the other eye nasal step (NS), 8 patients with monocular PS and the other eye wedge-shaped depression (WSD), and 3 patients with monocular NS and the other eye WSD. There were 17 primary open angle glaucoma (POAG) patients (9 males, 8 females) with a mean age of 67.29 ± 7.30, and there was no statistical difference in age between PACG patients and POAG patients (independent sample t test, $p = 0.156$). The delay time ranged from 3 to 24 months with a median of 15 (10, 20.5) months. There was a significant difference between the two groups in delayed first ophthalmological consultation (Wilcoxon rank sum test, $p = 0.008$). Most of the caregivers were spouses (13/17, 76.47%), which is similar to that of PACG patients. Among these 17 POAG patients, 7 were retired, and 10 were other professionals, covering multiple occupations, but there were no unemployed individuals. The degree of visual field impairment from mild to severe was as follows: 2 individuals with monocular PS and NS in the other eye, 2 individuals with binocular NS, 2 individuals with monocular NS and WSD in the other eye, and the other 11 individuals with moderate to severe visual field injury (11/17, 64.71%). The general information of the respondents is shown in Table 1.

Analysis of the interview data resulted in the extraction of 1,396 effective semantic reference points, duplicate semantic reference points were 269 items. Four major themes and sixteen sub-themes were formed. The four themes were related to aspects of disease recognition, symptom confusion, hazard cognition, and the support system, and were defined as follows: (1) occult symptoms are difficult to identify; (2) insufficient knowledge and understanding of glaucoma-related risks and harm; (3) perceived difficulties in accessing medical care; and (4) inadequate support system. The specific interview content is shown in Table 2.

Glaucoma symptoms are occult and difficult to identify

The first major theme included five sub-themes, which covered the patient ignoring the prodrome and common pitfalls. Factors involved in ignoring the prodrome included atypical symptoms, low medical care level, and a lack of health education. Common pitfalls included thinking that symptoms were due to systemic disease or the natural aging process. These five sub-theme items and interview records are shown in Table 3.

Insufficient knowledge and understanding of glaucoma-related risk and harm

The second major theme included three sub-themes, which covered the following: a lack of awareness of the symptoms and harm caused by the disease, as well as neglected factors, such as

1 https://www.qsrinternational.com/nvivo-qualitative-data-analysis-software/home

TABLE 1 Baseline patient data (n =46).

NO.	Type of glaucoma	Sex	Age (years)	First ophthalmological consultation delay (months)	Affected eye and visual field	Caregiver	Profession	Medicare (yes/no)
N1	POAG	M	66	19	OD NS; OS WSD	Spouse	Government official	Yes
N2	POAG	M	67	7	OD NS; OS PS	Spouse	Teacher	Yes
N3	PACG	F	51	24	OD PS; OS TVF	Spouse	Blue-collar laborer	Yes
N4	PACG	F	73	10	OD WSD; OS NS	Spouse	Retiree	Yes
N5	POAG	M	65	8	OD NS; OS PS	Spouse	Farmer	No
N6	PACG	F	74	24	OD WSD; OS PS	Spouse	Unemployed	Yes
N7	POAG	M	73	24	OD TVF; OS WSD	Son	Retiree	Yes
N8	PACG	M	55	3	OD PS; OS PS	Spouse	Kitchen worker	Yes
N9	PACG	M	61	23	OD WSD; OS TVF	No one	Retiree	Yes
N10	POAG	F	67	13	OD WSD; OS WSD	Spouse	Farmer	Yes
N11	POAG	F	77	22	OD WSD; OS TVF	Spouse	Retiree	Yes
N12	PACG	F	65	10	OD NS; OS WSD	Spouse	Unemployed	Yes
N13	PACG	M	68	3	OD NS; OS PS	No one	Farmer	Yes
N14	POAG	M	73	24	OD TVF; OS NS	Spouse	Policeman	Yes
N15	PACG	F	54	3	OD PS; OS PS	Spouse	Accountant	Yes
N16	PACG	F	55	3	OD PS; OS PS	Spouse	Tailor	No
N17	PACG	M	73	20	OD WSD; OS WSD	Son	Retiree	Yes
N18	POAG	M	53	10	OD NS; OS NS	Spouse	Attendant	Yes
N19	PACG	F	68	21	OD TVF; OS TVF	Daughter	Retiree	Yes
N20	PACG	F	64	18	OD WSD; OS WSD	Spouse	Farmer	Yes
N21	POAG	M	76	14	OD NS; OS TVF	Son	Retiree	Yes
N22	POAG	F	72	19	OD TVF; OS WSD	Son	Retiree	Yes
N23	PACG	M	70	3	OD PS; OS WSD	Son	Retiree	Yes
N24	PACG	F	59	6	OD WSD; OS PS	Spouse	Unemployed	No
N25	PACG	F	57	17	OD PS; OS WSD	Spouse	Barber	Yes
N26	PACG	F	70	5	OD WSD; OS PS	Spouse	Unemployed	Yes
N27	POAG	M	52	3	OD NS; OS NS	Spouse	Mechanic	Yes
N28	PACG	M	59	5	OD PS; OS NS	Spouse	Policeman	Yes
N29	PACG	F	73	11	OD TI; OS NS	Spouse	Unemployed	Yes
N30	PACG	F	78	9	OD TI; OS TVF	Spouse	Retiree	Yes
N31	POAG	F	67	15	OD WSD; OS WSD	Spouse	Retiree	Yes

(Continued)

10.3389/fmed.2023.1161980

TABLE 1 (Continued)

NO.	Type of glaucoma	Sex	Age (years)	First ophthalmological consultation delay (months)	Affected eye and visual field	Caregiver	Profession	Medicare (yes/no)
N32	PACG	F	60	5	OD WSD; OS NS	No one	Retiree	Yes
N33	PACG	M	63	3	OD NS; OS PS	No one	Unemployed	Yes
N34	POAG	M	61	10	OD NS; OS TVF	Spouse	Professor	Yes
N35	POAG	F	62	17	OD TVF; OS NS	Spouse	Farmer	No
N36	PACG	M	70	3	OD PS; OS NS	Spouse	Retiree	Yes
N37	POAG	F	72	16	OD WSD; OS WSD	Spouse	Retiree	Yes
N38	PACG	F	64	3	OD PS; OS PS	Spouse	Unemployed	Yes
N39	PACG	F	67	8	OD WSD; OS PS	Spouse	Unemployed	Yes
N40	PACG	M	61	6	OD PS; OS PS	Spouse	Blue-collar laborer	Yes
N41	PACG	F	63	7	OD WSD; OS NS	Spouse	Retiree	Yes
N42	PACG	M	62	5	OD TVF; OS WSD	No one	Engineer	Yes
N43	PACG	F	50	10	OD PS; OS WSD	Spouse	Journalist	Yes
N44	POAG	F	75	12	OD WSD; OS NS	Son	Retiree	Yes
N45	PACG	M	71	8	OD PS; OS WSD	Spouse	Retiree	Yes
N46	POAG	F	66	23	OD IT; OS WSD	Spouse	Farmer	Yes

M, male; F, female; POAG, primary open-angle glaucoma; PACG, primary angle-closure glaucoma; OD, Right eye; OS, Left eye, PS, paracentral scotoma; NS, nasal step; WSD, wedge-shaped depression; TVF, tube visual field; TI, temporal island

10.3389/fmed.2023.1161980

TABLE 2 Major themes: factors involved in the delay to first ophthalmological consultation by patients with primary glaucoma.

Major themes	Content of the interview
Symptoms are occult and difficult to identify	"In the beginning, I always had migraine, a burst of pain; I thought that was nerve pain!" (N15)
	"When I worked in a restaurant, I often felt dizzy and struggled to see things. The room was so hot that I thought I was *Shanghuo*." (N18)
	"I did not know I had glaucoma. I visited a doctor, every time the medical eye examination was normal." (N34)
Insufficient knowledge and understanding of glaucoma-related risk and harm	"Many years ago my eyes pained; I had no pain over the past 2 years. Recently I had eye pain for 2 days, but I did not mind." (N6)
	"I do not know the purpose of checking the visual field; my visual acuity was not affected, and I thought my eyes were normal. But visual field damage is so serious" (N22)
Perceived difficulties in accessing medical care	"I do not have pension or healthcare insurance. I rely on my husband's pension of 3,000 Chinese Yuan per month; how can I go to see a doctor with this amount of money?" (N4)
	"My home is far from the hospital, more than 30 miles. The only way to get there is to take a shuttle car, and then take a bus." (N5)
Inadequate support system	"My eldest daughter is a teacher and her work keeps her very busy; her children are studying for their college entrance examination and have no time to take me to see the doctor." (N13)
	"We are not registered and rarely go to the hospital. We do not know how to register online and have to wait for our child to do this for us." (N45)

TABLE 3 Major theme 1: glaucoma symptoms are occult and difficult to identify.

Sub-themes	Content of the interview
Symptoms are not typical	"I went to the toilet in the middle of the night. Wow! My eyes blurred; I thought that I got up too fast. I did not care, and went back to sleep, got up in the morning, and it was all right." (N16)
	"Blurred vision was not severe and did not affect my work, so I did not buy any medicine. I had been deceived that it was *Shanghuo*, and did not pay much attention." (N27)
	"I was informed of glaucoma in the hospital. I went to the cataract department for surgery, and the doctor told me that I should make an appointment with the glaucoma specialist. Only then did I know that I had glaucoma." (N14)
Medical care level is poor	"The doctor of my county hospital checked my eyes, and she said my eyes were too dirty, and that I needed to massage my eyes. I immediately agreed! But the massage was very uncomfortable, was so uncomfortable that I burst into tears!" (N33)
	"The doctor of your hospital was very sure and said that I had glaucoma. I lived in Tianshui, Gansu province, where there was no local ophthalmologist. Doctor Ji of your hospital came to Tianshui once every month." (N1)
Lack of health education	"I never surf the internet. I do not understand the words. My medical knowledge is very poor." (N20)
	"I do not know anything about glaucoma. Take cataract for example, now everyone knows about that, but people really lack glaucoma knowledge." (N28)
Symptoms are affected by systemic disease	"I told my mother-in-law that I could not see anything. She said it was a side-effect of chemotherapy" (N3)
	"It's like catching a cold. I mistakenly thought I had a cold, and my blood pressure was so high that I could not see." (N11)
	"I'm old and I have a headache. I suspected that I had a tumor in my head. I got an MRI, but there was nothing wrong." (N5)
Symptoms are mistaken for symptoms of natural aging	"I have blurred vision. Since I was young, I have been weaving gloves, pasting matchboxes, and making toothbrushes. I thought my eyes were too tired because I used them too much." (N37)
	"When I was young, I had strong immunity and I was not easy to get sick. Now, I am old, and my immunity is weakened. That was why my eyes were bad." (N9)

self-medication. Common cognitive deficiencies included not being aware of the harm caused by glaucoma, poor willingness to seek medical care, and self-medication habits. The content of the three sub-themes and interview records are shown in Table 4.

Perceived difficulties in obtaining medical care

The third major theme included five sub-themes, which covered marked economic pressure, a lack of trust in seeking medical treatment, long travel distance required to access medical care, a lack of glaucoma specialists or examination facilities, and limited medical resources. The contents of the five sub-themes and interview records are shown in Table 5.

Inadequate support system

The fourth major theme included three sub-themes, which covered the following: being unable to see the doctor by themselves, being too busy with work or life; having an inadequate family support system. The three sub-theme contents and interview records are shown in Table 6.

TABLE 4 Major theme 2: insufficient knowledge and understanding of glaucoma-related risk and harm.

Sub-themes	Content of the interview
Not aware of glaucomatous harm	"I do not understand, I did not think it was so severe; anyway, I feel the eyes are covered but not serious." (N2)
	"When I was a child, I had good vision. I was fine all my life. I did not know glaucoma was so serious." (N27)
Poor willingness to seek medical care	"I also love to inquire. A neighbor was performed glaucoma surgery, I think the effect was not good. He said the treatment had no curative effect. I believed him, so I always delayed seeing a doctor." (N19)
	"I grew up in the countryside. When I got sick, I had no medicine. I had not gone to the hospital for decades." (N26)
Self-medication habits	"I used the eye drops that my children had brought back from Japan! They were meant for treatment of visual fatigue, and I felt a little better!" (N8)
	"My husband said I had cataracts, so I went to the pharmacy to buy eye drops. I used the eye drops for 2 years." (N46)

TABLE 5 Major theme 3: perceived difficulties in obtaining medical care.

Sub-themes	Content of the interview
Marked economic pressure	"I was born in a village. When I married my husband, I came to live in the city. I had no retirement fee, and no money to see a doctor!" (N29)
	"Medical insurance does not cover the outpatient expenses. It usually takes me more than 10,000 Chinese Yuan a year to pay for my systemic disease (diabetes, hypertension, heart disease). So, I did not check for glaucoma before." (N39)
Lack of trust in seeking medical treatment	"I do not really believe what the doctor said, I am afraid that the doctor wants to prescribe more medicine and do more surgery. And your hospital has interns, so I am even more afraid that the doctor will be selfish." (N7)
	"My father is also a doctor, not of ophthalmology, and he advocated going to other hospitals and get comprehensive opinions from different hospitals." (N43)
Medical institutions is far away	"It was a long way away. It took more than an hour to drive here. There was no vacant parking space in the hospital, my son stopped his car two kilometers away, walked to the hospital and rented a wheelchair. Then, he walked back and picked up me with a wheelchair from parking to hospital. It took me another hour." (N17)
	"It took me 23 h to come here by train, it will not save much time even by plane (sigh)." (N42)
No glaucoma specialist or examination facilities	"Work unit physical examination and community physical examination do not involve the eyes, the county hospital only checks the common diseases." (N24)
	"Doctors in the village only screen cataracts; they can do cataract surgery, but not glaucoma surgery." (N35)
Limited medical resources	"I made an appointment with my smartphone. For next week's clinic, the fastest you can see a doctor is in 3 or 4 days." (N25)

TABLE 6 Major theme 4: inadequate support system.

Sub-themes	Content of the interview
Inability to see the doctor by themselves	"I need my son when I go to see a doctor, not because of my poor eyesight: I cannot make an appointment online and pay electronically, I cannot do it." (N31)
	"I cannot go to the hospital by myself. I do not know where to go. My daughter, daughter-in-law, son-in-law and my son, they take turns in going to hospital with me." (N12)
Being busy with work or life	"I just got a job 6 months ago. Every colleague has his own task, and there is nobody to spare. I got the position by other's recommendation. I am too embarrassed to ask for leave, ah!" (N40)
	"I pick up my grandson from school every day. I have to cook for my family and have no time to see a doctor." (N44)
Inadequate family support system	"Since last year, I felt something like hair floating in front of my eyes, but I did not have long hair … I told my husband, and he did not care." (N10)
	"My eyes were uncomfortable for 2 weeks, and my children did not have time at that time. Now, they are free and they took me to the hospital." (N23)

All the above first ophthalmological consultation delay factors are shown in Figure 2.

Discussion

In this study, we interviewed 46 patients with primary glaucoma who had delayed seeking their first ophthalmological consultation. From the general data of the patients, the visual field damage in PACG was milder, with 20 patients experienced mild to moderate visual field damage (20/29, 68.97%), while only 6 POAG patients (6/17, 35.29%) had mild to moderate visual field damage. This may be due to the longer delay and the more insidious symptoms in POAG. In this study, the median of delayed medical visit time in POAG patients was significantly greater than that of PACG patients, indicating that POAG patients had longer delay in first ophthalmological consultation. Therefore, it is necessary to conduct more in-depth research on the delayed treatment of POAG patients in the future. Ophthalmologists

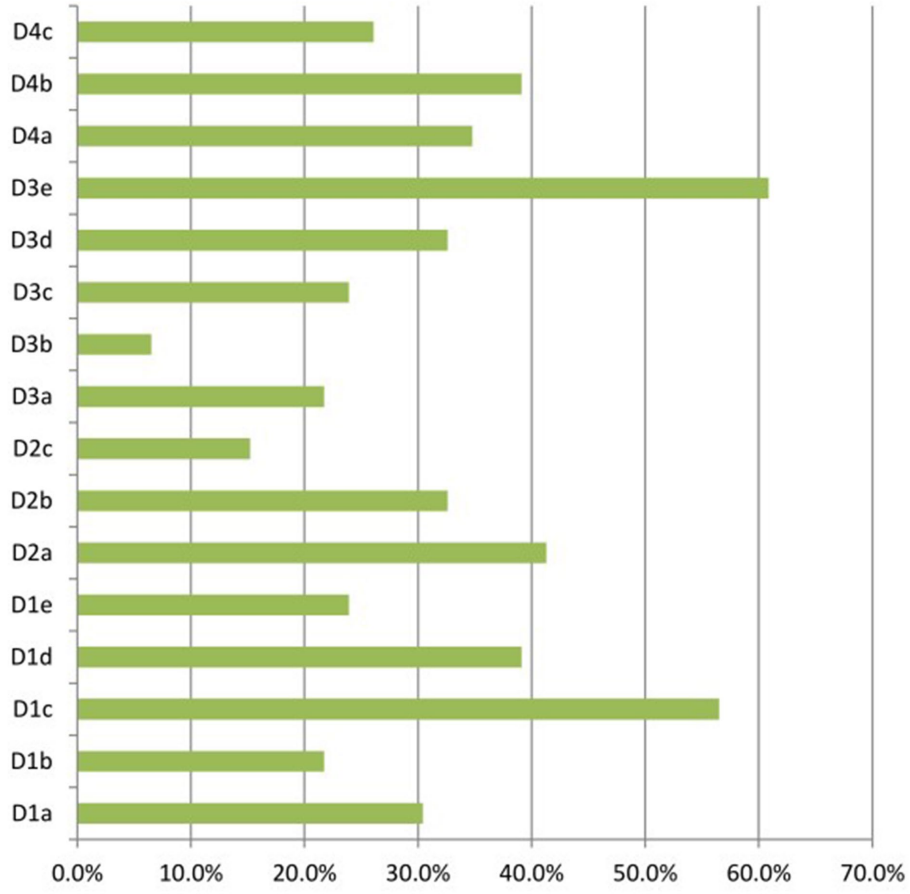

FIGURE 2
The first ophthalmological consultation delay factors. D1: symptoms are occult and difficult to identify (D1a: symptoms are not typical; D1b: medical care level is poor; D1c: lack of health education; D1d: symptoms are affected by systemic disease; D1e: symptoms are mistaken for symptoms of natural aging); D2: insufficient knowledge and understanding of glaucoma-related risks and harm (D2a: not aware of glaucomatous harm; D2b: poor willingness to seek medical care; D2c: self-medication habits); D3: perceived difficulties in accessing medical care (D3a: marked economic pressure; D3b: lack of trust in seeking medical treatment. D3c: medical institutions is far away; D3d: no glaucoma specialist or examination facilities; D3e: limited medical resources); D4: inadequate support system (D4a: inability to see the doctor by themselves; D4b: being busy with work or life; D4c: inadequate family support system).

should take more time to consider how to reduce the delay in POAG. Although PACG had a slightly shorter delay in seeking ophthalmological consultation and less severe visual field damage in this study, a targeted intervention in PACG patients with mild to moderate visual field damage would better maintain their residual visual function and effectively avoid blindness. Therefore, more attention should be paid to delayed seeking of medical treatment in both types of glaucoma. In addition, although no jobless people were found in POAG group, the POAG patients presented greater consultation delay, indicating economic level may not be the determinant factor of delayed medical attendance.

From the results of the 46 patient interviews, the most important reasons for the delay was the difficulty in identifying glaucoma symptoms, which was recounted by 31 patients (31/46, 67.39%). Other common reasons for the delay in seeking medical treatment in ophthalmology departments included the lack of awareness of the harm caused by glaucoma, perceived difficulties in obtaining medical treatment, and an inadequate support system. In contrast to previous studies, we used an in-depth interview process to address disease cognition, life rhythm, work intensity, medical habits, local medical resources, physical care, economic status, family support, and other aspects. Thus, our results provide a more accurate reflection of the primary causes of first ophthalmological consultation delay.

Improve disease awareness of both doctors and patients through social media and standardized training

Glaucoma damages the optic nerve through high intraocular pressure, which subsequently leads to an irreversible visual field defect and eventual blindness (1). In the process of visual field damage, glaucoma commonly causes symptoms such as nose pain, headache, and a transient decline in visual acuity. Most patients are unaware that they have glaucoma in the early stages of the disease. Indeed, our results indicated that insufficient knowledge and understanding of glaucoma-related harm was a major issue, consistent with the findings of previous studies (16). Due to the atypical symptoms, 21 patients (21/46, 45.65%) did not realize the importance and urgency of ophthalmological consultation. Thus, there is an immediate need to popularize the knowledge of glaucoma. Previous studies (17, 18) have called for the problem of glaucoma perception to be addressed

through the mass media. In addition, symptom identification and the early diagnosis of glaucoma are not focal points in current standardized training programs for non-ophthalmic medical staff. Komolafe et al. (19) recommended the strengthening of glaucoma knowledge among medical staff, in order to educate the general population about glaucoma and the importance of avoiding ophthalmological consultation delay. In the present study, 14 patients (11 POAG and 3 PACG) complained of undetected glaucoma-related symptoms, highlighting the urgent need to popularize knowledge about glaucoma, especially for POAG patients. Celebi (20) recommended the strengthening of community education. A feasible public health strategy would be to screen high-risk groups, such as older individuals and those with a family history of glaucoma in the community, on the premise of enhancing the awareness of glaucoma.

Use internet resources to carry out glaucoma health education projects and change medication habits

While the initial symptoms of glaucoma are atypical, the visual field damage is progressive, and causes a sharp decline in patients' quality of life and increases treatment costs, thus emphasizing the value of early intervention (21, 22). Progressive glaucoma is associated with decreased reading ability and mobility, inability to drive and work (23–25), as well as adverse psychological effects (26, 27). In this study, 19 patients (19/46, 41.30%) had delayed their first ophthalmological consultation for 12 months or longer; this included 12 cases of primary open-angle glaucoma and 7 cases of primary angle-closure glaucoma. While the symptoms of the two types of glaucoma differ, a general lack of awareness of disease harm typically leads to a delay in seeking medical treatment, regardless of glaucoma type. Indeed, consultation delay remains a major problem and challenge for the medical industry.

The first step in overcoming this challenge would be to increase the willingness of high-risk groups with glaucoma to actively seek medical care (28). In the early stage of glaucoma, it is difficult for most patients to comprehend the potential serious decline in quality of life that would be caused by visual field damage (29). In addition, the attitude toward the disease needs to be changed through health education (30). Twenty-six patients (26/46, 56.52%) mentioned "lack of health education" in the interviews, urging us to promote the quality of patients' health education. At present, internet medical care services are available in various forms (31–33), particularly in low- and middle-income countries and regions. We suggest that special glaucoma health education internet projects should be increased, health education for high-risk groups should be strengthened, and habits of avoiding medical care consultation should be changed.

Medical union and medical multi-point practice for resolving practical difficulties

The medical union model of some developing countries requires that all tertiary hospitals participate in and play a leading role in regional medical care; furthermore, health services should be responsible for medical management of the region (34). The imbalance of medical resources, long waiting time for medical resources, long travel distances to medical treatment facilities, and low rate of medical insurance reimbursement should be resolved. Medical unions may be particularly effective in resolving issues related to the marked economic pressures and long travel distances faced by patients, as well as limited medical resources. Indeed, 28 patients (28/46, 60.87%) in the present study cited insufficient medical resources as the cause of their delay in obtaining ophthalmology treatment. A previous study reported that the medical union model was able to remedy registration difficulties and long waiting times for ophthalmological consultation (35).

However, in the process of promoting the work of the medical union, issues with insufficient medical staff and an inability to achieve homogenization will exacerbate the lack of trust in medical treatment (36). In the process of promoting the multi-site practice of medical staff, some countries have also set up prescribing rights for specialized nurses in community hospitals, which to some extent solves problems such as insufficient manpower, insufficient medical resources, and the fact that many older people cannot use the online appointment registration system (37, 38). The promotion of medical technology from tertiary hospitals to primary hospitals is conducive to glaucoma examination, ensures homogenization, and increases the trust of patients through the provision of high-quality medical services.

Improving the whole social medical support system through multiple channels

Three themes in the present study highlighted an inadequate support system: the inability of the patient to see a doctor by themselves; being too busy with work or life; and having an inadequate family support system. To solve these three problems, it is necessary to establish a multi-channel social-family support model. Many countries currently implement the checkout mode of seeking medical treatment before payment, which can effectively resolve the issue of patients who are unable to see a doctor alone. Although the "medical and postpayment" model and electronic payment channels in various countries have achieved some successful results, many problems remain (39, 40). Improvements are still required in terms of the strength and integrity of the doctor-patient relationship, the number of medical and auxiliary personnel, and communication to patients at key points, such as inspection item notification and cost settlement. At the same time, social health science should be popularized to enhance the awareness of glaucoma and to enhance family support. As middle-aged patients with glaucoma are particularly affected by a busy work schedule, fast pace-of-life, and other problems, internet hospitals should be promoted (41, 42). Internet hospitals would allow patients who are proficient in using the internet to quickly and conveniently complete preliminary consultation and screening for glaucoma, thereby reducing the incidence of ophthalmological consultation delay.

Limitations

We acknowledge the limitations of this study. First, this was a preliminary pilot study and the sample size was small. Second, the research participants in this study were older individuals with primary glaucoma. As older patients may be less able to perceive symptoms

and typically experience more practical difficulties, they are also more prone to ophthalmological consultation delay than younger patients. In addition, the incidence of primary glaucoma is higher among older individuals. A study with larger sample size (especially younger patients with glaucoma) is needed to address the cause of consultation delay among young patients.

Conclusion

A delay in ophthalmological consultation and treatment for glaucoma leads to an irreversible damage to visual function. In this study, we elucidated real-life reasons for the delay of ophthalmological consultation. This information can be used as the basis for the continuous improvement of management protocols and systems to prevent glaucoma-related blindness.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

This study was reviewed and approved by the Medical Ethics Committee of Tianjin Medical University Eye Hospital (2020KY(L)-48). All participants provided written informed consent.

Author contributions

HL interviewed patients with glaucoma and was a major contributor in writing the manuscript. CC, ZC, QiL, and QuL transcribed the recording into the text. Data analysis was performed by HL and WL. All authors contributed to the article and approved the submitted version.

Funding

This study was funded by the Tianjin Key Medical Discipline (Specialty) Construction Project (TJYXZDXK-037A). The funder has no roles in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Acknowledgments

The researchers appreciate all the glaucoma patients who participated in the study. We also would like to thank the doctors and nurses of Glaucoma Department who allowed and provided the necessary conditions for the study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Zhao KX, Yang PZ. *Ophthalmology. 8th* ed. Beijing: The People's Health Publishing House (2013). 163 p.

2. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040. *Ophthalmol Retina*. (2014) 121:2081–90. doi: 10.1016/j.ophtha.2014.05.013

3. Bourne RRA, Jonas JB, Bron AM, Cicinelli MV, das A, Flaxman SR, et al. Prevalence and causes of vision loss in high-income countries and in eastern and central Europe in 2015: magnitude, temporal trends and projections. *Br J Ophthalmol*. (2018) 102:575–85. doi: 10.1136/bjophthalmol-2017-311258

4. Allison K, Patel D, Alabi O. Epidemiology of glaucoma: the past, present, and predictions for the future. *Cureus*. (2020) 12:e11686. doi: 10.7759/cureus.11686

5. Burton MJ, Ramke J, Marques AP, Bourne RRA, Congdon N, Jones I, et al. The lancet global health commission on global eye health: vision beyond 2020. *Lancet Glob Health*. (2021) 9:e489–551. doi: 10.1016/S2214-109X(20)30488-5

6. Abdull MM, Chandler C, Gilbert C. Glaucoma, "the silent thief of sight": patients' perspectives and health seeking behaviour in Bauchi, northern Nigeria. *BMC Ophthalmol*. (2016) 16:44. doi: 10.1186/s12886-016-0220-6

7. Neustaeter A, Nolte I, Snieder H, Jansonius NM. Genetic pre-screening for glaucoma in population-based epidemiology: protocol for a double-blind prospective screening study within lifelines (EyeLife). *BMC Ophthalmol*. (2021) 21:18. doi: 10.1186/s12886-020-01771-9

8. Neustaeter A, Vehof J, Snieder H, Jansonius NM. Glaucoma in large-scale population-based epidemiology: a questionnaire-based proxy. *Eye*. (2021) 35:508–16. doi: 10.1038/s41433-020-0882-4

9. Song X, Li P, Li Y, Yan X, Yuan L, Zhao C, et al. Strong association of glaucoma with atherosclerosis. *Sci Rep*. (2021) 11:8792. doi: 10.1038/s41598-021-88322-4

10. Gallo JS, Pack GT. Early diagnosis and treatment of cancer. *Public Health Nurs*. (1931) 1946:538–43.

11. Eissa IM, Abu Hussein NB, Habib AE, El Sayed YM. Examining delay intervals in the diagnosis and treatment of primary open angle glaucoma in an Egyptian population and its impact on lifestyle. *J Ophthalmol*. (2016) 2016:1–6. doi: 10.1155/2016/7012826

12. Prior M, Francis JJ, Azuara-Blanco A, Anand N, Burr JM. Glaucoma screening platform study group. Why do people present late with advanced glaucoma? A qualitative interview study. *Br J Ophthalmol*. (2013) 97:1574–8. doi: 10.1136/bjophthalmol-2013-303813

13. Jones PR, Philippin H, Makupa WU, Burton MJ, Crabb DP. Severity of visual field loss at first presentation to glaucoma clinics in England and Tanzania. *Ophthalmic Epidemiol*. (2020) 27:10–8. doi: 10.1080/09286586.2019.1661499

14. Cook C. Glaucoma in Africa: size of the problem and possible solutions. *J Glaucoma*. (2009) 18:124–8. doi: 10.1097/IJG.0b013e318189158c

15. Colaizzi P In: R Valle and M King, editors. *Psycholgical research as a phenomenolgist views it*. Oxford, England: Oxford University Press (1978). 5–7.

16. Becerril-Ledezma V, Alvarez-Ascencio D, Del Hierro-Gutiérrez CE, Hernandez-Oteyza A, Jiménez-Román J. Knowledge and awareness of glaucoma in Mexican patients with and without glaucoma diagnosis in an ophthalmology referral center. *Int J Ophthalmol*. (2022) 15:990–6. doi: 10.18240/ijo.2022.06.18

17. Alemu DS, Gudeta AD, Gebreselassie KL. Awareness and knowledge of glaucoma and associated factors among adults: a cross sectional study in Gondar town, northwest Ethiopia. *BMC Ophthalmol*. (2017) 17:154. doi: 10.1186/s12886-017-0542-z

18. Chen X, Zhong YL, Chen Q, Tao YJ, Yang WY, Niu ZQ, et al. Knowledge of glaucoma and associated factors among primary glaucoma patients in Kunming, China. *BMC Ophthalmol*. (2022) 22:95. doi: 10.1186/s12886-022-02322-0

19. Komolafe OO, Omolase CO, Bekibele CO, Ogunleye OA, Komolafe OA, Omotayo FO. Awareness and knowledge of glaucoma among workers in a Nigerian tertiary health care institution. *Middle East Afr J Ophthalmol*. (2013) 20:163–7. doi: 10.4103/0974-9233.110609

20. Celebi ARC. Knowledge and awareness of Glaucoma in subjects with glaucoma and their normal first-degree relatives. *Med Hypothesis Discov Innov Ophthalmol*. (2018) 7:40–7.

21. Kastner A, King AJ. Advanced glaucoma at diagnosis: current perspectives. *Eye*. (2020) 34:116–28. doi: 10.1038/s41433-019-0637-2

22. Harper RA, Gunn PJG, Spry PGD, Fenerty CH, Lawrenson JG. Care pathways for glaucoma detection and monitoring in the UK. *Eye*. (2020) 34:89–102. doi: 10.1038/s41433-019-0667-9

23. Sleath B, Sayner R, Vitko M, Carpenter DM, Blalock SJ, Muir KW, et al. Glaucoma patient-provider communication about vision quality-of-life. *Patient Educ Couns*. (2017) 100:703–9. doi: 10.1016/j.pec.2016.11.018

24. Ayele FA, Zeraye B, Assefa Y, Legesse K, Azale T, Burton MJ. The impact of glaucoma on quality of life in Ethiopia: a case-control study. *BMC Ophthalmol*. (2017) 17:248. doi: 10.1186/s12886-017-0643-8

25. Blumberg DM, de Moraes CG, Prager AJ, Yu Q, Al-Aswad L, Cioffi GA, et al. Association between undetected 10^{-2} visual field damage and vision-related quality of life in patients with glaucoma. *JAMA Ophthalmol*. (2017) 135:742–7. doi: 10.1001/jamaophthalmol.2017.1396

26. Khachatryan N, Pistilli M, Maguire MG, Chang AY, Samuels MR, Mulvihill K, et al. A review of studies of the association of vision-related quality of life with measures of visual function and structure in patients with Glaucoma in the United States. *Ophthalmic Epidemiol*. (2021) 28:265–76. doi: 10.1080/09286586.2020.1863992

27. Kalyani VKS, Dayal A, Chelerkar V, Deshpande M, Chakma A. Assessment of psychosocial impact of primary glaucoma and its effect on quality of life of patients in western India. *Indian J Ophthalmol*. (2020) 68:2435–8. doi: 10.4103/ijo.IJO_2117_19

28. Robin A, Grover DS. Compliance and adherence in glaucoma management. *Indian J Ophthalmol*. (2011) 59:93. doi: 10.4103/0301-4738.73693

29. Kowal M, Choragiewicz T, Mietlicka K, Wyszyńska A, Zarnowski T. Obstacles to medication compliance for patients with glaucoma. *Postęp okulistyczny*. (2008) 110:347–51.

30. Sleath B, Davis S, Sayner R, Carpenter DM, Johnson T, Blalock SJ, et al. African American patient preferences for glaucoma education. *Optom Vis Sci*. (2017) 94:482–6. doi: 10.1097/OPX.0000000000001059

31. Peng Y, Wu X, Atkins S, Zwarentein M, Zhu M, Zhan XX, et al. Internet-based health education in China: a content analysis of websites. *BMC Med Educ*. (2014) 14:16. doi: 10.1186/1472-6920-14-16

32. Holst C, Stelzle D, Diep LM, Sukums F, Ngowi B, Noll J, et al. Improving health knowledge through provision of free digital health education to rural communities in Iringa, Tanzania: nonrandomized intervention study. *J Med Internet Res*. (2022) 24:e37666. doi: 10.2196/37666

33. Bujnowska-Fedak MM. Trends in the use of the internet for health purposes in Poland. *BMC Public Health*. (2015) 15:194. doi: 10.1186/s12889-015-1473-3

34. The General Office of the State Council. *The guiding opinions of the General Office of the State Council on promoting the construction and development of the medical consortium*. (2017) Document 32. Available at: http://www.nhc.gov.cn/yzygj/s3594q/201704/fa1949ec95e34cd78f35fecf665aeec4.shtml (Accessed April 27, 2017).

35. Hillman E, Paul J, Neustadt M, Reddy M, Wooldridge D, Dall L, et al. Establishing a multi-institutional quality and patient safety consortium: collaboration across affiliates in a community-based medical school. *Acad Med*. (2020) 95:1864–73. doi: 10.1097/ACM.0000000000003552

36. du L, Xu J, Chen X, Zhu X, Zhang Y, Wu R, et al. Rebuild doctor-patient trust in medical service delivery in China. *Sci Rep*. (2020) 10:21956. doi: 10.1038/s41598-020-78921-y

37. Laurant M, van der Biezen M, Wijers N, Watananirun K, Kontopantelis E, van Vught AJAH, et al. Nurses as substitutes for doctors in primary care. *Cochrane Database Syst Rev*. (2018) 2019:CD001271. doi: 10.1002/14651858.CD001271.pub3

38. Sturgiss EA, Elmitt N, Haelser E, van Weel C, Douglas KA. Role of the family doctor in the management of adults with obesity: a scoping review. *BMJ Open*. (2018) 8:e019367. doi: 10.1136/bmjopen-2017-019367

39. Shen J, Zhang J, He Q, Pan H, Wu Z, Nie L, et al. "Without the need for a second visit" initiative improves patient satisfaction with updated services of outpatient clinics in China. *BMC Health Serv Res*. (2021) 21:267. doi: 10.1186/s12913-021-06260-3

40. Shen YQ, Ji J, Liu SN. Exploration and practice of the outpatient process reengineering of "post-medical payment". *Chin J Hosp Manag*. (2019) 12:1020–2. doi: 10.3760/cma.j.issn.1000-6672.2019.12.014

41. Lai Y, Chen S, Li M, Ung COL, Hu H. Policy interventions, development trends, and service innovations of internet hospitals in China: documentary analysis and qualitative interview study. *J Med Internet Res*. (2021) 23:e22330. doi: 10.2196/22330

42. Zhi L, Yin P, Ren J, Wei G, Zhou J, Wu J, et al. Running an internet hospital in China: perspective based on a case study. *J Med Internet Res*. (2021) 23:e18307. doi: 10.2196/18307

frontiers | Frontiers in Medicine

TYPE Systematic Review
PUBLISHED 28 July 2023
DOI 10.3389/fmed.2023.1159316

OPEN ACCESS

EDITED BY
Fabrizio Giansanti,
University of Florence, Italy

REVIEWED BY
Jan Lešťák,
Eye Clinic JL, Czechia
Silvia Sgambellone,
University of Florence, Italy
Lenin David Ochoa-de La Paz,
National Autonomous University of Mexico, Mexico

*CORRESPONDENCE
Hamed Ghoshouni
✉ hamedghoshouni@gmail.com

RECEIVED 05 February 2023
ACCEPTED 07 July 2023
PUBLISHED 28 July 2023

CITATION
Mohammadi M, Yarmohammadi A, Salehi-Abargouei A, Ghasemirad H, Shirvani M and Ghoshouni H (2023) Uric acid and glaucoma: a systematic review and meta-analysis. *Front. Med.* 10:1159316. doi: 10.3389/fmed.2023.1159316

Uric acid and glaucoma: a systematic review and meta-analysis

Mohammad Mohammadi[1,2], Adeleh Yarmohammadi[3], Amin Salehi-Abargouei[4,5,6], Hamidreza Ghasemirad[1], Mohammad Shirvani[7,8] and Hamed Ghoshouni[1]*

[1]Students' Research and Technology Committee, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, [2]NeuroTRACT Association, Student's Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran, [3]Assil Gaur Eye Institute, Beverley Hills, CA, United States, [4]Research Center for Food Hygiene and Safety, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, [5]Yazd Cardiovascular Research Center, Non-communicable Diseases Research Institute, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, [6]Department of Nutrition, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, [7]Geriatric Ophthalmology Research Center, Shahid Sadoughi University of Medical Science, Yazd, Iran, [8]Poostchi Ophthalmology Research Center, Department of Ophthalmology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

Background: Glaucoma, the leading cause of irreversible blindness, is a common disorder that contributes to gradual optic nerve degeneration. The beneficial impacts of uric acid (UA) have been reported in some neurodegenerative conditions such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis. But the results of current studies about the association between serum UA level and glaucoma are conflicting. The present meta-analysis was conducted to provide a better understanding of the association between serum UA level and glaucoma.

Methods: We searched the databases of PubMed, Scopus, Web of Science, and Google Scholar systematically until November 20, 2022 to identify case-control studies, comparing the serum UA concentrations of the patients with glaucoma and controls. The mean ± standard division difference was used to assess the difference in serum UA concentrations between the glaucoma patients and controls.

Results: Six studies involving 1,221 glaucoma patients and 1,342 control group were included in the present meta-analysis. This meta-analysis using a random effect model indicated that the mean UA level in glaucoma patients was 0.13 (I^2 = 91.92%, 95% CI = −0.42 to 0.68) higher than the controls; however, it was not statistically significant.

Conclusions: Our findings provide evidence that glaucoma patients have a higher serum UA level compared to the controls, but this difference is not statistically significant. Prospective studies are needed to determine the possible association between increased UA and glaucoma pathogenesis.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022364055, identifier: CRD42022364055.

KEYWORDS

glaucoma, intraocular pressure, uric acid, oxidative stress, systematic review, meta-analysis

Introduction

Glaucoma is the leading cause of irreversible blindness in the world (1). The prevalence of this disorder is rising and varies globally (2, 3), and it is predicted that the number of glaucoma patients will exceed 110 million people by 2040 (4).

In the early stages, glaucoma might be asymptomatic, or patients may experience blurred or missing areas in their vision field (5). However, the late stages of the condition can result in irreversible blindness, especially if untreated (6).

Although the harmful effects of glaucoma on vision are irreversible, early diagnosis and treatment of this condition can decrease the risk of permanent blindness (7).

Due to the asymptomatic nature of glaucoma, early detection of the disease is challenging, and the number of diagnosed patients with glaucoma is lower than undiagnosed patients (8, 9).

Intraocular pressure (IOP) measurement is one of the main diagnostic tests for the diagnosis and progress monitoring of glaucoma (10). Evaluated IOP is the leading risk factor for glaucoma (11). IOP reflects the balance between the aqueous humor generation and its drainage from the eye through the trabecular meshwork and the Schlemm canal outflow pathway (12). Dysfunction of this outflow pathway elevates IOP, which results in glaucomatous optic neuropathy, but it has been shown that normal IOP also may be found in some glaucoma patients (13). This suggests that other factors may involve in the underlying mechanism of glaucoma and underline the need to prioritize research in this area to promote the clinicians' insight into the development of glaucoma.

Glaucoma has traditionally been considered an eye disease, but recent studies have linked it to central nervous system degeneration (14–16). The neurodegeneration associated with glaucoma contributes to gradual optic nerve degeneration with progressive retinal ganglion cell (RGC) loss, which is the main cause of progressive vision loss (17, 18).

The underlying pathogenesis of glaucomatous optic neuropathy is still unknown. It has been suggested that glaucoma destroys neurons through neuroinflammation and oxidative stress (18). Antioxidants can be protective against glaucoma through different mechanisms such as IOP reduction, promoting vascular health, and prevention of RGC loss (19).

Uric acid (UA) is a purine metabolite that detects intracellularly and in all body fluids (20) and that shown to have both pro-oxidant and antioxidant features *in-vitro* by production and scavenging of reactive oxygen species (21, 22). The beneficial impacts of UA have been shown in other neurodegenerative conditions, such as Parkinson's disease (23), Huntington's disease (24), Alzheimer's disease (25), and amyotrophic lateral sclerosis (26). However, the role of UA in the underlying mechanism of glaucoma is still unclear.

By exploring the association between uric acid and glaucoma, we can identify potential abnormal metabolic processes in glaucoma patients, thereby considering UA as a biomarker. Data from several case-control studies suggest a significant inverse association between serum concentrations of UA and glaucoma risk (27–29). However, this was not confirmed in all studies, and some studies even reported a significant association between high serum UA concentrations and the risk of glaucoma (30–32). Hence, the current meta-analysis aimed to evaluate the relationship between serum UA concentration and glaucoma in case-control studies.

Method

The present study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (33). The protocol has been registered in the PROSPERO database (registration number: CRD42022364055).

Eligibility criteria

The present systematic review focused on case-control studies that reported the serum UA concentrations in patients with glaucoma and compared them to controls. The investigations should be conducted *in vivo* in humans, and the subjects could be controls or glaucoma patients.

We included only studies in the English language. We excluded conference meetings and abstracts that were not published in peer-reviewed journals. If original data or exact numbers were unavailable in both groups of patients with glaucoma and controls, they were not included in our quantitative analysis.

Search strategy and literature screening

To identify studies to be included in this review, a systematic search was performed via PubMed, Scopus, Google Scholar, and Web Of Science databases from inception through November 20, 2022. We used the following search strategy: ("uric acid"[Mesh]) AND ("glaucoma"[Mesh] OR "Intraocular Pressure"[Mesh] OR "Ocular Hypertension" [Mesh]). Moreover, the reference lists of studies obtained in the initial search were manually searched for more relevant articles.

Study selection

After removing duplicate records, two reviewers (MM and HRG) independently analyzed all titles and abstracts obtained from the searches to identify relevant papers.

The full text of studies that appeared to meet the inclusion criteria were obtained and independently analyzed by two reviewers (MM and HG). The authors resolved the disagreement through a discussion with a third author (AS). Eventually, studies that did not meet the inclusion criteria were discarded.

Risk of bias assessment

We applied the Newcastle-Ottawa Quality Assessment Scale (NOS) for case-control studies to evaluate the methodological quality of the studies (34). The NOS contains a star system in which a study is assessed on three domains (Supplementary Table S1); representativeness of study group selection (four items), comparability of groups (two items), and ascertainment of the exposure (three items). Studies scored one star for each area addressed, with a maximum score of 9, of which 7–9, 4–6, 0–3, and scores considered high, fair, low, and quality, respectively. Disagreements were resolved by discussion, and a third author arbitrated unresolved discrepancies.

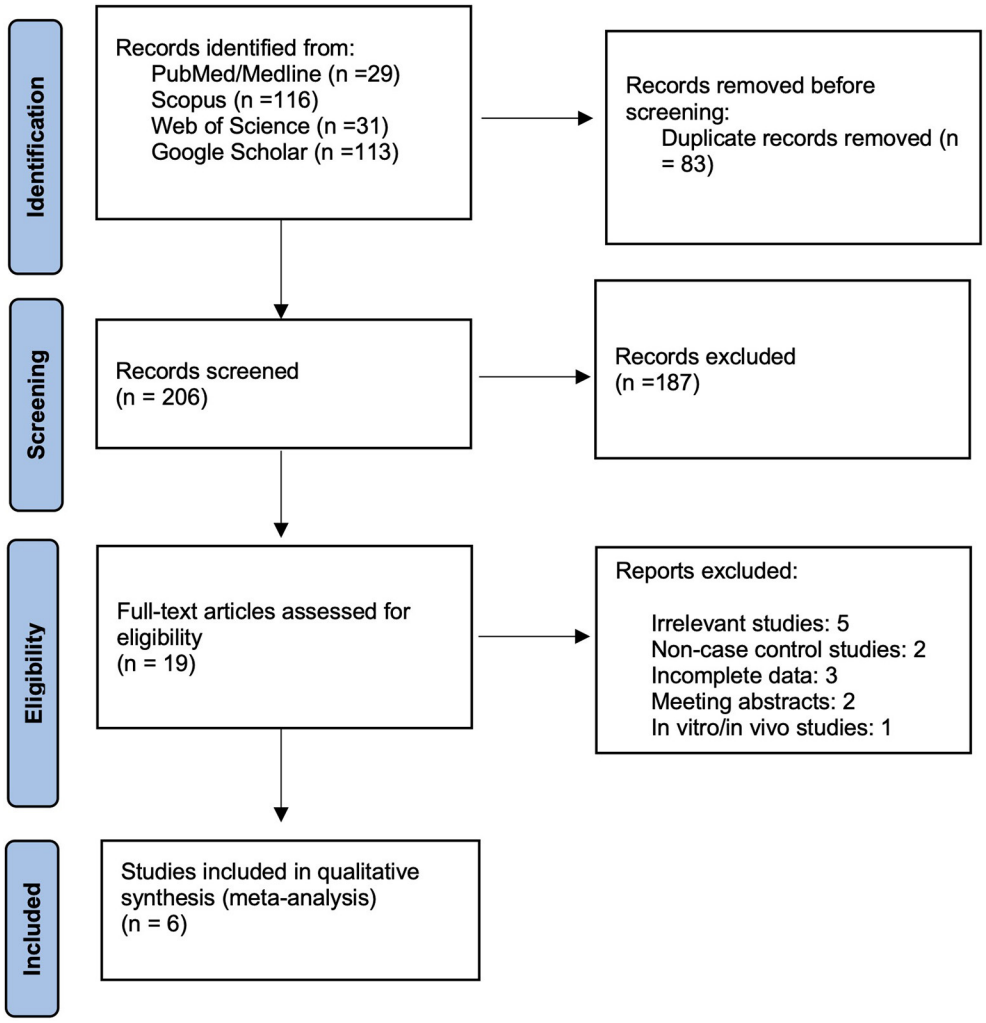

FIGURE 1
PRISMA flow diagram of included studies.

Data extraction

Using standardized data extraction forms, two reviewers (MM and AS) extracted data independently. In cases of disagreement between the reviewers, a third reviewer (HG) was consulted. The following data were extracted from selected studies: authors' name, publication year, country of study, glaucoma type, number of subjects, age range of subjects, definition, and the mean and standard deviation of serum UA levels. Data were extracted separately for each entity groups (glaucoma patients or controls).

Statistics

The mean difference (MD) and its corresponding standard error (SE) were calculated by using the mean values and their standard deviations reported/calculated for case and control groups. Then MDs extracted from each study were used as effect size for meta-analysis. The meta-analyses were performed using DerSimonian-Laird random-effects model, which takes the between-study heterogeneity into account. Stata software, version 17.0 (Stata Corp, College Station, TX), was used to analyze the data. Both the Q statistic and I^2 statistic measures were used for the evaluation of heterogeneity between studies. P-values < 0.05 for Cochran's Q test and an I^2 higher than 25% will be considered as significant heterogeneity (35).

P-values < 0.05 were considered statistically significant. To conduct a sensitivity analysis, each article was removed from the final analysis. Begg's funnel plots and Egger's and Begg's asymmetry tests were used to assess the presence of publication bias (36).

Result

Study selection

After the systematic search in databases, 289 records were retrieved. By removing 83 duplicate records, 206 were screened, and finally, the six studies met the inclusion criteria and were included in this meta-analysis. The Prisma flowchart shows this process in detail in Figure 1.

Study characteristics

Among six studies evaluating the level of UA in serum, 1,221 glaucoma patients were compared to the 1,342 control group. One study recruited patients with normal-tension glaucoma (NTG), another study with primary angle closure glaucoma (PACG), while the patients in the other four studies all were primary open-angle glaucoma (POAG). The largest sample size between these studies included 886 primary angle closure glaucoma patients, with 994 participants as a control group. In comparison, the smallest contained 23 primary open-angle glaucoma patients with 15 participants as a control group. These studies were performed in China ($n = 2$), Tunis ($n = 1$), Greece ($n = 1$), Italy ($n = 1$), and Japan ($n = 1$).

The mean UA level across all glaucoma patients ranged between 4.00 ± 0.66 mg/dl In Serra et al. to 6.2 ± 1.9 mg/dl in Elisaf et al. The characteristics of each included study are shown in Table 1.

For quality assessment of included studies, the Newcastle-Ottawa Scale score was used. Almost all studies have good-quality scores, and Supplementary Table S1 shows these scores in detail.

Results of syntheses

The pooled analysis included all six studies, showing that serum UA level was higher in glaucoma patients than in other patients without glaucoma. In detail, A meta-analysis using a random effect model indicates that the mean UA level in glaucoma patients was 0.13 ($I^2 = 91.92\%$, 95% CI $= -0.42$ to 0.68) higher than the controls; however, it was not statistically significant (Figure 2).

Each article was removed from the analysis to perform a sensitivity analysis, and no significant effect of a single study was found. The funnel plot and Begg and Egger test showed no evidence of publication bias ($P > 0.05$) (Supplementary Figure S1).

Discussion

So far, the association between serum UA concentrations and glaucoma is under debate. To the best of our knowledge, this is the first meta-analysis to examine the relationship between serum UA level and glaucoma.

In the present meta-analysis of 1,221 glaucoma patients compared to 1,342 controls included in 6 case-control studies, serum UA concentration in patients with glaucoma was higher than in the controls, but this association was not statistically significant.

Three out of six case-control studies (27–29) within this meta-analysis found a significant inverse association. In comparison, three other studies (30–32) have reported a positive association between high UA levels and glaucoma (Table 1). These various results may be reflected by the heterogeneity found in the present meta-analysis. The inclusion of various glaucoma types in this meta-analysis and the differences in disease etiology could contribute to this heterogeneity (Table 1).

Some authors have recently found decreased total antioxidant capacity levels in the blood and aqueous humor samples of glaucoma patients (37, 38). Oxidative stress is also suggested to play a role in the physiologic changes in aqueous humor outflow, leading to increased IOP and RGC degeneration in glaucoma (39, 40).

UA is one of the main antioxidants of plasma (21, 41). Wayner et al. (42) reported that urate contributes up to 65% of the overall antioxidant capacity of the plasma. Meanwhile, experimental animal studies and human clinical trials have suggested that higher serum UA concentrations can prevent neuronal degeneration (43, 44).

Li et al. investigated the association between the progression of recently diagnosed PACG and pretreatment UA levels of serum. In this prospective observational study, there was a correlation between a lower baseline serum UA concentration and a higher risk of PACG progression. These findings suggested that higher serum UA values may protect against PACG and suppress the disease progression (45).

On the other hand, some studies have suggested that systemic inflammation is related to glaucomatous damage (46). A recent study by Astafurov et al. (46) showed that glaucoma patients had greater bacterial oral counts in compression to controls and low-dose lipopolysaccharide administration in glaucoma animal models led to neuronal loss and axonal degeneration. In addition, recent studies have reported a significant association between *Heliobacter pylori* infection and glaucoma (47, 48).

As mentioned above, it seems that glaucoma patients are in a low antioxidative and high oxidative state in the body. UA may be consumed in glaucoma by preferentially reacting with oxidizing agents in the body. These findings are consistent with former studies reporting that subjects with higher UA levels have a decreased risk of glaucoma (27–29) and that the level of UA was negatively related to the glaucoma severity (28, 29).

However, another previous study compared the serum UA levels between pseudoexfoliation patients (the leading cause of secondary glaucoma) and controls and reported that serum UA levels of subjects with and without pseudoexfoliation were similar (49).

The other three studies included in our meta-analysis (30–32) suggested higher serum UA concentrations were found in glaucoma patients in comparison with controls.

Regarding this subject interestingly, elevated levels of UA have been reported in the aqueous humor of some patients with glaucoma (50). Additionally, it has been suggested that oxidative stress can accelerate the apoptosis of trabecular meshwork cells and extracellular matrix accumulation in the trabecular meshwork, leading to increased resistance of the aqueous humor outflow pathway and an increase in IOP (51). It is possible that elevated serum UA may reduce the outflow facility of aqueous humor by impairing the trabecular meshwork physiology, ultimately leading to an increase in IOP and glaucomatous optic neuropathy.

Nevertheless, IOP elevation is insufficient to explain the underlying pathophysiology of glaucoma (52). Therefore, other involving risk factors, particularly the impairment of the vasculature supplying the optic nerve and the tissues around it, have also been suggested (53).

According to the growing body of clinical and experimental research, UA-induced inflammatory response and oxidative stress contribute to microvascular impairments (54, 55). Some *in vitro* and *in vivo* findings suggested that UA may contribute to endothelial dysfunction by causing antiproliferative impacts on the

TABLE 1 Characteristics of the six included studies in the present meta-analysis.

References	Country	Glaucoma type	Patients				Controls			
			Number (M/F)	Age range	Definition	Serum UA level (mg/dl)	Number (M/F)	Age range	Definition	Serum UA level (mg/dl)
Bouchemi et al. (32)	Tunis	POAG	100 (46/54)	68.33 ± 1.44	IOP > 21 mm Hg + open-angle glaucoma + visual field loss + glaucomatous optic nerve head alternations	5.44 ± 4.30	114 (52/62)	70.18 ± 1.14	Normal IOP + senile cataract + not received topical drugs	4.55 ± 2.77
Elisaf et al. (30)	Greece	POAG	49 (34/15)	65 ± 9	Visual field defect + optic disk damage on the open-angle of anterior chamber + deep anterior chamber	6.2 ± 1.9	72 (52/20)	63 ± 8	Normal IOP	5.0 ± 1.2
Li et al. (29)	China	POAG	163 (108/55)	49.99 ± 17.24	Inpatients scheduled for glaucoma surgery + age ≥ 18 years + open anterior chamber angle + visual field with characteristic glaucomatous damage consistent with nerve fiber layer loss	5.4 ± 1.41	103 (77/26)	51.42 ± 16.14	IOP < 21 mm Hg + age ≥ 18 years + open anterior chamber angle + VCDR ≤ 0.5 + no family/personal history of glaucoma + no prior eye surgery + no systemic disease	6.09 ± 0.89
Li et al. (28)	China	PACG	886 (302/584)	63.17 ± 10.65	IOP > 21 mm Hg + narrow eye angles + at least 180 of angle-closure obliterating the pigmented part of the trabecular meshwork + too extensive degree of peripheral anterior synechiae to be managed by laser peripheral iridotomy	4.81 ± 1.38	994 (370/624)	63.26 ± 10.12	N/d	4.96 ± 1.43
Serra et al. (27)	Italy	POAG	23 (10/13)	68.68 ± 7.54	IOP > 21 mm Hg+ visual field defect + optic disk damage + open iridocorneal angle + deep anterior chamber	4.00 ± 0.66	15 (5/10)	65 ± 4.56	BCVA [d] ≥ 0.0 logMAR + IOP < 21 mm Hg + no glaucomatous optic nerve head alterations + no family history of optic nerve head diseases + no cause of hyperuricemia	4.95 ± 0.86
Yuki et al. (31)	Japan	NTG	47 (18/29)	59.5 ± 10.2	Non-occludable and open anterior chamber angles + glaucomatous optic disc cupping + visual field defect	5.8 ± 1.5	44 (16/28)	62.7 ± 14.8	N/d	4.9 ± 1.4

M/F, male/female; VCDR, vertical cup-to-disc ratio; N/d, not defined; BCVA, best corrected visual acuity.

10.3389/fmed.2023.1159316

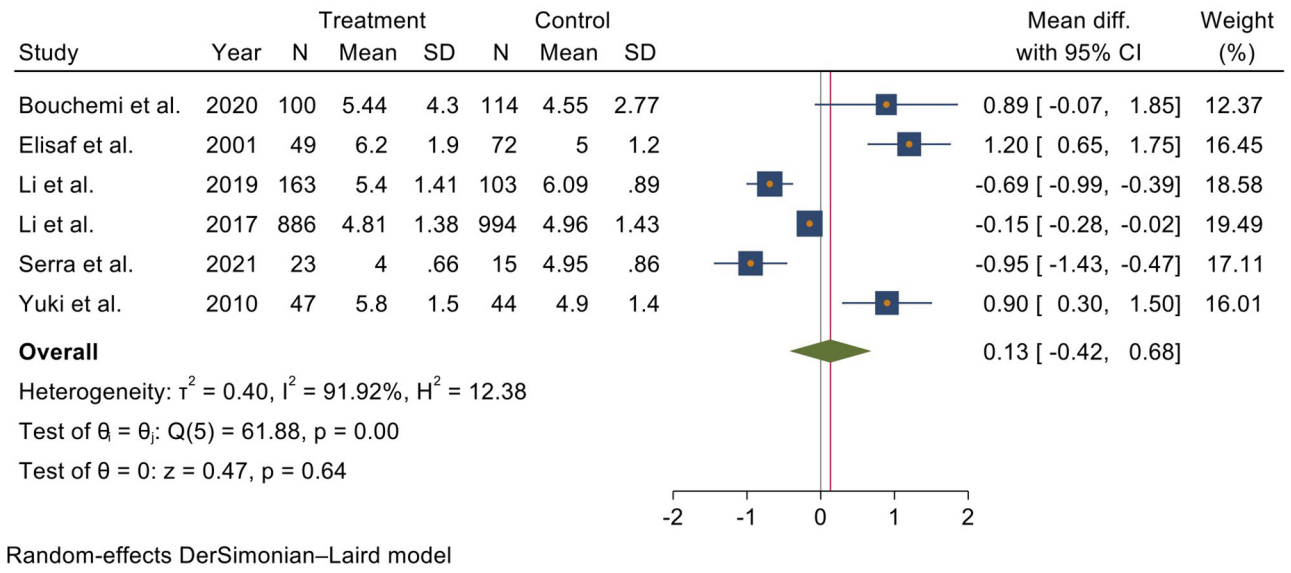

FIGURE 2
Forest plot of meta-analysis for serum uric acid level in glaucoma patients and control groups.

endothelium (56, 57), which has been shown to have an important association with open-angle glaucoma (58).

Moreover, it has been reported that an elevated serum UA and its fluctuations were independently related to impaired choroidal and retinal microcirculation (59).

In a recent study, Yang et al. reported that higher serum UA concentrations were noticeably associated with decreased retinal capillary plexus vessel density. These results may support the damaging impact of high serum UA concentrations on the retinal microvasculature and suggest the necessity of regulating serum UA to prevent microvascular alteration (60). In addition, interestingly, it has been reported that a history of chronic renal disease is significantly associated with the higher risk of development of subsequent glaucoma (61).

Serum UA is known as a potential risk factor for the development and progression of chronic renal disease. It has been reported that elevated serum UA levels can cause an increase in glomerular blood pressure leading to renal diseases. Additionally, pilot studies have suggested that lowering serum UA therapies may slow the progression of chronic renal disease (62). In this regard, it is suggested that both the choroid plexus in the human eye and the renal glomerulus have extensive vascular networks with similar structures (63). The underlying mechanism of glaucoma development may be similar to the chronic renal disease. According to these findings, it is possible that higher levels of UA may be contributing to glaucomatous optic neuropathy.

With all these interpretations, this study was a meta-analysis of the case-control studies, and we cannot consider a precise causal role for UA in the pathogenesis of glaucoma.

Due to the limited number of primary studies available, we were unable to perform a separate analysis for UA levels in each glaucoma subtype. Therefore, it is important to interpret the results cautiously, considering the potential variations in UA levels among different glaucoma types.

In addition, systemic diseases and some medications administration may affect the serum UA level (64–66). Except for Bouchemi et al. (32), all the studies analyzed in this meta-analysis excluded individuals with systemic diseases or those taking medications that could affect serum UA levels. Bouchemi et al. (32) did not clearly state the criteria for excluding patients with systemic diseases or those using medications that could impact serum UA levels.

The observational nature of the included studies does not allow us to determine whether UA-lowering interventions can influence the development of glaucoma. Further randomized clinical trials are required to assess whether the UA-lowering medications may be beneficial in managing glaucoma.

The primary objective of our study was to compare serum UA levels between patients with glaucoma and the control group. We did not analyze and compare the concentration of UA levels in the vitreous and/or aqueous humor. Prior studies have shown that UA levels in aqueous humor of patients with glaucoma were higher than controls (32, 50). The exact mechanism by which UA is transferred into the aqueous humor remains unclear. However, several urate transporters that are involved in UA homeostasis, such as the ATP-binding cassette transporters, organic anion transporters, and solute carrier transporters have been identified in the retina and/or ciliary body of human eyes (67–70). These transporters may be involved in regulating of UA levels in human eyes. Future studies should consider comparing the UA levels in the vitreous and/or aqueous humor to gain a more comprehensive insight into its role in the development of glaucoma.

Furthermore, the study population of included studies in our meta-analysis was limited, and it is necessary to conduct more extensive prospective cohort studies to determine the potential link between serum UA levels and glaucoma.

Conclusion

This meta-analysis summarized a large body of evidence from case-control studies on the association between serum UA level and glaucoma. These findings provided evidence that serum UA concentrations are higher in glaucoma patients in comparison with controls, but this association is not statistically significant. However, prospective studies are needed to confirm the exact effect of serum UA concentrations on the risk of glaucoma.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

MM and HGho designed the study. HGha, MM, and AY performed a systematic search and extracted the data. AS-A and HGho conducted statistical analysis. MM, HGho, and MS drafted the paper. All authors read, revised the manuscript, contributed to the article, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1159316/full#supplementary-material

References

1. Steinmetz JD, Bourne RR, Briant PS, Flaxman SR, Taylor HR, Jonas JB, et al. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the Right to Sight: an analysis for the Global Burden of Disease Study. *Lancet Global Health.* (2021) 9:e144–e60. doi: 10.1016/S2214-109X(20)30489-7

2. Pant AB, Wang Y, Mielcarz DW, Kasper EJ, Telesford KM, Mishra M, et al. Alteration of CD39+Foxp3+ CD4 T cell and cytokine levels in EAE/MS following anti-CD52 treatment. *J Neuroimmunol.* (2017) 303:22–30. doi: 10.1016/j.jneuroim.2016.12.010

3. Wang W, Gawlik K, Lopez J, Wen C, Zhu J, Wu F, et al. Erratum: genetic and environmental factors strongly influence risk, severity and progression of age-related macular degeneration. *Signal Transduct Target Ther.* (2016) 1:16023. doi: 10.1038/sigtrans.2016.23

4. Tham YC Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology.* (2014) 121:2081–90. doi: 10.1016/j.ophtha.2014.05.013

5. Crabb DP, Smith ND, Glen FC, Burton R, Garway-Heath DF. How does glaucoma look?: Patient perception of visual field loss. *Ophthalmology.* (2013) 120:1120–6. doi: 10.1016/j.ophtha.2012.11.043

6. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. The AGIS Investigators. *Am J Ophthalmol.* (2000) 130:429–40. doi: 10.1016/S0002-9394(00)00538-9

7. Tatham AJ, Weinreb RN, Medeiros FA. Strategies for improving early detection of glaucoma: the combined structure-function index. *Clin Ophthalmol.* (2014) 8:611–21. doi: 10.2147/OPTH.S44586

8. Burgoyne CF, Downs JC, Bellezza AJ, Suh JK, Hart RT. The optic nerve head as a biomechanical structure: a new paradigm for understanding the role of IOP-related stress and strain in the pathophysiology of glaucomatous optic nerve head damage. *Prog Retin Eye Res.* (2005) 24:39–73. doi: 10.1016/j.preteyeres.2004.06.001

9. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. *JAMA.* (2014) 311:1901–11. doi: 10.1001/jama.2014.3192

10. Stein JD, Khawaja AP, Weizer JS. Glaucoma in adults—screening, diagnosis, and management: a review. *JAMA.* (2021) 325:164–74. doi: 10.1001/jama.2020.21899

11. Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Archives of ophthalmology.* (2002) 120:701–13. doi: 10.1001/archopht.120.6.701

12. To CH, Kong CW, Chan CY, Shahidullah M, Do CW. The mechanism of aqueous humour formation. *Clin Exp Optom.* (2002) 85:335–49. doi: 10.1111/j.1444-0938.2002.tb02384.x

13. Fechtner RD, Weinreb RN. Mechanisms of optic nerve damage in primary open angle glaucoma. *Surv Ophthalmol.* (1994) 39:23–42. doi: 10.1016/S0039-6257(05)80042-6

14. Yücel YH, Zhang Q, Weinreb RN, Kaufman PL, Gupta N. Effects of retinal ganglion cell loss on magno-, parvo-, koniocellular pathways in the lateral geniculate nucleus and visual cortex in glaucoma. *Prog Retin Eye Res.* (2003) 22:465–81. doi: 10.1016/S1350-9462(03)00026-0

15. Weber AJ, Chen H, Hubbard WC, Kaufman PL. Experimental glaucoma and cell size, density, and number in the primate lateral geniculate nucleus. *Invest Ophthalmol Vis Sci.* (2000) 41:1370–9.

16. Gupta N, Ang LC, Noël de Tilly L, Bidaisee L, Yücel YH. Human glaucoma and neural degeneration in intracranial optic nerve, lateral geniculate nucleus, and visual cortex. *Br J Ophthalmol.* (2006) 90:674–8. doi: 10.1136/bjo.2005.086769

17. Usategui-Martin R, Fernandez-Bueno I. Neuroprotective therapy for retinal neurodegenerative diseases by stem cell secretome. *Neural Regen Res.* (2021) 16:117–8. doi: 10.4103/1673-5374.283498

18. Gauthier AC, Liu J. Neurodegeneration and neuroprotection in glaucoma. *Yale J Biol Med.* (2016) 89:73–9.

19. Jabbehdari S, Chen JL, Vajaranant TS. Effect of dietary modification and antioxidant supplementation on intraocular pressure and open-angle glaucoma. *Eur J Ophthalmol.* (2021) 31:1588–605. doi: 10.1177/11206721209603337

20. Squadrito GL, Cueto R, Splenser AE, Valavanidis A, Zhang H, Uppu RM, et al. Reaction of uric acid with peroxynitrite and implications for the mechanism of neuroprotection by uric acid. *Arch Biochem Biophys.* (2000) 376:333–7. doi: 10.1006/abbi.2000.1721

21. Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant-and radical-caused aging and cancer: a hypothesis. *Proc Nat Acad Sci USA.* (1981) 78:6858–62. doi: 10.1073/pnas.78.11.6858

22. Sautin YY, Nakagawa T, Zharikov S, Johnson RJ. Adverse effects of the classic antioxidant uric acid in adipocytes: NADPH oxidase-mediated oxidative/nitrosative stress. *Am J Physiol Cell Physiol.* (2007) 293:C584–C96. doi: 10.1152/ajpcell.00600.2006

23. Tana C, Ticinesi A, Prati B, Nouvenne A, Meschi T. Uric acid and cognitive function in older individuals. *Nutrients*. (2018) 10. doi: 10.3390/nu10080975

24. Auinger P, Kieburtz K, McDermott MP. The relationship between uric acid levels and Huntington's disease progression. *Mov Disord*. (2010) 25:224–8. doi: 10.1002/mds.22907

25. Scheepers L, Jacobsson LTH, Kern S, Johansson L, Dehlin M, Skoog I. Urate and risk of Alzheimer's disease and vascular dementia: a population-based study. *Alzheimers Dement.* (2019) 15:754–63. doi: 10.1016/j.jalz.2019.01.014

26. Bakshi R, Xu Y, Mueller KA, Chen X, Granucci E, Paganoni S, et al. Urate mitigates oxidative stress and motor neuron toxicity of astrocytes derived from ALS-linked SOD1(G93A) mutant mice. *Mol Cell Neurosci.* (2018) 92:12–6. doi: 10.1016/j.mcn.2018.06.002

27. Serra R, Coscas F, Pinna A, Peri M, Zucca I, Sellam A, et al. Detection of serum uric acid in primary open angle glaucoma: a pilot study. *Eur J Ophthalmol.* (2021) 31:1857–61. doi: 10.1177/1120672120944012

28. Li S, Shao M, Tang B, Zhang A, Cao W, Sun X. The association between serum uric acid and glaucoma severity in primary angle closure glaucoma: a retrospective case-control study. *Oncotarget.* (2017) 8:2816. doi: 10.18632/oncotarget.13745

29. Li S, Shao M, Li D, Tang B, Cao W, Sun X. Association of serum uric acid levels with primary open-angle glaucoma: a 5-year case–control study. *Acta Ophthalmologica*. (2019) 97:e356–63. doi: 10.1111/aos.13789

30. Elisaf M, Kitsos G, Bairaktari E, Kalaitzidis R, Kalogeropoulos C, Psilas K. Metabolic abnormalities in patients with primary open-angle glaucoma. *Acta Ophthalmol Scand.* (2001) 79:129–32. doi: 10.1034/j.1600-0420.2001.079002129.x

31. Yuki K, Murat D, Kimura I, Ohtake Y, Tsubota K. Reduced-serum vitamin C and increased uric acid levels in normal-tension glaucoma. *Graefes Arch Clin Exp Ophthalmol.* (2010) 248:243–8. doi: 10.1007/s00417-009-1183-6

32. Bouchemi M, Soualmia H, Midani F, El Afrit MA, El Asmi M, Feki M. impaired nitric oxide production in patients with primary open-angle glaucoma nitric oxide levels in patients with glaucoma Diminution de la production du monoxyde d'azote chez des patients atteints de glaucome primitif à angle ouvert. *La Tunisie Méd.* (2020) 98:144–9.

33. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* (2009) 62:e1–e34. doi: 10.1016/j.jclinepi.2009.06.006

34. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol.* (2010) 25:603–5. doi: 10.1007/s10654-010-9491-z

35. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* (2002) 21:1539–58. doi: 10.1002/sim.1186

36. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. *Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022).* Cochrane (2022). Available online at: www.training.cochrane.org/handbook

37. Ergan E, Ozturk F, Beyazyildiz E, Elgin U, Sen E, Cankaya AB, et al. Oxidant/antioxidant balance in the aqueous humor of patients with glaucoma. *Int J Opthalmol*. (2016) 9:249. doi: 10.18240/ijo.2016.02.12

38. Nucci C, Di Pierro D, Varesi C, Ciuffoletti E, Russo R, Gentile R, et al. Increased malondialdehyde concentration and reduced total antioxidant capacity in aqueous humor and blood samples from patients with glaucoma. *Mol Vis*. (2013) 19:1841.

39. Lei Y, Zhang X, Song M, Wu J, Sun X. Aqueous humor outflow physiology in NOS3 knockout mice. *Invest Ophthalmol Vis Sci.* (2015) 56:4891–8. doi: 10.1167/iovs.15-16564

40. Green K. Free radicals and aging of anterior segment tissues of the eye: a hypothesis. *Ophthal Res.* (1995) 27(Suppl. 1):143–9. doi: 10.1159/000267860

41. Ghiselli A, Serafini M, Natella F, Scaccini CJ. Total antioxidant capacity as a tool to assess redox status: critical view and experimental data. *Free Radic Biol Med*. (2000) 29:1106–14. doi: 10.1016/S0891-5849(00)00394-4

42. Wayner D, Burton G, Ingold K, Barclay L, Locke S. The relative contributions of vitamin E, urate, ascorbate and proteins to the total peroxyl radical-trapping antioxidant activity of human blood plasma. Biochim Biophys Acta. (1987) 924:408–19. doi: 10.1016/0304-4165(87)90155-3

43. Aoyama K, Matsumura N, Watabe M, Wang F, Kikuchi-Utsumi K, Nakaki T. Caffeine and uric acid mediate glutathione synthesis for neuroprotection. *Neuroscience*. (2011) 181:206–15. doi: 10.1016/j.neuroscience.2011.02.047

44. Du Y, Chen CP, Tseng CY, Eisenberg Y, Firestein BL. Astroglia-mediated effects of uric acid to protect spinal cord neurons from glutamate toxicity. *Glia*. (2007) 55:463–72. doi: 10.1002/glia.20472

45. Li S, Shao M, Cao W, Sun X. Association between pretreatment serum uric acid levels and progression of newly diagnosed primary angle-closure glaucoma: a prospective cohort study. *Oxid Med Cell Longev*. (2019). doi: 10.1155/2019/7919836

46. Astafurov K, Elhawy E, Ren L, Dong CQ, Igboin C, Hyman L, et al. Oral microbiome link to neurodegeneration in glaucoma. *PLoS ONE.* (2014) 9:e104416. doi: 10.1371/journal.pone.0104416

47. Zeng J, Liu H, Liu X, Ding C. The relationship between Helicobacter pylori infection and open-angle glaucoma: a meta-analysis. *Invest Ophthalmol Vis Sci.* (2015) 56:5238–45. doi: 10.1167/iovs.15-17059

48. Kim JM, Kim SH, Park KH, Han SY, Shim HS. Investigation of the association between *Helicobacter pylori* infection and normal tension glaucoma. *Invest Ophthalmol Vis Sci.* (2011) 52:665–8. doi: 10.1167/iovs.10-6096

49. Simavli H, Bucak YY, Tosun M, Erdurmuş M. Serum uric acid, alanine aminotransferase, hemoglobin and red blood cell count levels in pseudoexfoliation syndrome. *J Ophthalmol.* (2015). doi: 10.1155/2015/914098

50. Jampel HD, Moon JI, Quigley HA, Barron Y, Lam K-W. Aqueous humor uric acid and ascorbic acid concentrations and outcome of trabeculectomy. *Arch Ophthalmol.* (1998) 116:281–5. doi: 10.1001/archopht.116.3.281

51. Saccà SC, Pascotto A, Camicione P, Capris P, Izzotti A. Oxidative DNA damage in the human trabecular meshwork: clinical correlation in patients with primary open-angle glaucoma. *Archi Ophthalmol.* (2005) 123:458–63. doi: 10.1001/archopht.123.4.458

52. Huck A, Harris A, Siesky B, Kim N, Muchnik M, Kanakamedala P, et al. Vascular considerations in glaucoma patients of A frican and E uropean descent. *Acta ophthalmologica.* (2014) 92:e336–e40. doi: 10.1111/aos.12354

53. Abegão Pinto L, Willekens K, Van Keer K, Shibesh A, Molenberghs G, Vandewalle E, et al. Ocular blood flow in glaucoma–the Leuven Eye Study. *Acta Ophthalmol.* (2016) 94:592–8. doi: 10.1111/aos.12962

54. Xiong Q, Liu J, Xu Y. Effects of uric acid on diabetes mellitus and its chronic complications. *Int J Endocrinol*. (2019). doi: 10.1155/2019/9691345

55. Zhu D-D, Wang Y-Z, Zou C, She X-P, Zheng Z. The role of uric acid in the pathogenesis of diabetic retinopathy based on Notch pathway. *Biochem Biophys Res Commun*. (2018) 503:921–9. doi: 10.1016/j.bbrc.2018.06.097

56. Choi YJ, Yoon Y, Lee KY, Hien TT, Kang KW, Kim KC, et al. Uric acid induces endothelial dysfunction by vascular insulin resistance associated with the impairment of nitric oxide synthesis. *FASEB J*. (2014) 28:3197–204. doi: 10.1096/fj.13-247148

57. Kanellis J, Kang D-H, editors. Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. *Semin Nephrol.* (2005) 39–42. doi: 10.1016/j.semnephrol.2004.09.007

58. Cellini M, Strobbe E, Gizzi C, Balducci N, Toschi PG, Campos EC. Endothelin-1 plasma levels and vascular endothelial dysfunction in primary open angle glaucoma. *Life Sci.* (2012) 91:699–702. doi: 10.1016/j.lfs.2012.02.013

59. Lu Y, Yue J, Chen J, Li X, Wang L, Huang W, et al. Retinal microvasculature and choriocapillaris flow deficit in relation to serum uric acid using swept-source optical coherence tomography angiography. *Transl Vis Sci Technol.* (2022) 11:9. doi: 10.1167/tvst.11.8.9

60. Yang K, Li C, Shi K, Zhu X, Xiao Y, Su B, et al. Association of serum uric acid with retinal capillary plexus. *Front Endocrinol.* (2022) 13:855430. doi: 10.3389/fendo.2022.855430

61. Cho HK, Han JC, Choi JA, Chae JE, Kim RB. association between chronic renal disease and the risk of glaucoma development: a 12-year nationwide cohort study. *Invest Ophthalmol Vis Sci.* (2021) 62:27. doi: 10.1167/iovs.62.6.27

62. Johnson RJ, Nakagawa T, Jalal D, Sánchez-Lozada LG, Kang DH, Ritz E. Uric acid and chronic kidney disease: which is chasing which? *Nephrol Dial Transplant.* (2013) 28:2221–8. doi: 10.1093/ndt/gft029

63. Wong CW, Wong TY, Cheng C-Y, Sabanayagam C. Kidney and eye diseases: common risk factors, etiological mechanisms, and pathways. *Kidney Int.* (2014) 85:1290–302. doi: 10.1038/ki.2013.491

64. Jin M, Yang F, Yang I, Yin Y, Luo JJ, Wang H, et al. Uric acid, hyperuricemia and vascular diseases. *Front Biosci.* (2012) 17:656–69. doi: 10.2741/3950

65. Kim G-H, Jun J-B. Altered serum uric acid levels in kidney disorders. *Life*. (2022) 12:1891. doi: 10.3390/life12111891

66. Daskalopoulou S, Tzovaras V, Mikhailidis D, Elisaf M. Effect on serum uric acid levels of drugs prescribed for indications other than treating hyperuricaemia. *Curr Pharm Des.* (2005) 11:4161–75. doi: 10.2174/1381612057749 13309

67. Nigam SK, Bhatnagar V. The systems biology of uric acid transporters: the role of remote sensing and signaling. *Curr Opin Nephrol Hypertens.* (2018) 27:305. doi: 10.1097/MNH.0000000000000427

68. Sun H-L, Wu Y-W, Bian H-G, Yang H, Wang H, Meng X-M, et al. Function of uric acid transporters and their inhibitors in hyperuricaemia. *Front Pharmacol.* (2021) 12:667753. doi: 10.3389/fphar.2021.667753

69. Liu L, Liu X. Roles of drug transporters in blood-retinal barrier. *Adv Exp Med Biol.* (2019) 1141:467–504. doi: 10.1007/978-981-13-7647-4_10

70. Lee J, Shahidullah M, Hotchkiss A, Coca-Prados M, Delamere NA, Pelis RM, et al. renal-like organic anion transport system in the ciliary epithelium of the bovine and human eye. *Mol Pharmacol.* (2015) 87:697–705. doi: 10.1124/mol.114.096578

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 23 November 2023
DOI 10.3389/fmed.2023.1273889

OPEN ACCESS

EDITED BY
Alessio Martucci,
University of Rome Tor Vergata, Italy

REVIEWED BY
Sheng Yang Lim,
Tan Tock Seng Hospital, Singapore
Ratnakar Tripathi,
University of Missouri, United States

*CORRESPONDENCE
Marta Hajduga-Szewczyk
martahajduga@wp.pl
Adrian Smedowski
asmedowski@sum.edu.pl

RECEIVED 07 August 2023
ACCEPTED 24 October 2023
PUBLISHED 23 November 2023

CITATION
Hajduga-Szewczyk M, Smedowski A, Filipecka I and Mrukwa-Kominek E (2023) The effectiveness and safety of one-stage iStent-based micro-invasive glaucoma surgery—A retrospective study.
Front. Med. 10:1273889.
doi: 10.3389/fmed.2023.1273889

The effectiveness and safety of one-stage iStent-based micro-invasive glaucoma surgery—A retrospective study

Marta Hajduga-Szewczyk[1,2]*, Adrian Smedowski[1,3,4]*, Iwona Filipecka[2] and Ewa Mrukwa-Kominek[1,3]

[1]Department of Ophthalmology, Professor K. Gibinski University Clinical Center, Medical University of Silesia, Katowice, Poland, [2]Okulus Plus Co, Bielsko-Biala, Poland, [3]Department of Ophthalmology, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland, [4]GlaucoTech Co, Katowice, Poland

Purpose: Micro-invasive glaucoma surgery involves a group of treatment methods associated with a low rate of side effects and good effectiveness outcomes. One of the most frequently performed procedures belonging to this group is iStent microstent implantation. The aim of this study was to perform a retrospective evaluation of the safety and efficacy of a combined procedure involving cataract phacoemulsification and single iStent microstent implantation, performed simultaneously.

Materials and methods: The complete medical records of 62 patients (91 eyes) were analyzed retrospectively, including the best corrected visual acuity, intraocular pressure, the mean defect of visual fields, and the number of active substances used in eye drops. The follow-up times were 1, 3, 6, 9, and 12 months after the surgical procedure.

Results: A significant improvement in the best corrected visual acuity and a reduction of the intraocular pressure were achieved after the surgery. On average, after 12 months, the best corrected visual acuity improved from 0.70 (0.25) to 0.91 (0.18; $p = 0.001$), the intraocular pressure reduced from 17.76 (3.95) to 14.91 (3.04; $p = 0.0001$), and the number of active substances used in eye drops reduced from 2.07 (1.08) to 0.70 (0.06; $p = 0001$). In addition, we found that patients who initially showed higher intraocular pressure values did not benefit from surgery in the aspect of the number of active substances used in their eye drops. Intraoperative and postoperative adverse events were transient and ultimately did not affect the outcomes.

Conclusion: Simultaneous cataract phacoemulsification with single iStent implantation in patients with open-angle glaucoma is a safe and effective method for reducing intraocular pressure and the number of topical medications that must be used. Having initially higher intraocular pressure values may limit the beneficial effects of iStent implantation by subordinating patients from topical treatment; thus, single iStent implantation may not be the most favorable choice in uncontrolled glaucoma cases.

KEYWORDS

glaucoma—surgery, iStent, intra ocular pressure, cataracts, MIGS

Introduction

Glaucoma refers to a heterogeneous group of diseases characterized by progressive optic neuropathy resulting from damage to retinal ganglion cells (RGCs) (1). According to estimates by the European Glaucoma Society, ∼76 million people worldwide suffered from glaucoma in 2020, and forecasts indicate that, by 2040, the number of patients may increase to as many as 112 million (2). Increased intraocular pressure (IOP), age, coexisting chronic diseases (e.g., diabetes or cardiovascular diseases), high refractive errors, and, potentially, genetic background are the leading risk factors for the development of glaucoma (1, 3–5). Primary open-angle glaucoma (POAG) affects approximately 2% of the population over 40 years of age, and the percentage of patients increases with age, reaching approximately 10% in the 8th and 9th decades of life (6). POAG is the leading cause of irreversible blindness in developed countries and is a serious health and socioeconomic problem (6–13).

The current glaucoma treatment features different options depending on the type and severity of the disease (1, 14, 15). Regardless of the stage of the disease, the goal is to treat the increased IOP, which is believed to be responsible for disease progression. Among the available treatments, several types of glaucoma surgeries are available, including the gold-standard trabeculectomy and modern micro-invasive glaucoma surgery (MIGS) techniques. MIGS is a state-of-the-art glaucoma surgery that uses small incisions and specialized devices to regulate the IOP (16–22). According to the American Academy of Ophthalmology, MIGS comprises five major features: a high safety profile, minimal disruption of normal eye anatomy, an ab interno approach, efficacy—offering a meaningful IOP-lowering effect - and ease of use for patients and physicians. The introduction of MIGS techniques represented a compromise between safety and efficacy in glaucoma surgery (17, 23). Although the gold-standard penetrating bleb surgery, trabeculectomy, continues to represent the most effective surgical method for lowering the IOP, it is burdened with a greater risk of complications, including but not limited to uveal effusion, endophthalmitis, blebitis, and hypotony (24, 25). Modern glaucoma surgeries, including MIGS procedures, tend to be safer but at the cost of efficacy (26).

The iStent was specifically designed for use during cataract surgery; however, it can also be implanted as an individual procedure (27, 28). By creating a bypass, the iStent increases the aqueous humor outflow from the anterior chamber into Schlemm's canal (29). The iStent can be an effective treatment option for individuals with mild-to-moderate open-angle glaucoma who are also undergoing cataract surgery (30). It is not suitable, however, for all types and stages of glaucoma. The decision to use the iStent—or any other glaucoma treatment—depends on various factors, including the patient's specific condition, the severity of the glaucoma, and the ophthalmologist's recommendation (31).

In the present study, we aimed to evaluate the risks and benefits of parallel cataract phacoemulsification with single iStent implantation in patients with open-angle glaucoma.

Materials and methods

Analysis strategy

We performed a retrospective analysis of the medical records of patients who underwent the combined procedure of single iStent implantation and cataract phacoemulsification, performed simultaneously. All the procedures were performed by the same two ophthalmology specialists (IF and EK), and all the patients signed informed consent for the surgery and data usage. The approval of the local ethical committee was also obtained. We selected the records of 62 Caucasian patients—40 women and 22 men, with a mean age of 69.6 (6.8) years—for inclusion in our analysis. Among these patients, 91 eyes underwent surgical interventions—89 eyes due to POAG and 2 eyes due to secondary glaucoma associated with pseudoexfoliation syndrome. In the case of bilateral surgery, the time gap between the procedures in the right and left eye was at least 2 weeks. The indications for iStent implantation were the failure to achieve the target IOP with the maximum topical treatment, patients' adherence problems due to frequent eye drop application requirements, patients' intolerance of topical treatment, or disease progression according to the visual field test. In addition, the indication for cataract phacoemulsification was lens clouding that affected the decimal visual acuity to a level of 0.70 or lower or anisometropia/polyopia after cataract phacoemulsification in the fellow eye.

The primary inclusion criteria for surgery were as follows: being diagnosed with primary or secondary open-angle glaucoma with coexisting cataracts meeting the eligibility criteria for cataract surgery; an age of more than 18 years; a minimum best-corrected visual acuity (BCVA) of 0.10 according to the Snellen chart; an IOP in the range of 10–30 mmHg at the maximum tolerated topical treatment; and features of glaucomatous optic nerve damage in perimetry. The primary exclusion criteria for surgery were as follows: patients who underwent previous glaucoma procedures, those in whom advanced glaucoma was noted in the visual fields (according to the Hodapp–Parrish–Anderson criteria), those who showed intolerance to topical treatment, those who were pregnant or breastfeeding, those with anterior peripheral synechiae, those with corneal opacities affecting angle visibility, those with associated eye conditions, such as a history of recurrent uveitis, wet age-related macular degeneration (AMD), status post-posterior vitrectomy, or advanced diabetic retinopathy, and a lack of the patient's informed consent.

For the purpose of this analysis, we selected patients with complete and available medical records from between 2017 and 2020 who underwent the described surgeries at the Department of Ophthalmology, Medical University of Silesia, Katowice, Poland and Okulus Plus Co.

Surgical procedures

When undergoing cataract surgery, the pupils were dilated with 1% tropicamide (Polfa, Poland); topical anesthesia was applied using 0.5% proxymetacaine hydrochloride eye drops (Alcaine, Alcon, Switzerland); and the ocular surface was rinsed with an

antiseptic solution of 10% povidone-iodine. Additional intraocular anesthesia, in the form of 0.2 ml of Mydrane (Laboratories Thea, France), was additionally administered into the anterior chamber with a viscoelastic solution cover. Cataract extraction was performed via a 2.2–2.7 mm superior–temporal incision in the clear cornea, followed by the implantation of an artificial intraocular lens. For the iStent (Glaukos Corporation, San Clemente, CA, USA) implantation, the MIOSTAT solution was administered via an intracameral injection (0.1 mg/ml carbachol, Alcon, Switzerland) to constrict the pupil. The patient's head and the microscope were then rotated to enable visualization of the iridocorneal angle in the surgical gonioscope. The single iStent was inserted into Schlemm's canal, opposite the clear corneal incision. After surgery, the anti-inflammatory prophylaxis was applied by injecting cefuroxime (Aprokam, Laboratories Thea, France) into the anterior chamber.

Follow-up strategy

The follow-up analysis assessed the BCVA, the IOP (using a Goldmann applanation tonometer), and the number of active topical substances (NAS) contained in the eye drops used by patients. The follow-up times were before the surgical procedure, followed by 1, 3, 6, 9, and 12 months after the surgery. In addition, the mean deviation (MD) of the visual fields was analyzed before and after surgery (using standard automated perimetry; Humphrey Field Analyzer 740, Zeiss, Germany, 24-2 SITA-Fast program). Intraoperative and postoperative complications were also assessed.

Statistical analysis

For the statistical analysis, we used the IBM SPSS software (Armonk, NY, USA). Descriptive statistics are reported as the mean standard deviation (SD). The distribution of data was evaluated using the Shapiro–Wilk test. For the pairwise comparisons, we used the Wilcoxon paired-samples test. Correlations were determined by calculating non-linear Spearman correlation coefficients. A $P < 0.05$ was considered to be statistically significant. For statistical purposes, we used logarithmic visual acuity to ensure a more reliable representation of data; however, decimal visual acuity was selected for the final presentation of data in the study.

Results

The analyzed group consisted of 62 patients (91 eyes) who underwent simultaneous cataract phacoemulsification with the implantation of an intraocular lens and a single iStent implant. The preoperative characteristics of the group are shown in Table 1. Because the analyzed patients represented a wide IOP range of 10–30 mmHg, we decided to divide them into two cohorts, depending on the preoperative IOP: subgroup A consisted of 78 eyes with preoperative IOP values of ≤ 21 mmHg, while subgroup B consisted of 13 eyes with preoperative IOP values of > 21 mmHg.

TABLE 1 Summary of mean preoperative measurements.

BCVA	0.70 (0.25)
IOP (mmHg)	17.76 (3.95)
The number of active substances in the eye drops	2.07 (1.08) 0, 1, or 2 substances: 55 eyes 3 or 4 substances: 36 eyes

Best-corrected visual acuity

When compared to the preoperative evaluation, the BCVA improved after 1 month of follow-up by 0.21 (0.18) and 0.23 (0.16) in subgroup A and 0.14 (0.06) in subgroup B. After 3 months, it improved by 0.25 (0.15); in subgroup A, it improved by 0.24 (0.15); and in subgroup B, it improved by 0.27 (0.17). After 6 months, the BCVA improved by 0.24 (0.17); in subgroup A, it improved by 0.22 (0.03), and in subgroup B, it improved by 0.23 (0.13). After 9 months, it improved by 0.21 (0.17) 0.20 (0.16) in subgroup A, and 0.18 (0.07) in subgroup B. Finally, after 12 months, it improved by 0.21 (0.15); in subgroup A, it improved by 0.20 (0.14); and in subgroup B, it improved by 0.20 (0.15). Thus, there was a significant improvement in the BCVA at all follow-up time points for both groups ($p < 0.05$, Wilcoxon test; Table 2).

IOP and NAS in eye drops

After 1 month of follow-up, an overall decrease in IOP by 3.22 (2.99) mmHg was achieved, which translates into an average decrease of 18.13% compared to the preoperative IOP values; in subgroup A, it decreased by 2.51 (2.34) or 15.10%, while in subgroup B, it decreased by 6.50 (4.00) or 26.40%. Moreover, the overall NAS was reduced by 1.60 (1.14) or 77.29% compared to the preoperative values; in subgroup A, it decreased by 1.64 (1.08) or 80.39%, while in subgroup B, it decreased by 1.33 (0.50), or 59.64%. After 3 months, the IOP decreased by 3.44 (2.91) mmHg, or 19.37% [in subgroup A by 2.58 (2.23) or 15.52%; in subgroup B by 8.92 (3.00) or 36.23%] compared to the IOP before surgery. The NAS was reduced by 1.56 (1.26) or 75.36% [in subgroup A by 1.65 (1.19) or 80.88% and in subgroup B by 1.00 (0.60) or 44.84%]. After 6 months, the IOP decreased by 3.36 (2.91) mmHg, or 18.92% [in subgroup A by 2.68 (2.61) or 16.13% and in subgroup B by 9.33 (3.89) or 37.90%], and the NAS was reduced by 1.61 (1.20) or 77.78% [in subgroup A by 1.67 (1.17) or 81.86% and in subgroup B by 1.18 (1.40) or 52.92%]. After 9 months of follow-up, the IOP decreased by 3.44 (3.16) mmHg or 19.37% [in subgroup A by 2.49 (2.3)] or 14.98% and in subgroup B by 9.33 (3.89) or 37.90%], and the NAS was reduced by 1.57 (1.23) or 75.85% [in subgroup A by 1.68 (1.15) or 82.35% and in subgroup B by 0.92 (0.51) or 41.26%] compared to the values before surgery. After 12 months, the IOP decreased by 2.85 (2.40) mmHg or 16.05% [in subgroup A by 1.95 (1.68) or 11.73% and in subgroup B by 8.23 (4.64) or 33.43%], and the NAS was reduced by 1.36 (1.26) or 65.70% [in subgroup A by 1.49 (1.18) or 73.04% and in subgroup B by 0.62 (0.50) or 27.80%].

These results are shown in Table 3 (p-values were calculated using the Wilcoxon paired-samples test) and in Figure 1. In the

TABLE 2 Statistical analysis of BCVA evolution after the surgical procedures.

Follow-up times [months]	0 vs. 1	0 vs. 3	0 vs. 6	0 vs. 9	0 vs. 12
Overall group	0.70 (0.25) vs. 0.92 (0.16)	0.70 (0.25) vs. 0.95 (0.14)	0.70 (0.25) vs. 0.92 (0.20)	0.70 (0.25) vs. 0.90 (0.19)	0.70 (0.25) vs. 0.91 (0.18)
	$p = 0.001$	$p = 0.001$	$p = 0.001$	$p = 0.001$	$p = 0.001$
Subgroup A	0.71 (0.25) vs. 0.94 (0.14)	0.71 (0.25) vs. 0.95 (0.14)	0.71 (0.25) vs. 0.92 (0.20)	0.71 (0.25) vs. 0.91 (0.19)	0.71 (0.25) vs. 0.91 (0.19)
	$p = 0.001$	$p = 0.01$	$p = 0.01$	$p = 0.01$	$p = 0.01$
Subgroup B	0.69 (0.29) vs. 0.83 (0.25)	0.69 (0.29) vs. 0.93 (0.14)	0.69 (0.29) vs. 0.93 (0.17)	0.69 (0.29) vs. 0.85 (0.20)	0.69 (0.29) vs. 0.89 (0.18)
	$p = 0.01$	$p = 0.001$	$p = 0.001$	$p = 0.01$	$p = 0.01$

Wilcoxon paired-samples test, mean (SD).

correlation analysis, we investigated whether there is a relationship between the IOP values and the NAS before and 12 months after the procedure. In the overall group, the Spearman rank correlation coefficient before surgery was 0.04 ($p = 0.6$); 12 months after surgery, the Spearman rank correlation coefficient was 0.2 ($p = 0.01$).

Visual fields

To assess the stage of the glaucomatous optic nerve damage, the MD of the visual fields was analyzed. In the overall group, the preoperative MD value was −4.49 (7.79), and 12 months after surgery, it was −3.27 (6.99; $p = 0.03$). In subgroup A, these values were −6.8 (7.01) and −6.4 (6.6), respectively ($p = 0.6$). In subgroup B, they were −4.94 (7.2) and −3.07 (6.8), respectively ($p = 0.03$).

Intraoperative and postoperative complications

Among the intraoperative complications, we identified the following in our retrospective analysis: detachment of the corneal endothelium (one case) and dislocation of the implant from Schlemm's canal into the anterior chamber (one case). In terms of postoperative complications, anterior chamber bleeding was reported in three eyes. In addition, 10 eyes developed posterior capsule opacification during the follow-up period, requiring a YAG laser capsulotomy. Out of the analyzed cases, there were no cases complicated with endophthalmitis, and during the entire follow-up period, no additional glaucoma surgery was required for any of the patients.

Discussion

The coexistence of cataracts and glaucoma is relatively common, and its prevalence increases with age (32, 33). In recent years, MIGS procedures have gained popularity, and the microstent iStent has become one of the most frequently used devices within the MIGS group (27, 29, 30, 34–39). In patients qualified for anti-glaucoma surgery who additionally show lens opacities, simultaneously combined procedures are often considered (33, 40). It is believed that cataract phacoemulsification with artificial intraocular lens implantation can be effectively and safely combined with glaucoma surgical procedures, achieving not only IOP reduction but also visual acuity improvement (33, 40).

The benefits of simultaneous cataract surgery and the implantation of an iStent have been suggested in many publications, which have also compared the results of combined procedures with those of cataract surgery alone (27, 29–32, 41). In a study conducted by Fernández-Barrientos et al. 33 eyes were randomly assigned either two iStent implants and cataract surgery (group 1) or cataract surgery alone (group 2). In group 1, the IOP and the NAS decreased significantly after 12 months of observation compared to group 2 (29). Spiegel et al. (32) conducted a 24-month multicenter study of 58 eyes after cataract phacoemulsification with the iStent implantation procedure; they reported the procedure to be safe and effective in reducing the IOP and NAS in eye drops. Arriola-Villalobos et al. (31) compared the results of 19 eyes with concomitant open-angle glaucoma (including pseudoexfoliative and pigmentary glaucoma) and cataracts that underwent phacoemulsification and the implantation of an intraocular lens, along with the implantation of a single iStent implant. The 3-year follow-up visit showed that this treatment method was both safe and effective.

Tan et al. (27) assessed the safety and efficacy of cataract phacoemulsification combined with single iStent implantation in open-angle glaucoma over a 3-year follow-up period. Forty-one eyes were examined, of which thirty-six completed the 3-year follow-up. According to the study report, the combined treatment turned out to be both safe and effective. Fea et al. (30) presented the results of the observation of 36 eyes with cataracts and POAG who were randomly assigned to cataract surgery combined with iStent implantation or phacoemulsification alone. The authors showed that both methods reduced the NAS in the drops used by patients. However, the efficacy of cataract phacoemulsification alone in reducing the IOP faded over time, while after the combined procedure, the lower IOP values remained constant over the observation period. In our study, the group of patients who underwent simultaneous cataract surgery and single iStent implantation showed an improvement in BCVA that was observed at all follow-up points, with the values being 30% better after 12 months compared to before the surgery. However, the BCVA improvement was mostly due to the cataract phacoemulsification rather than the implantation of the iStent implant itself. Tan et al. (27) included 41 patients in their study, implanting a single iStent in conjunction with cataract surgery. The authors observed an

TABLE 3 Statistical analysis of IOP and NAS values after the surgical procedures.

Follow-up times [months]		0 vs. 1	0 vs. 3	0 vs. 6	0 vs. 9	0 vs. 12
IOP	Overall group	17.76 (3.95) vs. 14.49 (3.39)	17.76 (3.95) vs. 14.27 (2.51)	17.76 (3.95) vs. 14.17 (2.73)	17.76 (3.95) vs. 14.36 (2.80)	17.76 (3.95) vs. 14.91 (3.04)
		$p = 0.0001$	$p = 0.0001$	$p = 0.0001$	$p = 0.0001$	$p = 0.0001$
	Subgroup A	16.62 (2.78) vs. 14.10 (2.95)	16.62 (2.78) vs. 14.01 (2.48)	16.62 (2.78) vs. 13.89 (2.69)	16.62 (2.78) vs. 14.17 (2.60)	16.62 (2.78) vs. 14.67 (2.76)
		$p = 0.003$	$p = 0.001$	$p = 0.001$	$p = 0.001$	$p = 0.002$
	Subgroup B	24.62 (2.81) vs. 17.00 (4.90)	24.62 (2.81) vs. 15.92 (2.15)	24.62 (2.81) vs. 16.09 (2.26)	24.62 (2.81) vs. 15.50 (3.73)	24.62 (2.81) vs. 16.38 (4.19)
		$p = 0.0001$	$p = 0.0001$	$p = 0.0001$	$p = 0.0001$	$p = 0.0001$
NAS	Overall group	2.07 (1.08) vs. 0.47 (0.14)	2.07 (1.08) vs. 0.51 (0.11)	2.07 (1.08) vs. 0.47 (0.10)	2.07 (1.08) vs. 0.52 (0.24)	2.07 (1.08) vs. 0.70 (0.16)
		$p = 0.0001$	$p = 0.0001$	$p = 0.0001$	$p = 0.0001$	$p = 0.0001$
	Subgroup A	2.04 (1.11) vs. 0.40 (0.19)	2.04 (1.11) vs. 0.39 (0.22)	2.04 (1.11) vs. 0.37 (0.11)	2.04 (1.11) vs. 0.39 (0.12)	2.04 (1.11) vs. 0.55 (0.25)
		$p = 0.0001$	$p = 0.0001$	$p = 0.0001$	$p = 0.0001$	$p = 0.0001$
	Subgroup B	2.23 (0.93) vs. 0.92 (0.16)	2.23 (0.93) vs. 1.25 (0.29)	2.23 (0.93) vs. 1.18 (0.33)	2.23 (0.93) vs. 1.33 (0.23)	2.23 (0.93) vs. 1.62 (0.26)
		$p = 0.01$	$p = 0.05$	$p = 0.05$	$p = 0.06$	$p = 0.2$

Wilcoxon paired-samples test, mean (SD).

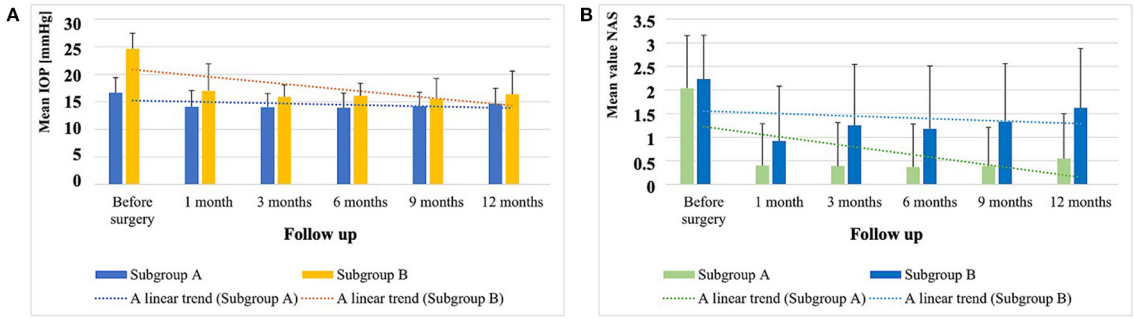

FIGURE 1
(A) Values of the mean IOP ± SD (mmHg) before surgery and during the following observation periods after surgery in subgroup A and subgroup B, and the linear trend of the result distribution. **(B)** NAS ± SD in eye drops before surgery and during the following observation periods after surgery in subgroup A and subgroup B, and the linear trend of the result distribution.

improvement in the postoperative BCVA by more than two lines as early as 1 month after the procedure. This value remained at a similar level for the next few months of observation. Katz et al. (35) carried out an 18-month follow-up study of 119 patients with POAG who had one, two, or three iStent implants. One group featured cases of pseudophakia (i.e., the single-stent group), and the other groups included eyes with their own lens. The postoperative BCVA values did not differ significantly compared to the preoperative ones. In the literature, one can find a comparison of the effectiveness of the implantation of an iStent alone or with simultaneous cataract surgery. In some studies, the results suggest that reducing the IOP in patients with POAG is sufficient using iStent implantation alone (42), while other researchers have found greater benefits when the two procedures are combined (19, 43–45). When comparing cataract surgery alone with glaucoma surgery, studies have shown that the second method gives better results (35). Another study showed that the implantation of two or three iStents gives even better results than a single implant (40).

We observed that, in the case of simultaneous iStent implantation and cataract surgery, after 12 months of observation, the IOP decreased by an average of 2.85 ± 4.40 mmHg (16.05%) to the level of 14.91 ± 3.04 mmHg, with an average NAS in eye drops of 0.70 ± 1.06 (i.e., a decrease by 1.36 ± 1.26). Moreover, after 12 months of observation in the overall group, the NAS used in eye drops—compared to the values before the surgery—decreased in 68 eyes (74.73%), while 54 eyes (59.34%) did not require the use of eye drops at all. For 20 eyes, the NAS remained at the same level, while for 3 eyes, it was necessary to increase the NAS. It should be noted that no additional glaucoma surgery

was required for any of the patients during the entire 12-month follow-up period.

Our results are comparable to those presented in the study by Spiegel et al. (32), who reported that the IOP decreased by an average of 4.3 mmHg and the NAS by 1.2 after 12 months of observation. In contrast, our results were more favorable than those in the study by Fea et al. (21), who reported that the IOP decreased by an average of 1.7 mmHg and the NAS by 0.4 after 12 months of observation. Finally, our results were worse than those in the study by Tan et al. (27), who reported that the IOP decreased by an average of 5.3 mmHg and the NAS by 1.6 after 12 months of observation. The differences between the results may arise from the different group sizes and baseline values used to qualify patients for the procedure.

The first-line treatment for glaucoma is usually IOP-lowering drops (14, 15). Considering that a large proportion of patients diagnosed with glaucoma are elderly people with many systemic diseases, it can be assumed that their adherence to the rules of using eye drops is often less than ideal. Non-compliance, in turn, may lead to disease progression and the gradual loss of vision, which translates into the disability of patients and high costs for health and social care (46). Based on our data and the analysis of the literature, we have shown that the reduced number of topical medications required after a single iStent implantation makes this type of surgery a good option for patients who are intolerant to eye drops and/or who have difficulties using them. Katz et al. (47) also suggested that if a greater reduction in the IOP is required, the implantation of more than one iStent may be considered.

There is strong evidence suggesting that IOP fluctuates daily when using eye drops and that their effect on IOP regulation may be limited (48, 49). In the analyzed group of patients before the procedure, the NAS did not correlate with the IOP values. It can therefore be concluded that topical medications did not achieve the target IOP. For this reason, the patients were referred for surgical treatment. After concurrent cataract surgery with single iStent implantation, the correlation between the NAS and IOP was restored, thus restoring the equilibrium state and achieving therapeutic success. In our study, we subtracted the uncontrolled glaucoma patients (subgroup B) from the overall study group to investigate whether higher initial IOP values would limit the effectiveness of single iStent implantation. Despite the effective lowering of the IOP 12 months after surgery, these patients did not benefit from the surgery in terms of the NAS used in eye drops, as this value was similar 12 months after surgery to that reported preoperatively. This may suggest that uncontrolled glaucoma patients with higher initial IOP values may not be the best candidates for single iStent implantation as they may require more radical surgery or the implantation of multiple iStents. Indeed, some studies have shown the triple implantation of the iStent infinite implant to be effective in the treatment of uncontrolled glaucoma cases (50). The implantation of the iStent not only reduces the IOP but also theoretically limits daily IOP fluctuations, thus minimizing the risk of glaucoma progression. We did not observe changes between the preoperative and postoperative visual field test results. However, a significant improvement in the visual field MD was obtained after 12 months compared with the results before the surgery, which could be explained by the following: First, we are aware that a follow-up period of 1 year could be too short to observe visual field changes. Second, the MD of visual fields considers the diffuse defects, which could be caused by the cataract itself. Finally, it is known that if the damaging factor is eliminated in the early stages of the disease—that is, the increased IOP—the function of the RGCs may improve; this is reflected in our analysis, especially in subgroup B, in which there were higher initial IOP values (51–53). The Advanced Glaucoma Intervention Study (AGIS) (54) also confirmed the relationship between low IOP and reduced glaucoma progression risk in patients with POAG. Myers et al. (55) included in their 4-year follow-up 80 patients (80 eyes) with open-angle glaucoma resistant to topical treatment. Each patient had a history of trabeculectomy and the subsequent implantation of two iStent implants and one iStent Supra implant. As a postoperative topical treatment, travoprost eye drops were recommended. None of the patients required additional anti-glaucoma surgery throughout the 4-year follow-up period. The applied combination treatment achieved IOP control, and the postoperative visual field results remained stable throughout the observation period.

The various intraoperative and postoperative complications that have occurred in patients have been reported in the literature. The most frequently mentioned complication was the presence of blood in the anterior chamber (36, 40). In our study, we found reports of three patients with this complication. However, it is known that some blood reflux through the iStent is often observed after implant placement, which indicates the correct placement of the implant in Schlemm's canal (44). In a study by Tan et al. (27), after cataract surgery with iStent implantation, blood cells were observed in the anterior chamber of the eye in one patient (2.44% of examined eyes). This symptom resolved within 1 week. Similarly, in a study by Buchacra et al. (41), among 10 examined eyes, there were three cases of blood reflux into the anterior chamber during the placement of the iStent implant in Schlemm's canal. Fernández-Barrientos et al. (29) described slight blood reflux from the implant as a positive sign, indicating the correct placement of the iStent in Schlemm's canal.

The analyzed literature also described difficulty inserting the implant into Schlemm's canal as a possible intraoperative complication (55). In this study, similar problems were described during surgery. In one case, implant dislocation from Schlemm's canal into the anterior chamber occurred, while in another case, detachment of the corneal endothelium occurred, caused by mechanical damage from the iStent guide.

There are several limitations of our study. The size of the study group and subgroups does not fully represent the glaucoma population. In addition, the retrospective construction of the study limited the analysis to the available medical records and did allow us to enrich the analysis with some more sensitive markers, such as the visual field pattern standard deviation (PSD), electrophysiology, or corneal endothelial cell count.

Conclusion

Simultaneous cataract phacoemulsification and single iStent implantation in patients with open-angle glaucoma is a safe

and effective method to reduce the IOP and the number of topical medications used and to prevent visual field deterioration. Initially, higher IOP values may limit the beneficial effects of iStent implantation because these patients continue to require topical treatment after the surgery; thus, a single iStent implantation may not be the most favorable choice in uncontrolled glaucoma cases. However, simultaneous cataract phacoemulsification and single iStent implantation in patients with uncontrolled open-angle glaucoma may help to restore the equilibrium state between the IOP and topical medications, resulting in therapeutic success.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the Ethical Committee of Medical University of Silesia. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MH-S: Data curation, Investigation, Methodology, Writing—original draft. AS: Formal analysis, Methodology, Supervision, Validation, Writing—review & editing. IF: Investigation, Methodology, Writing—review & editing. EM-K: Conceptualization, Data curation, Funding acquisition, Writing—review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

AS was employed by the GlaucoTech Co.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. *JAMA*. (2014) 311:1901–11. doi: 10.1001/jama.2014.3192

2. European Glaucoma Society Terminology and Guidelines for Glaucoma. Chapter 3: treatment principles and options supported by the EGS foundation: part 1: foreword; introduction; glossary; chapter 3 treatment principles and options. *Br J Ophthalmol*. (2021) 101: 130–191. doi: 10.1136/bjophthalmol-2016-EGSguideline.003

3. Nakazawa T, Fukuchi T. What is glaucomatous optic neuropathy? *Jap. J. Ophthalmol.* (2020) 64:243–249. doi: 10.1007/s10384-020-00736-1

4. Davis BM, Crawley L, Pahlitzsch M, Javaid F, Cordeiro MF. Glaucoma: the retina and beyond. *Acta Neuropathol.* (2016) 132:807–26. doi: 10.1007/s00401-016-1609-2

5. Jonas JB, Aung T, Bourne RR, Bron AM, Ritch R, Panda-Jonas S. Glaucoma. *Lancet*. (2017) 390:2183–93. doi: 10.1016/S0140-6736(17)31469-1

6. Tham YC Li X, Wong TY, Quigley HA, Aung T, Cheng CY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology.* (2014) 121:2081–90. doi: 10.1016/j.ophtha.2014.05.013

7. Leske MC, Heijl A, Hyman L, Bengtsson B, Dong LM, Yang Z, et al. Predictors of long-term progression in the early manifest glaucoma trial. *Ophthalmology.* (2007) 114:1965–72. doi: 10.1016/j.ophtha.2007.03.016

8. Chauhan BC, Garway-Heath DF, Goñi FJ, Rossetti L, Bengtsson B, Viswanathan AC, et al. Practical recommendations for measuring rates of visual field change in glaucoma. *Br J Ophthalmol.* (2008) 92:569–73. doi: 10.1136/bjo.2007.135012

9. Canadian Glaucoma Study Group. Canadian glaucoma study: 3. Impact of risk factors and intraocular pressure reduction on the rates of visual field change. *Archi Ophthalmol.* (2010) 128:1249–55. doi: 10.1001/archophthalmol.2010.196

10. Ahrlich KG, De Moraes CG, Teng CC, Prata TS, Tello C, Ritch R. Visual field progression differences between normal-tension and exfoliative high-tension glaucoma. *Inv Ophthalmol Visual Sci.* (2010) 51:1458–63. doi: 10.1167/iovs.09-3806

11. Bengtsson B, A. visual field index for calculation of glaucoma rate of progression. *Am J Ophthalmol.* (2008) 145:343–53. doi: 10.1016/j.ajo.2007.09.038

12. Peters D, Bengtsson B. Lifetime risk of blindness in open-angle glaucoma. *Am J Ophthalmol.* (2013) 156:724–30. doi: 10.1016/j.ajo.2013.05.027

13. Heijl A, Bengtsson B, Chauhan BC, Lieberman MF, Cunliffe I, Hyman L, et al. A comparison of visual field progression criteria of 3 major glaucoma trials in early manifest glaucoma trial patients. *Ophthalmology.* (2008) 115:1557–65. doi: 10.1016/j.ophtha.2008.02.005

14. Conlon R, Saheb H. Glaucoma treatment trends: a review. *Can J Ophthalmol.* (2017) 52:114–24. doi: 10.1016/j.jcjo.2016.07.013

15. Dikopf MS, Vajaranant TS, Edward DP. Topical treatment of glaucoma: established and emerging pharmacology. *Expert Opin Pharmacother.* (2017) 18:885–98. doi: 10.1080/14656566.2017.1328498

16. Wagner IV, Stewart MW, Dorairaj SK. Updates on the diagnosis and management of glaucoma. *Mayo Clin Proc Innov Qual Outcomes.* (2022) 6:618–35. doi: 10.1016/j.mayocpiqo.2022.09.007

17. Rowson AC, Hogarty DT, Maher D. Minimally invasive glaucoma surgery: safety of individual devices. *J Clin Med.* (2022) 11:6833. doi: 10.3390/jcm11226833

18. Birnbaum FA, Neeson C, Solá-Del Valle D. Microinvasive glaucoma surgery: an evidence-based review. *Semin Ophthalmol.* (2021) 36:772–86. doi: 10.1080/08820538.2021.1903513

19. Song Y, Zhang H, Zhang Y, Tang G, Wan KH, Lee JW, et al. Minimally invasive glaucoma surgery in primary angle-closure glaucoma. *The Asia-Pacific J Ophthalmol.* (2022) 11:460–9. doi: 10.1097/APO.0000000000000561

20. Khodeiry M, Sayed MS. New glaucoma drainage implants available to glaucoma surgeons. *Curr Opin Ophthalmol.* (2023) 34:176–80. doi: 10.1097/ICU.0000000000000936

21. Lavia C, Dallorto L, Maule M, Ceccarelli M, Fea AM. Minimally-invasive glaucoma surgeries (MIGS) for open angle glaucoma: a systematic review and meta-analysis. *PLoS ONE.* (2017) 12:0183142. doi: 10.1371/journal.pone.0183142

22. Gurnani B, Tripathy K. *Minimally Invasive Glaucoma Surgery*. London: StatPearls (2023).

23. Aref AA, Parker PR, Chen MY. Microinvasive glaucoma surgeries: critical summary of clinical trial data with and without phacoemulsification. *Curr Opin Ophthalmol.* (2023) 34:146–51. doi: 10.1097/ICU.0000000000000923

24. Zahid S, Musch DC, Niziol LM, Lichter PR. Risk of endophthalmitis and other long-term complications of trabeculectomy in the collaborative initial glaucoma treatment study (CIGTS). *Am J Ophthalmol.* (2013) 155:17. doi: 10.1016/j.ajo.2012.10.017

25. Jampel HD, Musch DC, Gillespie BW, Lichter PR, Wright MM, Guire KE, et al. Perioperative complications of trabeculectomy in the collaborative initial glaucoma treatment study (CIGTS). *Am J Ophthalmol.* (2005) 140:16–22. doi: 10.1016/j.ajo.2005.02.013

26. Rao A, Cruz RD. Trabeculectomy: Does it have a future? *Cureus.* (2022) 14:27834. doi: 10.7759/cureus.27834

27. Tan SZ, Au L. Manchester iStent study: 3-year results and cost analysis. *Eye.* (2016) 30:1365–70. doi: 10.1038/eye.2016.139

28. Wang SY, Singh K, Stein JD, Chang RT. Ocular antihypertensive medication use after iStent implantation concurrent with cataract surgery vs cataract surgery alone in a large US health care claims database. *JAMA Ophthalmol.* (2019) 137:21. doi: 10.1001/jamaophthalmol.2018.4461

29. Fernández-Barrientos Y, García-Feijoó J, Martínez-de-la-Casa JM, Pablo LE, Fernández-Pérez C. Fluorophotometric study of the effect of the glaukos trabecular microbypass stent on aqueous humor dynamics. *Invest Ophthalmol Vis Sci.* (2010) 51:3327–32. doi: 10.1167/iovs.09-3972

30. Fea AM, Consolandi G, Zola M, Pignata G, Cannizzo P, Lavia C, et al. Micro-bypass implantation for primary open-angle glaucoma combined with phacoemulsification: 4-year follow-up. *J Ophthalmol.* (2015) 2015:357. doi: 10.1155/2015/795357

31. Arriola-Villalobos P, Martínez-de-la-Casa JM, Díaz-Valle D, Fernández-Pérez C, García-Sánchez J, García-Feijoó J. Combined iStent trabecular micro-bypass stent implantation and phacoemulsification for coexistent open-angle glaucoma and cataract: a long-term study. *Br J Ophthalmol.* (2012) 96:645–49. doi: 10.1136/bjophthalmol-2011-300218

32. Spiegel D, Wetzel W, Neuhann T, Stürmer J, Höh H, García-Feijoo J, et al. Coexistent primary open-angle glaucoma and cataract: interim analysis of a trabecular micro-bypass stent and concurrent cataract surgery. *Eur J Ophthalmol.* (2009) 19:393–9. doi: 10.1177/112067210901900311

33. Tzu JH, Shah CT, Galor A, Junk AK, Sastry A, Wellik SR, et al. Refractive outcomes of combined cataract and glaucoma surgery. *J Glaucoma.* (2015) 24:161–4. doi: 10.1097/01.ijg.0000435773.20279.56

34. Malvankar-Mehta MS, Iordanous Y, Chen YN, Wang WW, Patel SS, Costella J, et al. iStent with phacoemulsification versus phacoemulsification alone for patients with glaucoma and cataract: a meta-analysis. *PLoS ONE.* (2015) 10:e0131770. doi: 10.1371/journal.pone.0131770

35. Samuelson TW, Katz LJ, Wells JM, Duh YJ, Giamporcaro JE. Randomized evaluation of the trabecular micro-bypass stent with phacoemulsification in patients with glaucoma and cataract. *Ophthalmology.* (2011) 118:459–67. doi: 10.1016/j.ophtha.2010.07.007

36. Belovay GW, Naqi A, Chan BJ, Rateb M, Ahmed IIK. Using multiple trabecular micro-bypass stents in cataract patients to treat open-angle glaucoma. *J Cataract Refract Surg.* (2012) 38:1911–7. doi: 10.1016/j.jcrs.2012.07.017

37. Salimi A, Watt H, Harasymowycz P. Long-term outcomes of two first-generation trabecular micro-bypass stents (iStent) with phacoemulsification in primary open-angle glaucoma: eight-year results. *Eye Vision.* (2021) 8:1–12. doi: 10.1186/s40662-021-00263-1

38. Inatani M, Kohama I, Chu A. iStent trabecular micro-bypass stent implantation combined with phacoemulsification for open-angle glaucoma: a 2-year post-marketing surveillance study in Japan. *Adv Ther.* (2022) 39:4076–93. doi: 10.1007/s12325-022-02207-0

39. Kozera M, Konopińska J, Mariak Z, Rekas M. Treatment of open-angle glaucoma with istent implantation combined with phacoemulsification in polish Caucasian population. *Clinical Ophthalmology.* (2021) 15:473–80. doi: 10.2147/OPTH.S293637

40. Bilgin G, Karakurt A, Saricaoglu MS. Combined non-penetrating deep sclerectomy with phacoemulsification versus non-penetrating deep sclerectomy alone. *Semin Ophthalmol.* (2014) 29:146–50. doi: 10.3109/08820538.2013.874466

41. Buchacra O, Duch S, Milla E, Stirbu O. One-year analysis of the iStent trabecular microbypass in secondary glaucoma. *Clin Ophthalmol.* (2011) 5:321–6. doi: 10.2147/OPTH.S15025

42. Hardin JS, Gauldin DW, Soliman MK, Chu CJ, Yang YC, Sallam AB, et al. Cataract surgery outcomes in eyes with primary epiretinal membrane. *JAMA Ophthalmol.* (2018) 136:148–54. doi: 10.1001/jamaophthalmol.2017.5849

43. Ang GS, Varga Z, Shaarawy T. Postoperative infection in penetrating versus non-penetrating glaucoma surgery. *Br J Ophthalmol.* (2010) 94:1571–6. doi: 10.1136/bjo.2009.163923

44. Fong CSU, Mitchell P, Rochtchina E, Hong T, Loryn TD, Wang JJ, et al. Incidence and progression of epiretinal membranes in eyes after cataract surgery. *Am J Ophthalmol.* (2013) 156:22. doi: 10.1016/j.ajo.2013.03.022

45. Kiessling D, Rennings C, Hild M, Lappas A, Dietlein TS, Roessler GF, et al. Predictability of success for combined iStent inject trabecular bypass implantation with phacoemulsification in the subsequent eye. *Clin Exp Ophthalmol.* (2023) 27:14227. doi: 10.1111/ceo.14227

46. Schwartz GF, Quigley HA. Adherence and persistence with glaucoma therapy. *Surv Ophthalmol.* (2008) 53:2. doi: 10.1016/j.survophthal.2008.08.002

47. Katz LJ, Erb C, Carceller GA, Fea AM, Voskanyan L, Wells JM, et al. Prospective, randomized study of one, two, or three trabecular bypass stents in open-angle glaucoma subjects on topical hypotensive medication. *Clin Ophthalmol.* (2015) 9:2313–20. doi: 10.2147/OPTH.S96695

48. Stewart WC, Konstas AGP, Nelson LA, Kruft B. Meta-analysis of 24-hour intraocular pressure studies evaluating the efficacy of glaucoma medicines. *Ophthalmology.* (2008) 115:4. doi: 10.1016/j.ophtha.2007.10.004

49. Friedman DS, Quigley HA, Gelb L, Tan J, Margolis J, Shah SN, et al. Using pharmacy claims data to study adherence to glaucoma medications: methodology and findings of the glaucoma adherence and persistency study (GAPS). *Inv Ophthal Visual Sci.* (2007) 48:5052–7. doi: 10.1167/iovs.07-0290

50. Sarkisian SR, Grover DS, Gallardo MJ, Brubaker JW, Giamporcaro JE, Hornbeak DM, et al. Effectiveness and safety of iStent infinite trabecular micro-bypass for uncontrolled glaucoma. *J Glaucoma.* (2023) 32:9–18. doi: 10.1097/IJG.0000000000002141

51. Fry LE, Fahy E, Chrysostomou V, Hui F, Tang J, van Wijngaarden P, et al. The coma in glaucoma: Retinal ganglion cell dysfunction and recovery. *Prog Retin Eye Res.* (2018) 65:77–92. doi: 10.1016/j.preteyeres.2018.04.001

52. Ventura LM, Porciatti V. Restoration of retinal ganglion cell function in early glaucoma after intraocular pressure reduction: a pilot study. *Ophthalmology.* (2005) 112:20–7. doi: 10.1016/j.ophtha.2004.09.002

53. Ventura LM, Feuer WJ, Porciatti V. Progressive loss of retinal ganglion cell function is hindered with IOP-lowering treatment in early glaucoma. *Invest Ophthalmol Vis Sci.* (2012) 53:659–63. doi: 10.1167/iovs.11-8525

54. Agis Investigators. The Advanced Glaucoma Intervention Study (AGIS) 7: the relationship between control of intraocular pressure and visual field deterioration. *Am J Ophthalmol.* (2000) 30:429–40. doi: 10.1016/S0002-9394(00)00538-9

55. Myers JS, Masood I, Hornbeak DM, Belda JI, Auffarth G, Jünemann A, et al. Prospective evaluation of two iStent® trabecular stents, one iStent Supra® suprachoroidal stent, and postoperative prostaglandin in refractory glaucoma: 4-year outcomes. *Adv Ther.* (2018) 35:395–407. doi: 10.1007/s12325-018-0666-4

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 10 January 2024
DOI 10.3389/fmed.2023.1300778

OPEN ACCESS

EDITED BY
Alessio Martucci,
University of Rome Tor Vergata, Italy

REVIEWED BY
Leonardo Bencivenga,
University of Naples Federico II, Italy
Valeria Albano,
Azienda Ospedaliero Universitaria Consorziale Policlinico di Bari, Italy

*CORRESPONDENCE
Hun Lee
✉ yhun777@gmail.com

†These authors have contributed equally to this work

RECEIVED 04 October 2023
ACCEPTED 28 December 2023
PUBLISHED 10 January 2024

CITATION
Lee SY, Lee JS, Kim JY, Tchah H and Lee H (2024) Visit-to-visit variability in blood pressure and the risk of open-angle glaucoma in individuals without systemic hypertension: a nationwide population-based cohort study.
Front. Med. 10:1300778.
doi: 10.3389/fmed.2023.1300778

Visit-to-visit variability in blood pressure and the risk of open-angle glaucoma in individuals without systemic hypertension: a nationwide population-based cohort study

Sang Yeop Lee[1,2†], Ji Sung Lee[3,4†], Jae Yong Kim[5], Hungwon Tchah[5] and Hun Lee[5*]

[1]Department of Ophthalmology, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, Republic of Korea, [2]Institute of Vision Research, Department of Ophthalmology, Yonsei University College of Medicine, Seoul, Republic of Korea, [3]Clinical Research Center, Asan Institute for Life Sciences, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [4]Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [5]Department of Ophthalmology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Purpose: We aimed to evaluate the effect of visit-to-visit variability in blood pressure (BP) on the risk of open-angle glaucoma (OAG) in individuals without systemic hypertension using a population-based retrospective cohort study design.

Methods: The Korean National Health Insurance Service-National Health Screening Cohort database, which collected data of 209,226 individuals between 2002 and 2015, was used to analyze the data of 140,910 eligible participants. The mean follow-up duration was 8.3 years. Visit-to-visit BP variability was assessed using standard deviation (SD), coefficient of variation (CV), and variability independent of the mean (VIM). Participants were categorized into four groups according to BP variability quartiles. We verified the effect of BP variability by comparing participants of the first to third quartiles of BP variability groups with those belonging to the fourth quartile group. A Cox proportional hazards model was used to determine the hazard ratio (HR) of BP variability in cases of newly diagnosed OAG. Moreover, we conducted subgroup analyses using baseline characteristics.

Results: In the multivariable analyses, BP variability did not significantly increase the risk of OAG development. However, subgroup analyses revealed significant interactions between age and systolic BP variability in the development of OAG (CV: $p = 0.008$; SD: $p = 0.007$). For participants aged <60 years, the risk of OAG development significantly increased with high systolic BP variability (CV: HR, 1.18; 95% confidence interval [CI], 1.00–1.39; $p = 0.049$). We observed a similar trend using the SD and VIM as the parameters for systolic BP variability.

Conclusion: Higher visit-to-visit systolic BP variability was associated with an increased risk of OAG development in participants younger than 60 years of age without systemic hypertension. These results suggest that BP variability can be the considerable factor when assessing the risk of OAG, especially in relatively young people without systemic hypertension.

KEYWORDS

blood pressure, blood pressure variability, KNHIS-HEALS, open-angle glaucoma, systemic hypertension

Introduction

Increased intraocular pressure (IOP) is a major risk factor, amongst several which are associated with the development of glaucoma (1, 2). Considering the multifactorial nature of glaucoma, its pathogenesis cannot be elucidated by the mechanical theory alone, which states that the increased IOP induces damage to the lamina cribrosa and retinal ganglion cell axons. In addition to this theory, perfusion abnormalities and vascular damage of the optic nerve head are also important mechanisms underlying the pathogenesis of glaucoma (3, 4). Arterial, venous, and intraocular pressures determine the perfusion pressure of the optic nerve head (5); thus, it is likely that blood pressure (BP) has an important role in the development and progression of glaucoma.

BP and glaucoma display varied associations owing to the complex correlation between IOP, BP, and ocular blood perfusion pressure (6). Some studies (7, 8) have demonstrated a positive correlation between BP and IOP, while others (9–11) have found that low BP correlated with optic nerve damage. One study (12), which analyzed the US National Health and Nutrition Examination Survey data, reported a nonlinear (i.e., U-shaped) relationship between the prevalence of glaucoma and systolic BP (SBP) or diastolic BP (DBP). The aforementioned relationship provides evidence for the correlation between high and low BPs and glaucoma. In addition, a high risk of open-angle glaucoma (OAG) development in patients with systemic hypertension provides evidence of the close relationship between BP and glaucoma (13).

BP does not have a constant value and changes with time. BP variability increases the risk of cardiovascular or cerebrovascular diseases such as arterial fibrillation, stroke, and dementia (14–16). Mortality in patients with diabetes is associated with BP variability (17). Considering the association between the perfusion pressure of the optic nerve head and glaucoma development, BP variability and glaucoma are likely to be associated. Lee et al. revealed that SBP variability was associated with the development of primary OAG, based on visit-to-visit BP data in a population-based cohort (18). Another population-based study using a continuous BP measurement method demonstrated a correlation between normal-tension glaucoma and BP variability (19). Thus, BP variability may also be an important factor in the development of glaucoma.

It is important to note that the aforementioned studies included participants with systemic hypertension. Systemic hypertension and the use of antihypertensive medications can be major confounding factors, thereby necessitating additional studies to determine the effect of BP variability on glaucoma development in participants without systemic hypertension. Therefore, we aimed to investigate the association between visit-to-visit BP variability and the incidence of OAG in participants without systemic hypertension by using large population-based data from the Korean National Health Insurance Service (KNHIS)-National Health Screening Cohort (HEALS).

Methods

Study design and population

This population-based retrospective cohort study used data from the KNHIS-HEALS database between 2002 and 2015. The health insurance system in South Korea is characterized by a nationwide, single-payer system managed by the KNHIS, which covers >98% of all South Koreans (20). It provides detailed information on age, sex, general health information, and disease diagnoses using the Korean Standard Classification of Disease (KCD) codes, similar to those of the International Classification of Disease (ICD). In addition, it provides data on prescribed medications and hospital visit history by exchanging all cost-related healthcare information between the KNHIS and medical providers using the electronic codes of the Korean Electronic Data Interchange medical procedures. All Koreans aged >40 years are eligible for the KNHIS health screening program at least once every 2 years (21). The KNHIS-HEALS database comprises publicly open data. Thus, the Institutional Review Board of the Asan Medical Center (Seoul, Korea) and the University of Ulsan College of Medicine (Seoul, Korea) approved a waiver to review the data for this study (2020–1713). This study was conducted according to the ethical principles outlined in the Declaration of Helsinki. The requirement for obtaining informed consent was waived.

We used a database comprising 209,226 Koreans who underwent health screening examinations in 2007 (i.e., the index year). We identified 177,668 participants who underwent three or more health examinations from January 1, 2002 to December 31, 2007. We excluded individuals with pre-existing OAG or angle-closure glaucoma (KCD codes H401 and H402, respectively), conditions that could cause secondary glaucoma (Supplementary Table S7), and hypertension up to the index year. Systemic hypertension was identified by the presence of ICD-10 clinical modification codes I10-I13 and I15, with a claim for the prescription of antihypertension medications. Since the first Korean hypertension diagnosis and management guideline was suggested by the Korean Society of Hypertension in 2000, the guideline underwent multiple amendments. South Korea's very first diagnostic and treatment criteria were derived from the recommendations of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC), and later adapted to account for the epidemiological characteristics of South Korean population. However, the cut-off line for diagnosing hypertension by Korean hypertension diagnosis and treatment guideline still remains to be SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg even in the most recent version in 2022. After excluding participants with missing data for one or more variables, a total of 140,910 participants were ultimately included in the final analysis.

Measurements of variables and comorbidities

Health screening examination data provided the results of laboratory tests and questionnaires on health behavior, along with anthropometric details such as height, weight, and waist circumference. Moreover, the database includes BP measurements. BMI is calculated as weight in kilograms divided by the squared height in meters (kg/m^2). Samples for the measurement of fasting serum glucose, total cholesterol, aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl transferase levels were collected through venous blood sampling after an overnight fast of more than 8 h. A diagnosis of diabetes mellitus was defined as follows: (1) fasting glucose level ≥ 126 mg/dL or (2) having at least one claim per year under ICD-10 codes E10-14 and a prescription for antidiabetic medications. Dyslipidemia was defined according to the following: (1) total cholesterol ≥240 mg/dL or (2) having at least one claim per year under ICD-10 code E78 with a prescription for lipid-lowering agents. Cataract was defined, based on the ICD-10 codes related to cataract (i.e., H25.0, H25.1, H25.2, H25.8, H25.9, H26.02, H26.21, H26.28, H26.3, H26.8, H26.9, H28.0, H28.1, and H28.2). We used the Charlson Comorbidity Index as a covariate to match the overall general health statuses between the groups. This score refers to a weighted index calculated by the presence of 17 systemic diseases. Thus, the higher the score, the greater the burden of systemic diseases (22). Current smoking status, alcohol consumption, regular exercise, and income level were defined by the questionnaire results. The response to cigarette smoking was "never," "ex-smoker," or "current smoker." In the present study, a current smoker was defined as a response of "current smoker" among the aforementioned three items. Alcohol consumption was defined as drinking 3–4 times a week or more, whereas regular exercise was defined as exercising five times or more a week. Low household income level was defined as an income level of <10%.

BP measurements and visit-to-visit BP variability

During the KNHIS health screening examination, a trained clinician measured brachial BP according to the protocol using a standardized sphygmomanometer. This measurement was conducted twice in participants after a five-minute rest period and their average BP was recorded. SBP and DBP were measured separately. Moreover, BP variability was assessed using the SD, CV, and VIM of BP until the index year. The CV was defined as the SD divided by the mean value, whereas the VIM was calculated as follows: $100 \times SD/mean^{\beta}$ (23), where β refers to the regression coefficient based on the natural logarithm of the SD over the natural logarithm of the mean. The number of BP measurements ranged from three to six per individual, as follows: three measurements (n = 68,698); four measurements (n = 15,436); five measurements (n = 21,207), and six measurements (n = 35,749).

Study outcomes and follow-up

Newly diagnosed OAG was the primary outcome. OAG development was defined when the following three criteria were met: (1) a diagnosis of OAG, based on the KCD code (H401), (2) undergoing a visual field test more than once, and (3) a prescription for antiglaucoma medications (13). We followed the cohort from the index date until the date of being newly diagnosed with OAG or until the end of the study (December 21, 2015), whichever occurred first. The mean and median follow-up duration was 8.2 years and 8.4 years, respectively. The interquartile range of the follow-up duration was 8.2–8.6 years.

Statistical analysis

Participants were classified into four groups based on the BP variability quartile. Differences in the distribution of baseline characteristics among the BP quartile groups were identified by using analysis of variance or the Chi-square test, as appropriate. We used the Cox proportional hazards model to estimate the hazard ratio (HR) and the 95% confidence interval (CI) of newly diagnosed OAG. Multivariable analyses were conducted using two models, based on the type of variables used for the adjustment. Model 1 was adjusted for age and sex; model 2 was adjusted for all variables used to demonstrate the baseline characteristics. We conducted subgroup analyses within the baseline characteristics for a better understanding of the effect of BP variability on newly diagnosed OAG. Therefore, the interaction effect between BP variability and each subgroup was evaluated using Cox regression analysis. A two-sided p-value of <0.05 was considered statistically significant. All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

Tables 1, 2 summarize the characteristics of the study participants, based on their variability independent of the mean (VIM) quartiles for SBP and DBP. Significant differences were observed in all variables among the VIM SBP groups, except for fasting glucose level (p = 0.679). In contrast, among the VIM DBP groups, significant differences were observed in all variables, except for fasting glucose level (p = 0.304) and alcohol consumption (p = 0.199). We observed similar results with defining BP variability by the standard deviation (SD) and coefficient of variation (CV) of BP (Supplementary Tables S1–S4). Upon defining SBP and DBP variabilities as SD, we observed a significant difference among the quartile groups for all variables. Upon defining SBP variability by the CV, all variables, except for the total cholesterol level, demonstrated significant differences among the quartile groups. In contrast, significant differences were observed in all variables, except for fasting glucose level and alcohol consumption, on defining diastolic BP variability by CV, which was similar to the VIM results.

Effect of BP variability on the development of OAG

Table 3 summarizes the HRs and 95% CIs of newly diagnosed OAG according to BP variability (per 10-unit increase). Only a

TABLE 1 Baseline characteristics of the study participants, based on the VIM quartiles for visit-to-visit variability of systolic blood pressure.

	Q1	Q2	Q3	Q4	*P*-value [a]
N	35,246	35,209	35,228	35,227	
Age (y)	55.2 ± 8.5	54.3 ± 7.9	54.8 ± 8.2	56.8 ± 9.1	<0.0001
Sex (male)	21,064 (59.8)	22,510 (63.9)	21,775 (61.8)	18,550 (52.7)	<0.0001
BMI (kg/m^2)	24.0 ± 2.8	23.9 ± 2.8	23.8 ± 2.8	23.8 ± 2.9	<0.0001
Mean SBP	126.2 ± 11.9	125.5 ± 12.7	124.8 ± 12.5	124.6 ± 13.9	<0.0001
Mean DBP	79.1 ± 7.7	78.9 ± 8.1	78.4 ± 7.9	77.9 ± 8.5	<0.0001
SBP variability					
CV (%)	3.7 ± 1.4	6.6 ± 0.9	9.0 ± 1.0	13.7 ± 3.2	<0.0001
SD	4.7 ± 1.9	8.3 ± 1.7	11.3 ± 2.2	17.2 ± 5.2	<0.0001
VIM	4.7 ± 1.8	8.3 ± 0.9	11.5 ± 1.0	17.5 ± 3.8	<0.0001
DBP variability					
CV (%)	7.1 ± 3.8	8.2 ± 3.8	9.5 ± 4.0	12.4 ± 5.2	<0.0001
SD	5.6 ± 3.1	6.4 ± 3.0	7.5 ± 3.3	9.7 ± 4.4	<0.0001
VIM	5.6 ± 3.1	6.5 ± 3.0	7.6 ± 3.2	9.9 ± 4.1	<0.0001
FPG	97.5 ± 23.3	97.4 ± 23.1	97.6 ± 24.0	97.6 ± 23.8	0.679
Total cholesterol	199.3 ± 36.3	198.6 ± 36.0	198.6 ± 36.1	198.7 ± 37.0	0.028
AST	26.0 ± 14.2	26.1 ± 15.3	26.2 ± 16.6	26.4 ± 16.4	0.007
ALT	25.2 ± 18.5	25.5 ± 19.0	25.2 ± 20.9	24.7 ± 19.9	<0.0001
GGT	38.2 ± 47.9	39.0 ± 49.0	39.2 ± 52.2	37.7 ± 52.5	0.0001
DM	4,966 (14.1)	5,324 (15.1)	5,438 (15.4)	5,545 (15.7)	<0.0001
Hyperlipidemia	11,461 (32.5)	11,351 (32.2)	11,504 (32.7)	11,953 (33.9)	<0.0001
Cataract	2,723 (7.7)	2,282 (6.5)	2,384 (6.8)	3,216 (9.1)	<0.0001
CCI					<0.0001
0	13,744 (39.0)	14,326 (40.7)	13,936 (39.6)	12,241 (34.7)	
1	9,922 (28.2)	9,930 (28.2)	9,846 (27.9)	9,891 (28.1)	
2	5,649 (16.0)	5,510 (15.6)	5,837 (16.6)	6,139 (17.4)	
≥3	5,931 (16.8)	5,443 (15.5)	5,609 (15.9)	6,956 (19.7)	
Current smoker	7,055 (20.0)	8,036 (22.8)	7,835 (22.2)	6,770 (19.2)	<0.0001
Alcohol consumption	3,455 (9.8)	3,504 (10.0)	3,555 (10.1)	3,280 (9.3)	0.003
Regular exercise	3,675 (10.4)	3,347 (9.5)	3,369 (9.6)	3,531 (10.0)	<0.0001
Income (<10%)	2,493 (7.1)	2,555 (7.3)	2,813 (8.0)	3,233 (9.2)	<0.0001

Data are expressed as the mean ± the SD or as *n* (%).[a]The *P*-value is derived from the analysis of variance and the Chi-square test.VIM, variability independent of the mean; N, number; Q1–4, quartile 1–4; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CV, coefficient of variation; SD, standard deviation; FPG, fasting plasma glucose; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transferase; DM, diabetes mellitus; and CCI, Charlson Comorbidity Index.

significant increase in the risk of OAG development correlated with SBP variability, defined by SD (HR, 1.13; 95% CI, 1.03–1.24). However, multivariable analyses revealed no significant findings in any BP variability parameter. As an additional method to verify the effect of BP variability, we compared the risk of OAG development in the highest quartile group (Q4) with that in the lower three quartiles (Q1–Q3) as the reference group (Table 4). Without an adjustment for the variables, we observed a significantly increased risk of OAG development in the Q4 group, compared with the Q1–Q3 group in all three parameters for BP variability. However, BP variability did not significantly increase the risk of OAG development in model 1 and model 2 analyses that adjusted for the variables.

Subgroup analyses

We conducted stratified analyses by age, sex, body mass index (BMI), diabetes mellitus, hyperlipidemia, cataract, smoking status, alcohol consumption status, regular exercise status, and income status. Table 5 summarizes the results of the stratified analyses for the effect of SBP variability on OAG development according to the CV. Based on the subgroup analysis of factors that could affect this development, we identified a significant interaction for age × SBP variability (CV, SD) ($p = 0.009$ for CV and $p = 0.007$ for SD) (Table 5; Supplementary Table S5). The risk of OAG development significantly increased with high SBP variability (CV) for participants aged

TABLE 2 Baseline characteristics of the study participants, based on the VIM quartiles for visit-to-visit variability of diastolic blood pressure.

	Q1	Q2	Q3	Q4	*P*-value [a]
N	35,228	35,224	35,232	35,226	
Age (y)	55.2 ± 8.3	54.9 ± 8.4	54.4 ± 7.9	56.6 ± 9.1	<0.0001
Sex (male)	21,003 (59.6)	21,428 (60.8)	22,131 (62.8)	19,337 (54.9)	<0.0001
BMI (kg/m^2)	24.0 ± 2.8	23.8 ± 2.8	23.8 ± 2.8	23.8 ± 2.9	<0.0001
Mean SBP	126.3 ± 12.4	124.3 ± 11.7	124.9 ± 13.0	125.7 ± 13.8	<0.0001
Mean DBP	79.5 ± 7.9	78.1 ± 7.2	78.4 ± 8.4	78.3 ± 8.7	<0.0001
SBP variability					
CV (%)	6.3 ± 3.2	7.2 ± 3.3	8.4 ± 3.5	11.0 ± 4.7	<0.0001
SD	8.0 ± 4.2	9.0 ± 4.3	10.5 ± 4.7	14.0 ± 6.6	<0.0001
VIM	8.0 ± 4.0	9.3 ± 4.2	10.7 ± 4.4	14.0 ± 5.9	<0.0001
DBP variability					
CV (%)	4.0 ± 2.0	7.4 ± 0.6	10.2 ± 1.0	15.6 ± 3.4	<0.0001
SD	3.2 ± 1.6	5.8 ± 0.7	8.0 ± 1.2	12.2 ± 3.2	<0.0001
VIM	3.2 ± 1.6	5.9 ± 0.5	8.1 ± 0.8	12.3 ± 2.7	<0.0001
FPG	97.7 ± 22.6	97.5 ± 24.2	97.4 ± 23.8	97.6 ± 23.6	0.304
Total cholesterol	199.7 ± 36.2	198.6 ± 36.1	198.2 ± 36.1	198.7 ± 36.9	<0.0001
AST	26.2 ± 15.7	26.0 ± 15.2	26.2 ± 15.6	26.3 ± 16.1	0.043
ALT	25.5 ± 20.4	25.1 ± 18.5	25.4 ± 20.0	24.7 ± 19.6	<0.0001
GGT	38.6 ± 49.2	37.8 ± 48.5	39.2 ± 49.9	38.5 ± 53.9	0.004
DM	5,067 (14.4)	5,102 (14.5)	5,479 (15.6)	5,625 (16.0)	<0.0001
Hyperlipidemia	11,471 (32.6)	11,225 (31.9)	11,504 (32.7)	12,069 (34.3)	<0.0001
Cataract	2,674 (7.6)	2,479 (7.0)	2,307 (6.5)	3,145 (8.9)	<0.0001
CCI					<0.0001
0	13,752 (39.0)	13,887 (39.4)	14,118 (40.1)	12,490 (35.5)	
1	9,837 (27.9)	9,921 (28.2)	10,014 (28.4)	9,817 (27.9)	
2	5,784 (16.4)	5,601 (15.9)	5,637 (16.0)	6,113 (17.4)	
≥3	5,855 (16.6)	5,815 (16.5)	5,463 (15.5)	6,806 (19.3)	
Current smoker	7,176 (20.4)	7,591 (21.6)	8,014 (22.7)	6,915 (19.6)	<0.0001
Alcohol consumption	3,526 (10.0)	3,488 (9.9)	3,388 (9.6)	3,392 (9.6)	0.199
Regular exercise	3,608 (10.2)	3,479 (9.9)	3,337 (9.5)	3,498 (9.9)	0.008
Income (<10%)	2,586 (7.3)	2,555 (7.3)	2,806 (8.0)	3,147 (8.9)	<0.0001

Data are expressed as the mean ± the SD or as *n* (%).[a]The *P*-value is derived from the analysis of variance and the Chi-square test.VIM, variability independent of the mean; N, number; Q1–4, quartile 1–4; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CV, coefficient of variation; SD, standard deviation; FPG, fasting plasma glucose; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transferase; DM, diabetes mellitus; and CCI, Charlson Comorbidity Inde.

<60 years (HR, 1.18; 95% CI, 1.00–1.39; $p = 0.0485$). We observed a similar trend when using SD and VIM as the parameters for SBP variability (SD: HR, 1.18; 95% CI, 0.99–1.39; $p = 0.061$; VIM: HR, 1.18; 95% CI, 1.00–1.39; $p = 0.048$) (Supplementary Tables S5, S6). However, no condition significantly affected the relationship between DBP variability and the risk of OAG development.

Discussion

In the present study, we investigated the association between visit-to-visit BP variability and OAG development in participants without systemic hypertension by using a large longitudinal population-based cohort. BP variability significantly increased the risk of OAG development, according to the unadjusted analyses; however, this finding was not confirmed after adjusting for the variables. In the subgroup analyses, the visit-to-visit SBP variability, which was defined using three different indicators, was associated with an increased risk of OAG development in participants aged <60 years without systemic hypertension. Previously, researchers have reported the association between BP variability and the development of primary OAG using the National Sample Cohort of the KNHIS (18). Moreover, there are reports which verify the association between BP variability and glaucoma (19, 24). However, these studies included participants with systemic hypertension. Thus, confounding factors related to BP variability, such as the use of antihypertensive medications, would likely affect the results. Unlike previous studies, only data of participants without systemic hypertension were analyzed in this

TABLE 3 Hazard ratios and 95% confidence intervals of newly diagnosed open angle glaucoma, based on visit-to-visit variability of blood pressure (per 10-unit increase).

BP variability (per 10-unit increase)	Unadjusted		Model 1		Model 2	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
SBP						
CV	1.12 (0.99–1.27)	0.076	0.96 (0.85–1.09)	0.525	0.96 (0.85–1.08)	0.477
SD	1.13 (1.03–1.24)	0.008	0.97 (0.89–1.06)	0.536	0.96 (0.87–1.05)	0.387
VIM	1.05 (0.95–1.16)	0.318	0.97 (0.88–1.07)	0.496	0.97 (0.88–1.07)	0.518
DBP						
CV	1.10 (0.99–1.23)	0.086	1.03 (0.92–1.14)	0.642	1.02 (0.92–1.13)	0.718
SD	1.14 (1.00–1.30)	0.052	1.02 (0.90–1.16)	0.737	1.02 (0.89–1.16)	0.802
VIM	1.13 (0.98–1.29)	0.091	1.03 (0.90–1.18)	0.636	1.03 (0.90–1.17)	0.713

Model 1 is adjusted for age and sex. Model 2 is adjusted for the variables in Model 1 + the other variables in Table 1.
OAG, open-angle glaucoma; BP, blood pressure; HR, hazard ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; VIM, variability independent of the mean; CV, coefficient of variation; and SD, standard deviation; VIM, variability independent of the mean.

study. The difference in the inclusion of participants with systemic hypertension in previous studies may explain why our subgroup analysis demonstrated that SBP variability induced a significantly increased risk of OAG development.

Under physiological condition, BP naturally fluctuates, which is essential for maintaining appropriate multiple-organ perfusion. Therefore, failure to control BP fluctuations results in a high possibility of impaired organ function. Longitudinal and cross-sectional studies have reported that an increase in the visit-to-visit BP variability is associated with a greater risk of organ damage, cardiovascular events, and mortality (16, 25, 26). In addition, researchers have verified its association with the occurrence of neurodegenerative diseases such as dementia and Alzheimer's disease (15, 27, 28). Nonetheless, investigators have not clearly elucidated the mechanism underlying the effect of BP variability on various pathologic conditions, including OAG. Considering the involvement of vascular dysregulation in the pathophysiology of glaucoma (29, 30), the association between BP variability and cardiovascular homeostasis is supposedly a key factor that explains the correlation between glaucoma development and BP variability (16). Arterial stiffness is another important factor in the relationship between BP variability and glaucoma. Arterial stiffness has an important role in BP variability (31). A recent study using optical coherence tomography angiography verified that a high pulse-wave velocity was associated with decreased macular vessel density in patients with normal-tension glaucoma (32). Pulse-wave velocity is a representative parameter of arterial stiffness. Therefore, the aforementioned result indicates a possible correlation between arterial stiffness and the pathogenesis of normal-tension glaucoma. Autonomic dysfunction may also play a role in the relationship between BP variability and glaucoma; it induces BP variability and reduces ocular perfusion pressure (33–36). Although there is insufficient data from previous studies regarding the exact mechanism, it is not difficult to conclude that a relationship exists between BP variability and glaucoma is related to vascular dysregulation. Further studies are warranted to directly verify the relationship between BP variability and ocular blood supply and the mechanism underlying the effect of BP variability on glaucoma development, particularly with the use of devices such as coherence tomography angiography. Nevertheless, our study is of sufficient value in that it supports the vascular theory underlying the pathogenesis of glaucoma and identified clinical factors associated with OAG development.

In the present study, the age of the Q4 group was higher than that of the other groups. In addition, in the subgroup analyses, the Q4 group included a relatively higher number of participants aged ≥60 years than participants aged <60 years. These results are similar to those of previous studies demonstrating that BP variability increases with age (37, 38). Many of the possible underlying mechanisms associated with aging, such as hemodynamic instability, advanced arterial remodeling, atherosclerosis, arterial stiffness, baroreflex impairment, endothelial dysfunction, and subclinical inflammation, are interconnected (39). Although further investigations are necessary to establish whether elevated blood pressure variability constitutes a hallmark of aging, it has recently garnered attention as a potential candidate marker for aging, owing to its associations with the mechanisms mentioned above. Age-related impairment to the baroreflex or an increase in arterial stiffness is the primary mechanism underlying the relationship between BP variability and age (38). Therefore, an increase in BP variability at a relatively young age indicates a more pathological condition, unlike age-related changes, which may be a factor that increases susceptibility to organ damage. SBP variability exerts a greater effect on stroke risk at a young age (23). Glaucoma requires an early diagnosis and lifelong treatment to reduce the likelihood of progression of visual function impairment. The development of glaucoma at a young age increases the likelihood of encountering various problems caused by the progression of visual function impairment. Therefore, the finding of the subgroup analysis that large SBP variability significantly increased the risk of OAG development in relatively young participants without systemic hypertension has clinical significance. Investigators should perform additional research, such as determining clinical factors affecting the impact of SBP variability on the risk of OAG development with age to accurately verify the relationship between them. However, our findings likely have clinical significance in that they identified a notable factor to be considered (i.e., BP variability), while classifying and monitoring a high-risk group for OAG.

The following limitations of the current study should be considered when interpreting these results. First, determining the presence of a disease based on diagnostic codes is a representative

TABLE 4 Hazard ratios and 95% confidence intervals of newly diagnosed OAG with comparison between quartile 1–3 and quartile 4 of visit-to-visit variability of blood pressure.

				Unadjusted		Model 1		Model 2	
	Events (n)	F/U duration (person-years)	Incidence (95% CI)	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
SBP variability									
CV									
Q1–Q3	1,027	872,203	1.18 (1.11–1.25)	1 (ref)		1 (ref)		1 (ref)	
Q4	394	288,432	1.37 (1.24–1.51)	1.16 (1.03–1.30)	0.012	1.01 (0.90–1.14)	0.866	1.00 (0.89–1.13)	0.958
SD									
Q1–Q3	1,016	872,710	1.16 (1.09–1.24)	1 (ref)		1 (ref)		1 (ref)	
Q4	405	287,926	1.41 (1.28–1.55)	1.21 (1.08–1.36)	0.001	1.01 (0.90–1.13)	0.900	0.99 (0.88–1.12)	0.904
VIM									
Q1–Q3	1,022	871,817	1.17 (1.10–1.25)	1 (ref)		1 (ref)		1 (ref)	
Q4	399	288,818	1.38 (1.25–1.52)	1.18 (1.05–1.32)	0.006	1.06 (0.95–1.20)	0.291	1.06 (0.95–1.19)	0.306
DBP variability									
CV									
Q1–Q3	1,025	871,536	1.18 (1.11–1.25)	1 (ref)		1 (ref)		1 (ref)	
Q4	396	289,099	1.37 (1.24–1.51)	1.16 (1.04–1.31)	0.010	1.06 (0.95–1.19)	0.309	1.06 (0.94–1.19)	0.352
SD									
Q1–Q3	1,018	872,155	1.17 (1.10–1.24)	1 (ref)		1 (ref)		1 (ref)	
Q4	403	288,480	1.40 (1.27–1.54)	1.20 (1.07–1.34)	0.002	1.06 (0.94–1.19)	0.326	1.06 (0.94–1.19)	0.373
VIM									
Q1–Q3	1,028	871,770	1.18 (1.11–1.25)	1 (ref)		1 (ref)		1 (ref)	
Q4	393	288,865	1.36 (1.23–1.50)	1.15 (1.03–1.30)	0.016	1.05 (0.94–1.18)	0.390	1.05 (0.93–1.18)	0.442

Model 1 is adjusted for age and sex. Model 2 is adjusted for the variables in Model 1 + the other variables in Table 1.
OAG, open-angle glaucoma; BP, blood pressure; F/U, follow-up; HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure; CV, coefficient of variation; Q1–4, quartile 1–4; SD, standard deviation; VIM, variability independent of the mean; DBP, diastolic blood pressure.

limitation of studies using claim data. To minimize possible diagnostic inaccuracies, we used additional parameters, such as medication use and clinical examination. Second, we only included participants who had visited a hospital. Thus, we cannot exclude the possibility of underestimating the presence of OAG and other diseases. Third, there was no control of the BP measurement conditions, which we presumed was not performed accurately. This is a common limitation of previous studies that verified a relationship between visit-to-visit BP variability and pathologic conditions using KNHIS data. However, BP measurements obtained during health screening examinations, based on the protocol of medical institutions certified by the KNHIS, alleviated the risk of measurement bias. Fourth, the BP variability was based on a range of three to six BP measurements per subjects. Furthermore, the temporal intervals between BP measurements exhibited non-uniformity. In investigating visit-to-visit BP variability, it is important to define the BP measurement interval and number of BP measurements. Given the characteristics of the data collected for this research, it is unfeasible to obtain BP measurements at consistent intervals or at the same frequency. Nonetheless, it is noteworthy that the methodology employed for characterizing BP variability in our study has been consistently utilized in several prior studies (14, 18, 40, 41) that defined BP variability using KNHIS data. Fifth, our findings were obtained from a database with data for an overwhelmingly large population of Koreans. This factor warrants cautiously applying the present findings to other ethnic groups. Finally, despite using longitudinal follow-up results with a large sample size, our study was based on a retrospective design. Therefore, our findings should be confirmed by additional prospective longitudinal studies that include other ethnic groups.

In conclusion, high visit-to-visit SBP variability significantly increased the risk of OAG development in participants aged <60 years; however, our results did not demonstrate an effect of high BP

TABLE 5 Subgroup analyses for the effect of visit-to-visit variability of systolic blood pressure (CV) on the development of open angle glaucoma.

	Q1–Q3	Q4	HR (95% CI)	*P*-value	*P* for interaction
Age					0.008
<60 y	563/79689	191/22333	1.18 (1.00–1.39)	0.049	
≥60 y	464/25990	203/12898	0.86 (0.73–1.01)	0.073	
Sex					0.546
Female	402/40923	172/16088	0.96 (0.80–1.15)	0.676	
Male	625/64756	222/19143	1.03 (0.89–1.21)	0.664	
BMI (kg/m^2)					0.395
<25	689/71711	252/23388	0.97 (0.84–1.12)	0.649	
≥25	338/33968	142/11843	1.07 (0.88–1.31)	0.475	
DM					0.639
No	856/90430	313/29207	0.99 (0.87–1.13)	0.878	
Yes	171/15249	81/6024	1.06 (0.81–1.38)	0.656	
Hyperlipidemia					0.921
No	657/71784	240/22857	1.00 (0.86–1.16)	0.984	
Yes	370/33895	154/12374	1.01 (0.84–1.22)	0.912	
Cataract					0.411
No	869/98412	324/31893	1.03 (0.90–1.17)	0.695	
Yes	158/7267	70/3338	0.90 (0.68–1.19)	0.470	
Current smoker					0.230
No	836/82839	338/28375	1.04 (0.91–1.18)	0.595	
Yes	191/22840	56/6856	0.85 (0.63–1.14)	0.283	
Alcohol consumption					0.923
No	920/95426	351/31690	1.00 (0.88–1.13)	0.985	
Yes	107/10253	43/3541	1.02 (0.72–1.45)	0.914	
Regular exercise					0.564
No	886/95360	344/31628	1.02 (0.90–1.15)	0.795	
Yes	141/10319	50/3603	0.92 (0.66–1.27)	0.606	
Income (<10%)					0.956
No	940/97923	353/31893	1.00 (0.89–1.14)	0.946	
Yes	87/7756	41/3338	0.99 (0.68–1.44)	0.971	

Hazard ratios were calculated based on multivariate Cox regression after being adjusted for variables belonging to model 2.
Data are expressed as the number of events/number of patients. Model 1 is adjusted for age and sex. Model 2 is adjusted for the variables in Model 1 + the other variables in Table 1.
BP, blood pressure; OAG, open-angle glaucoma; CV, coefficient of variation; Q1–4, quartile 1–4; HR, hazard ratio; CI, confidence interval; BMI, body mass index; DM, diabetes mellitus.

variability on an increased risk of OAG development for all age groups. Although it needs to be verified through further research, our results indicate that BP variability may be a factor to consider when assessing the risk of OAG development in relatively young people without systemic hypertension. In addition, the importance of BP variability in the development of glaucoma is likely to be considered as remarkable evidence that supports the vascular theory, which explains the pathophysiology of glaucoma.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The Institutional Review Board of the Asan Medical Center (Seoul, Korea) and the University of Ulsan College of Medicine (Seoul, Korea) approved a waiver to review the data for this study (2020-1713). This study was conducted according to the ethical principles outlined in the Declaration of Helsinki. The requirement for obtaining informed consent was waived. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because the KNHIS-HEALS database comprises publicly opened data.

Author contributions

SL: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. JL: Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing, Formal analysis, Validation. JK: Conceptualization, Formal analysis, Investigation, Methodology, Writing – review & editing. HT: Conceptualization, Investigation, Methodology, Resources, Supervision, Writing – review & editing. HL: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing, Resources.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Korea Medical Device Development Fund, granted by the Korean government (the Ministry of Science and ICT; the Ministry of Trade, Industry, and Energy; the Ministry of Health and Welfare; and the Ministry of Food and Drug Safety), (Project number: 1711174348, RS-2020-KD000148); by the National Research Foundation of Korea (NRF) grant funded by the Korea government(MSIT) (RS-2023-00214125); and by a grant from the Asan Institute for Life science, Asan Medical Center, Korea (2023IP0069-1).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1300778/full#supplementary-material

References

1. Jonas JB, Aung T, Bourne RR, Bron AM, Ritch R, Panda-Jonas S. Glaucoma. *Lancet*. (2017) 390:2183–93. doi: 10.1016/s0140-6736(17)31469-1

2. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. *JAMA*. (2014) 311:1901–11. doi: 10.1001/jama.2014.3192

3. Flammer J, Orgül S, Costa VP, Orzalesi N, Krieglstein GK, Serra LM, et al. The impact of ocular blood flow in glaucoma. *Prog Retin Eye Res*. (2002) 21:359–93. doi: 10.1016/s1350-9462(02)00008-3

4. Yanagi M, Kawasaki R, Wang JJ, Wong TY, Crowston J, Kiuchi Y. Vascular risk factors in glaucoma: a review. *Clin Exp Ophthalmol*. (2011) 39:252–8. doi: 10.1111/j.1442-9071.2010.02455.x

5. Costa VP, Harris A, Anderson D, Stodtmeister R, Cremasco F, Kergoat H, et al. Ocular perfusion pressure in glaucoma. *Acta Ophthalmol*. (2014) 92:e252–66. doi: 10.1111/aos.12298

6. Costa VP, Arcieri ES, Harris A. Blood pressure and glaucoma. *Br J Ophthalmol*. (2009) 93:1276–82. doi: 10.1136/bjo.2008.149047

7. Bonomi L, Marchini G, Marraffa M, Bernardi P, Morbio R, Varotto A. Vascular risk factors for primary open angle glaucoma: the Egna-Neumarkt Study. *Ophthalmology*. (2000) 107:1287–93. doi: 10.1016/s0161-6420(00)00138-x

8. Klein BE, Klein R, Knudtson MD. Intraocular pressure and systemic blood pressure: longitudinal perspective: the Beaver Dam Eye Study. *Br J Ophthalmol*. (2005) 89:284–7. doi: 10.1136/bjo.2004.048710

9. Cherecheanu AP, Garhofer G, Schmidl D, Werkmeister R, Schmetterer L. Ocular perfusion pressure and ocular blood flow in glaucoma. *Curr Opin Pharmacol*. (2013) 13:36–42. doi: 10.1016/j.coph.2012.09.003

10. Memarzadeh F, Ying-Lai M, Chung J, Azen SP, Varma R. Blood pressure, perfusion pressure, and open-angle glaucoma: the Los Angeles Latino eye study. *Invest Ophthalmol Vis Sci*. (2010) 51:2872–7. doi: 10.1167/iovs.08-2956

11. Quigley HA, West SK, Rodriguez J, Munoz B, Klein R, Snyder R. The prevalence of glaucoma in a population-based study of Hispanic subjects: Proyecto VER. *Arch Ophthalmol*. (2001) 119:1819–26. doi: 10.1001/archopht.119.12.1819

12. Kim H, Choi B. Nonlinear relationship between blood pressure and Glaucoma in US adults. *Am J Hypertens*. (2019) 32:308–16. doi: 10.1093/ajh/hpy186

13. Rim TH, Lee SY, Kim SH, Kim SS, Kim CY. Increased incidence of open-angle glaucoma among hypertensive patients: an 11-year nationwide retrospective cohort study. *J Hypertens*. (2017) 35:729–36. doi: 10.1097/hjh.0000000000001225

14. Lee SR, Choi YJ, Choi EK, Han KD, Lee E, Cha MJ, et al. Blood pressure variability and incidence of new-onset atrial fibrillation: a nationwide population-based study. *Hypertension*. (2020) 75:309–15. doi: 10.1161/hypertensionaha.119.13708

15. Ma Y, Tully PJ, Hofman A, Tzourio C. Blood pressure variability and dementia: a state-of-the-art review. *Am J Hypertens*. (2020) 33:1059–66. doi: 10.1093/ajh/hpaa119

16. Parati G, Torlasco C, Pengo M, Bilo G, Ochoa JE. Blood pressure variability: its relevance for cardiovascular homeostasis and cardiovascular diseases. *Hypertens Res*. (2020) 43:609–20. doi: 10.1038/s41440-020-0421-5

17. Hsieh YT, Tu ST, Cho TJ, Chang SJ, Chen JF, Hsieh MC. Visit-to-visit variability in blood pressure strongly predicts all-cause mortality in patients with type 2 diabetes: a 5·5-year prospective analysis. *Eur J Clin Investig*. (2012) 42:245–53. doi: 10.1111/j.1365-2362.2011.02574.x

18. Lee NY, Jung Y, Han K, Park CK. Fluctuation in systolic blood pressure is a major systemic risk factor for development of primary open-angle glaucoma. *Sci Rep*. (2017) 7:43734. doi: 10.1038/srep43734

19. Melgarejo JD, Maestre GE, Mena LJ, Lee JH, Petitto M, Chávez CA, et al. Normal-tension glaucomatous optic neuropathy is related to blood pressure variability in the Maracaibo aging study. *Hypertens Res*. (2021) 44:1105–12. doi: 10.1038/s41440-021-00687-1

20. Kwon S. Thirty years of national health insurance in South Korea: lessons for achieving universal health care coverage. *Health Policy Plan*. (2009) 24:63–71. doi: 10.1093/heapol/czn037

21. Seong SC, Kim YY, Park SK, Khang YH, Kim HC, Park JH, et al. Cohort profile: the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) in Korea. *BMJ Open*. (2017) 7:e016640. doi: 10.1136/bmjopen-2017-016640

22. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. (1987) 40:373–83. doi: 10.1016/0021-9681(87)90171-8

23. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet*. (2010) 375:895–905. doi: 10.1016/s0140-6736(10)60308-x

24. Lindemann F, Kuerten D, Koch E, Fuest M, Fischer C, Voss A, et al. Blood pressure and heart rate variability in primary open-angle glaucoma and normal tension glaucoma. *Curr Eye Res*. (2018) 43:1507–13. doi: 10.1080/02713683.2018.1506036

25. Mancia G, Facchetti R, Parati G, Zanchetti A. Visit-to-visit blood pressure variability, carotid atherosclerosis, and cardiovascular events in the European Lacidipine Study on Atherosclerosis. *Circulation*. (2012) 126:569–78. doi: 10.1161/circulationaha.112.107565

26. Chang TI, Reboussin DM, Chertow GM, Cheung AK, Cushman WC, Kostis WJ, et al. Visit-to-visit office blood pressure variability and cardiovascular outcomes in

SPRINT (systolic blood pressure intervention trial). *Hypertension*. (2017) 70:751–8. doi: 10.1161/hypertensionaha.117.09788

27. Lattanzi S, Luzzi S, Provinciali L, Silvestrini M. Blood pressure variability in Alzheimer's disease and frontotemporal dementia: the effect on the rate of cognitive decline. *J Alzheimers Dis*. (2015) 45:387–94. doi: 10.3233/jad-142532

28. de Heus RAA, Olde Rikkert MGM, Tully PJ, Lawlor BA, Claassen J. Blood pressure variability and progression of clinical Alzheimer disease. *Hypertension*. (2019) 74:1172–80. doi: 10.1161/hypertensionaha.119.13664

29. Hayreh SS. Blood flow in the optic nerve head and factors that may influence it. *Prog Retin Eye Res*. (2001) 20:595–624. doi: 10.1016/s1350-9462(01)00005-2

30. Harris A, Werne A, Cantor LB. Vascular abnormalities in glaucoma: from population-based studies to the clinic? *Am J Ophthalmol*. (2008) 145:595–7. doi: 10.1016/j.ajo.2007.12.019

31. Shimbo D, Shea S, McClelland RL, Viera AJ, Mann D, Newman J, et al. Associations of aortic distensibility and arterial elasticity with long-term visit-to-visit blood pressure variability: the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Hypertens*. (2013) 26:896–902. doi: 10.1093/ajh/hpt040

32. Lee T, Bae HW, Seong GJ, Kim CY, Lee SY. High pulse wave velocity is associated with decreased macular vessel density in normal-tension glaucoma. *Invest Ophthalmol Vis Sci*. (2021) 62:12. doi: 10.1167/iovs.62.10.12

33. Park HY, Jung KI, Na KS, Park SH, Park CK. Visual field characteristics in normal-tension glaucoma patients with autonomic dysfunction and abnormal peripheral microcirculation. *Am J Ophthalmol*. (2012) 154:466–75.e1. doi: 10.1016/j.ajo.2012.03.028

34. Kurysheva NI, Ryabova TY, Shlapak VN. Heart rate variability: the comparison between high tension and normal tension glaucoma. *EPMA J*. (2018) 9:35–45. doi: 10.1007/s13167-017-0124-4

35. Spallone V. Blood pressure variability and autonomic dysfunction. *Curr Diab Rep*. (2018) 18:1–14. doi: 10.1007/s11892-018-1108-z

36. Asefa NG, Neustaeter A, Jansonius NM, Snieder H. Autonomic dysfunction and blood pressure in glaucoma patients: the lifelines cohort study. *Invest Ophthalmol Vis Sci*. (2020) 61:25. doi: 10.1167/iovs.61.11.25

37. Imai Y, Aihara A, Ohkubo T, Nagai K, Tsuji I, Minami N, et al. Factors that affect blood pressure variability. A community-based study in Ohasama, Japan. *Am J Hypertens*. (1997) 10:1281–9. doi: 10.1016/s0895-7061(97)00277-x

38. Kim KI, Nikzad N, Quer G, Wineinger NE, Vegreville M, Normand A, et al. Real world home blood pressure variability in over 56,000 individuals with nearly 17 million measurements. *Am J Hypertens*. (2018) 31:566–73. doi: 10.1093/ajh/hpx221

39. Bencivenga L, De Souto BP, Rolland Y, Hanon O, Vidal JS, Cestac P, et al. Blood pressure variability: a potential marker of aging. *Ageing Res Rev*. (2022) 80:101677. doi: 10.1016/j.arr.2022.101677

40. Yoo JE, Shin DW, Han K, Kim D, Lee SP, Jeong SM, et al. Blood pressure variability and the risk of dementia: a nationwide cohort study. *Hypertension*. (2020) 75:982–90. doi: 10.1161/HYPERTENSIONAHA.119.14033

41. Yoo JE, Yoon JW, Park HE, Han K, Shin DW. Blood pressure variability and the risk of fracture: a nationwide cohort study. *J Clin Endocrinol Metab*. (2022) 107:e1488–500. doi: 10.1210/clinem/dgab856

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 14 February 2024
DOI 10.3389/fmed.2024.1288854

OPEN ACCESS

EDITED BY
Alessio Martucci,
University of Rome Tor Vergata, Italy

REVIEWED BY
Kun Shan,
Fudan University, China
Claudio Bucolo,
University of Catania, Italy

*CORRESPONDENCE
Mincheol Seong
✉ goddns76@hanmail.net
Yong Un Shin
✉ yushin@hanyang.ac.kr

†These authors have contributed equally to this work

RECEIVED 05 September 2023
ACCEPTED 25 January 2024
PUBLISHED 14 February 2024

CITATION
Yu HS, Hong EH, Kang JH, Lee YW, Lee WJ, Kang MH, Cho H, Shin YU and Seong M (2024) Expression of microRNAs related to apoptosis in the aqueous humor and lens capsule of patients with glaucoma. *Front. Med.* 11:1288854. doi: 10.3389/fmed.2024.1288854

Expression of microRNAs related to apoptosis in the aqueous humor and lens capsule of patients with glaucoma

Hyo Seon Yu[1†], Eun Hee Hong[1,2,3†], Ji Hye Kang[1,4], Yong Woo Lee[5], Won June Lee[1,3,6], Min Ho Kang[1,2], Heeyoon Cho[1,2,7], Yong Un Shin[1,2,3*] and Mincheol Seong[1,2,7*]

[1]Department of Ophthalmology, Hanyang University College of Medicine, Seoul, Republic of Korea, [2]Department of Ophthalmology, Hanyang University Guri Hospital, Guri, Gyeonggi-do, Republic of Korea, [3]Hanyang Institute of Bioscience and Biotechnology, Hanyang University, Seoul, Republic of Korea, [4]Graduate School of Biomedical Science & Engineering, Hanyang University, Seoul, Republic of Korea, [5]Department of Ophthalmology, Kangwon National University Graduate School of Medicine, Kangwon National University Hospital, Chuncheon, Republic of Korea, [6]Department of Ophthalmology, Hanyang University Hospital, Hanyang University College of Medicine, Seoul, Republic of Korea, [7]NOON Eye Clinic, Guri, Gyeonggi-do, Republic of Korea

Background: The aim of this study is to investigate the expression profiles of microRNAs (miRNAs) related to apoptosis in the aqueous humor (AH) and lens capsule (LC) of patients with glaucoma.

Methods: AH and LC samples were collected from patients with open-angle glaucoma and control participants who were scheduled for cataract surgery. A miRNA PCR array comprising 84 miRNAs was used to analyze the AH (glaucoma, $n = 3$; control, $n = 3$) and LC samples (glaucoma, $n = 3$; control, $n = 4$). Additionally, the AH and LC samples (glaucoma, $n = 3$; control, $n = 4$) were subjected to quantitative real-time PCR to validate the differentially expressed miRNAs determined using the PCR array. Bioinformatics analysis was performed to identify the interactions between miRNAs and diseases. Additionally, the differential expression of these miRNAs and the target gene was validated through *in vitro* experiments using a retinal ganglion cell (RGC) model.

Results: Expression levels of 19 and 3 miRNAs were significantly upregulated in the AH and LC samples of the glaucoma group, respectively ($p < 0.05$). Of these, the expression levels of hsa-miR-193a-5p and hsa-miR-222-3p showed significant differences in both AH and LC samples. Bioinformatics analysis showed experimentally validated 8 miRNA:gene pairs. Among them, *PTEN* was selected to analyze the expression level in AH and LC from separate cohort (glaucoma, $n = 5$; control, $n = 4$). The result showed downregulation of *PTEN* concurrent with upregulation of the two miRNAs in LC samples of glaucoma group. *In vitro* experiments validated that the expression levels of hsa-miR-193a-5p and hsa-miR-222-3p were significantly upregulated, and that of *PTEN* was significantly downregulated in the H_2O_2-treated RGC, while the level of *PTEN* was recovered through co-treatment with miR-193a inhibitor or miR-222 inhibitor.

Conclusion: This is the first study to investigate the differential expression of apoptosis-related miRNAs in the AH and LC of patients with glaucoma. Hsa-miR-193a-5p and hsa-miR-222-3p, which were upregulated in both AH and LC, may be considered potential biomarkers for glaucoma.

KEYWORDS
microRNA, glaucoma, aqueous humor, lens capsule, biomarker

1 Introduction

Glaucoma, a neurodegenerative disease, is characterized by retinal ganglion cell (RGC) death and optic nerve damage (1). The representative risk factors for glaucoma include aging, high intraocular pressure (IOP), and a family history of glaucoma (2). In particular, high IOP is a major risk factor that is regulated by the circulation of aqueous humor (AH). The damage or dysfunction of trabecular meshwork (TM) tissue, a passage through which AH flows, dysregulates the outflow of AH and consequently increases the IOP (3). Previous studies have reported TM alterations in eyes with glaucoma, which involve decreased cellularity (4) and the accumulation of apoptotic cells in TM tissue (5, 6). Functional and microstructural changes in TM tissue and TM cell apoptosis are among the significant pathological changes observed in open angle glaucoma (OAG) (7).

MicroRNAs (miRNAs), which are single-stranded non-coding RNAs with a length of approximately 22 nucleotides, regulate biological signals in various diseases by inhibiting the transcription of target genes (8). Growing evidence supports the role of miRNAs in the pathogenesis of neurodegenerative diseases, such as glaucoma, Alzheimer's disease, and Parkinson's disease, by regulating genes related to extracellular matrix (ECM)/cell proliferation, the immune system, and regulation of apoptosis (9, 10). MiRNAs play a crucial role in regulating apoptosis in various diseases (11), and their role in TM cell apoptosis in OAG has been actively investigated (12). Previous studies have explored differentially expressed miRNAs in glaucoma using peripheral blood mononuclear cell, plasma, and AH samples (13, 14). However, the expression profiles of miRNAs related to apoptosis in the lens capsule (LC) together with AH have not been analyzed in patients with OAG, except for those with lens-related glaucoma.

AH is continuously produced by the ciliary body and secreted out of the eye after directly coming in contact with the lens, iris, and surface of the corneal endothelium (15). As a body fluid secreted by many cells, AH can inform on conditions of the eye structures, such as lens epithelial cells and corneal endothelium, and the metabolites of the retina (16). The anterior LC lies in the monolayer subcapsular lens epithelium, which is the most important metabolic part of the lens (17). AH is in direct contact with the anterior LC and TM. Therefore, apoptotic factors in the AH can also affect or indicate the status of LC and TM. Moreover, LC may be an indirect indicator of the effect of AH cytokine/metabolites on the TM tissue. In contrast to AH which contains only extracellular biomaterials, the LC samples allow direct detection of biomaterials (such as microRNAs) from lens epithelial cells, providing useful insights into pathological mechanisms. Therefore, it may be helpful to evaluate the status of LC and AH simultaneously in patients with glaucoma.

In this study, we investigated the expression profiles of miRNAs associated with apoptosis in AH and LC samples obtained from patients with glaucoma. Furthermore, the potential mechanisms of differentially expressed miRNAs in glaucoma were examined based on their related proteins and signaling pathways.

2 Materials and methods

This prospective cross-sectional study included control participants and patients with glaucoma who visited the Department of Ophthalmology of Hanyang University Guri Hospital, Gyeonggi-do, South Korea between November 2019 and May 2021. The institutional review board (IRB) of Hanyang University Guri Hospital reviewed and approved the study protocol (IRB file no. 2019–05-022) and the protocol of this study adhered to the tenets of the Declaration of Helsinki. All study participants provided written informed consent to participate in this study.

2.1 Participants

This study recruited 29 participants who were scheduled for cataract surgery: 14 patients with open-angle glaucoma and 15 control participants. Glaucoma was diagnosed by a glaucoma specialist based on the clinical examination of the glaucomatous optic nerve head associated with typical and reproducible visual field defects. Glaucomatous visual field defects on the standard automated perimetry were defined based on a glaucoma hemifield test result outside the normal limits and the presence of at least three contiguous test points within the same hemifield on the pattern deviation plot at $p < 1\%$ (at least one point at $p < 0.5\%$) in at least two consecutive tests with reliability indices better than 15%. The inclusion criteria for patients with glaucoma were as follows: no history of ocular diseases other than glaucoma and cataract, no prior intraocular surgery, and no systemic diseases other than hypertension. Patients diagnosed with lens-related glaucoma using the slit lamp examination were excluded. The inclusion criteria for control participants were as follows: no prior intraocular surgery, no history of ocular diseases other than cataract, no use of any topical ocular medications, except the use of preoperative topical mydriatics and antibiotics, and no systemic diseases other than hypertension. The exclusion criteria for study subjects in both groups were as follows: received medication other than antihypertensive medication at any time during the study, a history of stroke or myocardial infarction, collection of insufficient amount of AH sample for analysis, or AH sample was judged as inappropriate for analysis.

All participants underwent standard ophthalmologic examinations, including IOP measurement, best-corrected visual acuity, slit lamp biomicroscopy, optical coherence tomography (swept source OCT, Topcon DRI OCT-1 Atlantis; Topcon, Inc., Tokyo, Japan), and Optos ultra-wide fundus photography (Optos, Dunfermline, Scotland). Patients with glaucoma additionally underwent gonioscopy, ultrasonic central corneal thickness measurements, IOP evaluation with Goldmann applanation

tonometry, stereoscopic optic nerve head examination, and visual field examination (30–2 strategy on Humphrey Perimeter).

2.2 Sample collection

AH samples were collected by the same operator (MS) at the start of the cataract surgery. Briefly, one or two drops of 0.5% proparacaine hydrochloride (Alcaine, Alcon, Ft. Worth, TX, United States) and 5% povidone-iodine were instilled after placing a sterile eyelid speculum. At the beginning of cataract surgery, anterior chamber paracentesis was performed under the surgical microscope using a 30-gauge needle mounted on a 1 mL tuberculin syringe to collect approximately 50–200 µL of AH. LC samples were obtained from the central anterior capsules of the lens (5–6 mm in diameter) via capsulorhexis during cataract surgery. Intact continuous curvilinear capsulorhexis was performed, avoiding vascular contact or damage to the iris and other intraocular structures. All AH and LC samples were transferred to tubes and immediately frozen at −80°C until further processing.

2.3 miRNA extraction and complementary DNA (cDNA) synthesis

2.3.1 Preparation of AH sample for miRNA polymerase chain reaction (PCR) array

miRNAs from AH samples were extracted using the miRNeasy serum/plasma kit (Qiagen, Hilden, Germany). For normalization, miRNeasy serum/plasma spike-in control (1.6×10^8 copies/µL; Qiagen) was added to all samples, following the manufacturer's instructions. RNA (45 ng) from AH samples was mixed with the miScript II RT kit (Qiagen) for cDNA synthesis according to manufacturer's instructions. The mixtures were incubated at 37°C for 60 min and 95°C for 5 min. The cDNA was immediately diluted in 20 µL of RNase-free water and stored at −20°C until use.

To perform the miRNA PCR array analysis, cDNA prepared from the AH samples was pre-amplified in a reaction mixture comprising Hot-Start Taq DNA polymerase, miScript PreAMP universal primers, miScript PreAMP buffer, miScript PreAMP primer mix, and RNase-free water in the miScript PreAMP PCR kit (Qiagen). The mixtures were incubated at 95°C for 15 min, followed by 21 cycles of 94°C for 30 s and 60°C for 3 min. The pre-amplified cDNA was diluted in 225 µL RNase-free water.

Real-time PCR was performed to confirm the quality of the pre-amplified cDNA. A 10× *Caenorhabditis elegans* miR-39 miScript primer, a 10× miRTC miScript primer, and a 10× miR-16 miScript primer were mixed with 2× QuantiTect SYBR Green PCR master mix, 10× miScript universal primer, and RNase-free water from the miScript PreAMP PCR kit and miScript SYBR Green PCR kit (Qiagen). The threshold cycle (Ct) values of the pre-amplification controls were determined.

2.3.2 Preparation of LC sample for miRNA PCR array

miRNAs from the LC samples were isolated using the miRNeasy micro kit (Qiagen). LC RNA samples (150 ng) were mixed with the miScript II RT kit (Qiagen) for cDNA synthesis. The cDNA was immediately diluted to perform miScript microarray analysis and stored at −20°C until use.

2.4 miRNA PCR array

A PCR array panel was used to identify the candidate miRNAs. Among several miRNA PCR array panels, a panel comprising miRNAs related to human apoptosis was selected, as apoptosis is one of the main alterations in TM tissues in eyes with glaucoma. miRNA PCR array was performed with an miScript miRNA PCR Array Human apoptosis kit (96-well format, Qiagen, #MIHS-114ZC) with 43 cycles, according to the manufacturer's specifications. For the AH samples, miRNA PCR array results were calibrated with cel-miR-39 and miRTC (miRNA reverse transcription control) and simultaneously normalized with RNU6-6P. Meanwhile, for the LC samples, the miRNA PCR array results were normalized with SNORD95 (Small Nucleolar RNA, C/D Box 95). A list of 84 genes from the human apoptosis PCR array panel, excluding 12 controls, is provided in Supplementary Table S1. miRNA expression was analyzed using the Qiagen Data Analysis Center.[1] The results are presented in the form of clustergrams and heatmaps, which are generated using the online Qiagen Data Analysis Center.[2]

2.5 Quantitative real-time PCR (qRT-PCR)

Total RNA was extracted from the AH and LC samples using the same protocol as described above. cDNA was synthesized using the miRCURY LNA RT kit (Qiagen) according to manufacturer's instructions. To validate the differential expression of hsa-miR-193a-5p and hsa-miR-222-3p determined using the PCR array, commercially available PCR primer mixes (Qiagen) were used with the miRCURY LNA miRNA PCR assay (Qiagen), following the manufacturer's instructions. UniSp6 expression was used as an internal control. Fluorescence data were collected, and the relative expression of miRNAs was calculated using delta C_T.

2.6 Reverse transcription-PCR (RT-PCR)

cDNA was synthesized using amfiRivert cDNA Synthesis Platinum Master Mix (GenDEPOT) according to the manufacturer's protocol. The RT-PCR was performed with Taq DNA polymerase (GenDEPOT) on a thermal controller (Applied Biosystems). The PCR reaction was initiated with a 2 min incubation at 94°C, followed by 40 cycles of denaturation at 94°C for 15 s, annealing at 55°C for 30 s, and extension at 72°C for 30 s, and terminated after a 10 min extension at 72°C. Each PCR product (5 µL) was electrophoresed in a 1.5% agarose gel, and bands were visualized using the SafePinky DNA Gel Staining Solution (GenDEPOT). The densities of the DNA bands were analyzed using an image analyzer (ImageQuant LAS 4000).

1 https://geneglobe.qiagen.com/

2 https://geneglobe.qiagen.com/kr/analyze/

2.7 Bioinformatics

2.7.1 Prediction the experimentally validated miRNA target genes

Target annotation analysis was performed using R (version 3.6.3),[3] and appropriate packages according to the corresponding reference manuals. Identification of miRNA-gene regulatory interactions was performed in silico between selected miRNAs and glaucoma-associated genes harvested from DisGeNET 7.0 database[4] (18), (using multiMiR 1.10.0 package,[5] database version: 2.3.0, updated on 2020–04-15) (19, 20). The analysis included the identification of both experimentally validated (miRecords, miRTarBase, and TarBase databases) and predicted (DIANA-microT-CDS, ElMMo, MicroCosm, miRanda, miRDB, PicTar, PITA, and TargetScan databases) miRNA-gene interactions. Among the identified miRNA-gene regulatory interactions, those validated based on experiments known as strong evidence, including western blotting, qRT-PCR, and reporter assays, were included in target gene selection for expression level analysis using AH and LC samples and gene ontology enrichment analysis to identify significant pathways.

2.7.2 Gene ontology enrichment analysis

The interactions of validated target genes were analyzed using ClueGO in Cytoscape. The enrichment analysis revealed a list of statistically significant genes and the connection between biological processes. Pathway networks and gene ontology terms were identified using Kyoto Encyclopedia of Genes and Genomes (KEGG) (21), biological process, and Reactome database of protein complex in ClueGO. All images represent statistically significant pathways ($p < 0.05$).

2.7.3 Bioinformatics analysis with Laverne

The relationship between miRNA genes and glaucoma was analyzed using the Laverne Bioinformatics Tool from Novus Biologicals.[6] The lines of the bioinformatic images are based on the supporting evidence.

2.8 *In vitro* experiment

To validate the findings from samples of patients with glaucoma, *in vitro* experiments using a glaucomatous cell model (RGC) were conducted.

2.8.1 Primary RGC isolation

A total of 28 pregnant Sprague Dawley rats were purchased form Orientbio (Gyeonggi-do, South Korea), and 280 2-days old rats were used for RGC isolation. Newborn rats were euthanized by decapitation, conducted by an expert to minimize the number and pain of animals used in the experiment. Each experiment was conducted in duplicate and repeated three or four times from different cell harvests. Retinal tissues of 2-days old rats were incubated in Hank's balanced salt solution (Gibco) containing 5 mg/mL of papain (Sigma), 0.24 mg/mL of L-cysteine (Sigma), 0.5 mmoL/L of EDTA (Sigma), and 10 U/mL of DNase I (Worthington) for 30 min. Dissociated retinal cells were collected as a suspension. The retinal cell suspension was incubated with rabbit anti-rat macrophage antibody (1:50 dilution; Fitzgerald) for 5 min. The suspension was treated in a 100-mm Petri dish coated with goat anti-rabbit antibody (1:200 dilution; Jackson laboratory) for 30 min. Non-adherent cells were incubated with anti-Thy1 microbeads (1:10, Miltenyi Biotec) for 30 min at 4°C, and the magnetic-labeled RGCs were collected using a magnetic separating unit. All procedures were performed under the approve of Institutional Animal Care and Use Committee (IACUC) of Hanyang university.

2.8.2 RGC culture and hydrogen peroxide (H_2O_2) treatment

The cells were cultured in neurobasal media (Gibco) containing 1% penicillin/streptomycin (Gibco), B-27™ Supplement (50X, Gibco), 4.0 mg/L of Forskolin (Sigma), 80 mg/L of brain-derived neurotrophic factor, and 80 mg/L of ciliary neurotrophic factor. Cells were seeded on a 6-well plate precoated with poly-L-ornithine and laminin. The seeding density was approximately 1×10^6 cells per well. The cultures were incubated at 37°C in humidified 5% CO_2 and 95% air. To measure changes in the expression levels of the miRNAs and *PTEN*, the RGCs (1×10^6/well) were exposed to 100 μM H_2O_2 for 6 h in a 6-well plate.

2.8.3 miRNA regulation

Transfection of inhibitors of the miRNAs were performed a day before H_2O_2 treatment. 20 pmol rno-miR-193a inhibitor (Invitrogen) and 20 pmol rno-miR-222 inhibitor (Invitrogen) were used for transfection. Inhibitors were incubated for 20 min at room temperature before transfection. The inhibitors were transfected into the RGC using lipofectamine RNAiMAX Transfection Reagent (Invitrogen) for 24 h, and then transfected-RGCs were treated with H_2O_2. All cells were collected for RT-PCR analysis.

2.9 Statistical analysis

All data are presented as mean ± standard deviation from at least three independent experiments. The means of different groups were compared using Student's t-test. Differences were considered significant at $p < 0.05$. Correlation analysis between AH and LC samples was performed using Spearman correlation analysis.

3 Results

Among 14 patients with glaucoma and 15 control participants, the AH samples from 3 patients with glaucoma and 3 control participants and the LC samples from 3 patients with glaucoma and 4 control participants were used for miRNA PCR array analysis. Additionally, both AH and LC samples from 3 patients with glaucoma and 4 control participants were used for qRT-PCR analysis. AH and LC samples from the remaining 5 patients with glaucoma and 4 control participants were used for RT-PCR of *PTEN* and qRT-PCR of miRNAs. Table 1 shows the baseline clinical characteristics of enrolled participants.

3 https://www.r-project.org/
4 https://www.disgenet.org/
5 https://bioconductor.org/packages/release/bioc/html/multiMiR.html
6 http://www.novusbio.com/explorer/

TABLE 1 Characteristics and types of experiment and sample of study participants.

	Sex	Age (years)	Diagnosis	Laterality	Underlying disease	miRNA PCR array_AH	miRNA PCR array_LC	miRNA qRT-PCR*	RT-PCR, miRNA qRT-PCR†
Control									
1	Female	73	Cataract	OS	None	√			
2	Female	66	Cataract	OS	None	√			
3	Male	84	Cataract	OS	None	√			
4	Female	68	Cataract	OD	None		√		
5	Male	77	Cataract	OD	None		√		
6	Male	66	Cataract	OS	None		√		
7	Female	79	Cataract	OD	HTN		√		
8	Female	71	Cataract	OD	None			√	
9	Male	72	Cataract	OD	None			√	
10	Female	74	Cataract	OD	None			√	
11	Female	69	Cataract	OD	None			√	
12	Female	58	Cataract	OS	None				√
13	Male	60	Cataract	OD	None				√
14	Female	75	Cataract	OS	None				√
15	Female	55	Cataract	OD	HTN				√
Glaucoma									
1	Female	67	OAG	OD	HTN	√			
2	Male	71	OAG	OD	HTN	√			
3	Male	84	OAG	OD	HTN	√			
4	Male	61	OAG	OD	None		√		
5	Female	81	OAG	OS	HTN		√		
6	Female	80	OAG	OD	HTN		√		
7	Female	74	OAG	OD	HTN			√	
8	Female	75	OAG	OD	HTN			√	
9	Female	68	OAG	OD	HTN			√	
10	Male	43	OAG	OD	HTN				√
11	Male	61	OAG	OS	None				√
12	Female	71	OAG	OD	None				√
13	Male	69	OAG	OS	None				√
14	Male	72	OAG	OD	HTN				√

*Performed using both AH and LC samples from each participant. †RT-PCR was performed using both AH and LC samples for each participant and miRNA qRT-PCR was performed using LC samples. AH, aqueous humor; LC, lens capsule; OAG, open-angle glaucoma; HTN, hypertension; OS, oculus sinister; OD, oculus dexter; PCR, polymerase chain reaction; qRT-PCR, quantitative real-time PCR; RT-PCR, Reverse Transcription-PCR; miRNA, microRNA.

3.1 miRNA PCR array in AH and LC

In the AH, 19 miRNAs showed significantly differential expression between the glaucoma and control groups (Figure 1A). All 19 miRNAs (hsa-let-7a-5p, hsa-miR-125a-5p, hsa-miR-1285-3p, hsa-miR-181d-5p, hsa-miR-185-5p, hsa-miR-192-5p, hsa-miR-193a-5p, hsa-miR-194-5p, hsa-miR-195-5p, hsa-miR-210-3p, hsa-miR-221-3p, hsa-miR-222-3p, hsa-miR-25-3p, hsa-miR-31-5p, hsa-miR-365-3p, hsa-miR-512-5p, hsa-miR-542-3p, hsa-miR-9-5p, and hsa-miR-92a-5p) were significantly upregulated in the glaucoma group ($p < 0.05$; Table 2). The results of miRNA PCR array analysis of AH samples are shown in Supplementary Table S1.

In the LC, three miRNAs showed significantly differential expression between the glaucoma and control groups (Figure 1B). All three miRNAs (hsa-let-7e-5p, hsa-miR-193a-5p, and has-miR-222-3p) were significantly upregulated in the glaucoma group ($p < 0.05$; Table 2). The results of miRNA PCR array analysis of LC samples are shown in Supplementary Table S2.

Among the miRNAs evaluated, hsa-miR-193a-5p and hsa-miR-222-3p were significantly upregulated in both AH and LC samples of the glaucoma group.

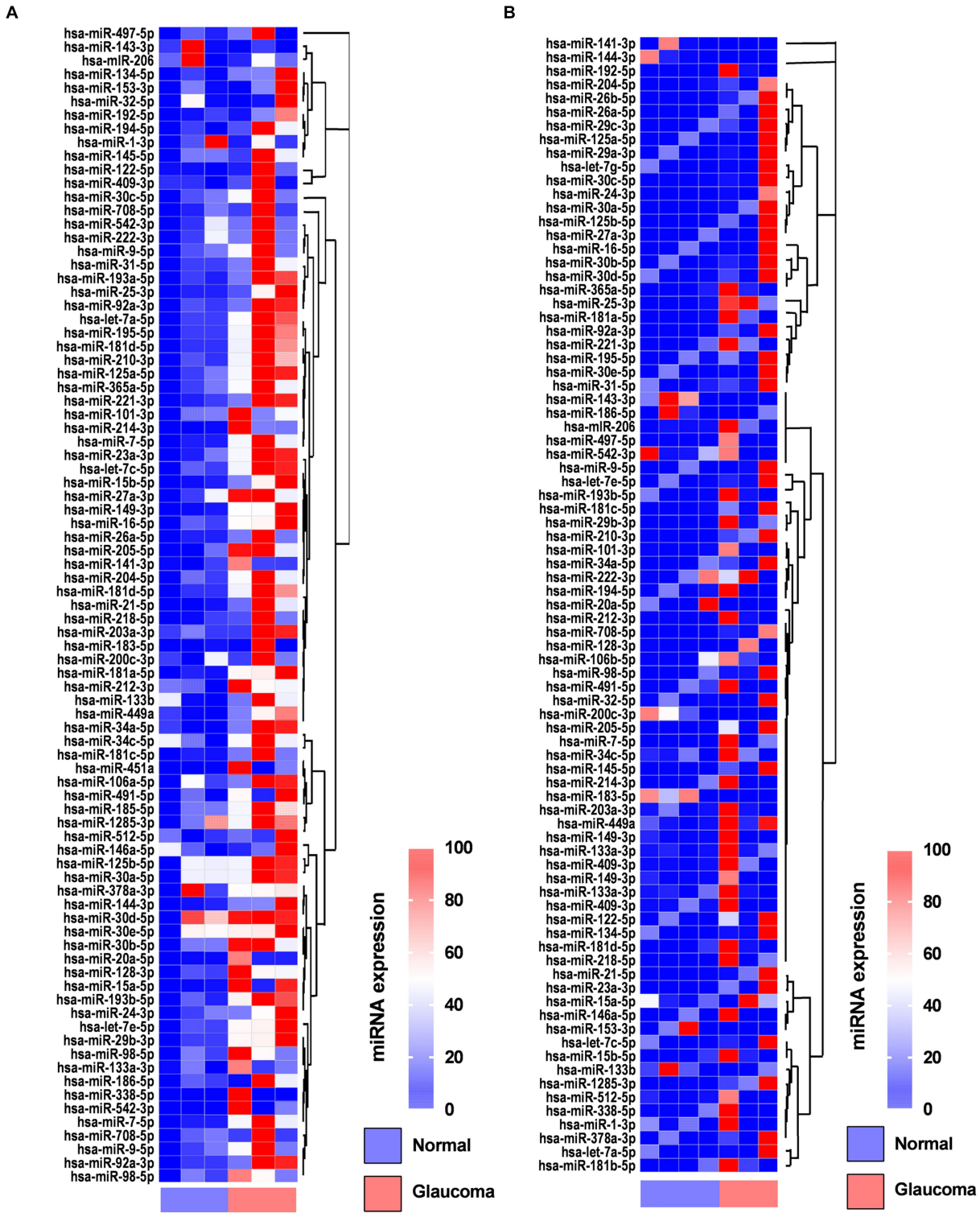

FIGURE 1
Heatmaps showing the regulated genes in the aqueous humor **(A)** and lens capsule **(B)** of patients with glaucoma and control participants using the miScript miRNA PCR array. Log2 values of 84 genes in the glaucoma group compared with the control group are represented. Colors reflect the magnitude of gene expression. Heatmaps are generated using the online Qiagen Data Analysis Center (https://geneglobe.qiagen.com/kr/analyze/).

3.2 Quantitative real-time PCR in both AH and LC

qRT-PCR analysis revealed that hsa-miR-193a-5p and hsa-miR-222-3p, which were determined to be significantly upregulated in the AH and LC samples of patients with glaucoma using miRNA PCR array, were also significantly upregulated in the AH and LC samples of patients ($p < 0.05$, Figure 2). As this analysis was done from the AH and LC samples from the identical subjects, the correlation of each miRNA level between AH and LC was performed. The level of

TABLE 2 List of differentially expressed miRNAs from miRNA PCR arrays using aqueous humor (AH) and lens capsule (LC) samples of patients with glaucoma with statistical significance, corresponding C_T values, and fold change data.

miRNA	AVG ΔC_T		$2^{-\Delta Ct}$		Fold change	*p* value
	Glaucoma	Control	Glaucoma	Control		
AH						
hsa-let-7a-5p	−9.64	−7.65	799.71	200.85	3.98	0.021
hsa-miR-125a-5p	−10.66	−7.99	1618.00	254.23	6.36	0.013
hsa-miR-1285-3p	−3.33	0.5	10.03	0.71	14.16	0.024
hsa-miR-181d-5p	−5.66	−2.16	50.56	4.46	11.34	0.017
hsa-miR-185-5p	−4.5	−1.66	22.58	3.16	7.14	0.012
hsa-miR-192-5p	−4.33	0.67	20.11	0.63	31.93	0.018
hsa-miR-193a-5p	−5.99	−3.33	63.70	10.08	6.32	0.005
hsa-miR-194-5p	−2.33	3.87	5.03	0.07	73.69	0.025
hsa-miR-195-5p	−6.66	−3.99	101.13	15.93	6.35	0.017
hsa-miR-210-3p	−5.67	−1.99	50.91	3.98	12.79	0.017
hsa-miR-221-3p	−5.32	−2.33	39.85	5.02	7.94	0.025
hsa-miR-222-3p	−5.82	−3	56.36	7.98	7.06	0.016
hsa-miR-25-3p	−6.99	−3.66	127.41	12.64	10.08	0.000
hsa-miR-31-5p	−4.82	−3	28.31	7.98	3.55	0.002
hsa-miR-365-3p	−5.67	−3.33	50.80	10.08	5.04	0.018
hsa-miR-512-5p	−3.32	4.18	10.01	0.06	181.44	0.017
hsa-miR-542-3p	1.01	4.82	0.50	0.04	14.06	0.006
hsa-miR-9-5p	−0.65	1.68	1.57	0.31	5.02	0.046
hsa-miR-92a-5p	−9.99	−6.33	1019.28	80.26	12.7	0.000
LC						
hsa-let-7e-5p	−2.83	−0.74	7.093	1.6753	4.23	0.001226
hsa-miR-193a-5p	0.82	2.36	0.5661	0.1942	2.91	0.043613
hsa-miR-222-3p	2.71	4.51	0.1525	0.0438	3.48	0.027515

The miRNAs that showed significantly differential expression in the miRNA PCR array in both AH and LC samples of patients with glaucoma were miR-193a-5p and miR-222-3p. miRNA, microRNA; AH, aqueous humor; LC, lens capsule; ΔC_T, delta C_T; AVG ΔC_T, average ΔC_T; $\Delta C_T = C_T$ ([target gene] − C_T [reference gene]).

hsa-miR-193a-5p of the AH sample and that of the LC sample showed a positive correlation ($R = 0.886$, $p = 0.009$), and the level of hsa-miR-222-3p of the AH sample and that of the LC sample also showed a positive correlation ($R = 0.754$, $p = 0.042$).

3.3 Bioinformatics

We performed *in silico* target annotation analysis between 770 glaucoma-associated genes received from DisGeNET 7.0 database (Concept Unique Identifier "C0017601" was queried) and two upregulated miRNAs (hsa-miR-193a-5p and hsa-miR-222-3p). Target annotation analysis revealed 57 validated miRNA:gene pairs (Supplementary Table S3) and 69 top 10% predicted miRNA:gene pairs obtained with the highest probability (Supplementary Table S4). Among the experimentally validated miRNA-gene regulatory interactions, eight miRNA:gene pairs were validated based on the experiments known as strong evidences (Table 3).

To indicate the biological processes in which miRNA-regulated genes are involved, gene ontology (GO) enrichment analysis with significant pathways was performed using 57 validated target genes. GO enrichment analysis using ClueGO of Cytoscape revealed that 23 terms, including "regulation of wound healing, spreading of epidermal cells," "regulation of extrinsic apoptotic signaling pathway via death domain receptors," and "positive and negative regulation of vascular-associated smooth muscle cell proliferation," were associated with the validated target genes of the two miRNAs (Figure 3A). Supplementary Table S5 summarizes the related terms and genes included in each term. The top three groups were as follows: regulation of vascular-associated smooth muscle cell proliferation (52.17%), regulation of wound healing, spreading of epidermal cells (21.74%), and regulation of pentose-phosphate shunt (8.7%; Figure 3B). Figure 3C shows the percentage of the number of validated target genes associated with each term out of the total number of genes associated with that term (%Genes/Term). The % Genes/Term was the highest in the term "Regulation of wound healing, spreading of epidermal cells."

Bioinformatics analysis revealed that the two miRNAs (hsa-miR-193a-5p and hsa-miR-222-3p), apoptosis signaling pathways, and glaucoma were correlated (Supplementary Figure S1). These two miRNAs were associated with survival or apoptosis-related factors,

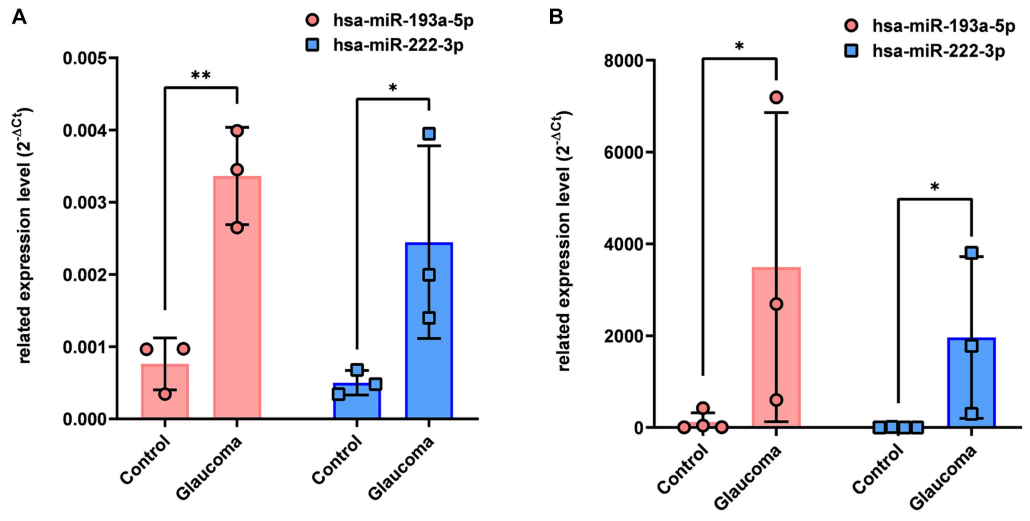

FIGURE 2
Differential expression of two microRNAs (hsa-miR-193a-5p, hsa-miR-222-3p) in aqueous humor **(A)** and lens capsule **(B)** samples of control participants and patients with glaucoma. Total RNA was isolated and expression of miRNAs for hsa-miR-193a-5p and has-miR-222-3p were analyzed using quantitative real-time PCR. Each sample was analyzed in replicate. Values on the y-axis are reported as $2^{-\Delta Ct}$. *$p < 0.05$, **$p < 0.01$ relative to the control group. Data are expressed as mean ± standard deviation. miRNA, microRNA.

TABLE 3 **List of experimentally validated miRNA:gene pairs between 770 glaucoma-associated genes received from the DisGeNET 7.0 database and two miRNAs (hsa-miR-193a-5p and hsa-miR-222-3p) using multiMiR 1.10.0 package.**

Target gene name	
hsa-miR-193a-5p	hsa-miR-222-3p
MTOR	*CDKN1B*
WT1	*ETS1*
	MMP1
	PTEN
	SOD2
	TIMP3

The pairs here only include those validated with strong evidence, including luciferase reporter assay, western blot, and RT-PCR. The whole list is listed in the Supplementary Table S3. MTOR; mammalian target of rapamycin, WT1; Wilms tumor protein, CDKN1B; cyclin dependent kinase inhibitor 1B, ETS1; ETS proto-oncogene 1 (transcription factor), MMP-1; matrix metalloproteinase-1, PTEN; phosphatase and tensin homolog, SOD2; superoxide dismutase 2, TIMP3; TIMP.

such as *TGFB1*, *PI3K*, *BAX*, *BCL2*, *TP53*, *PTEN*, *CASP3*, *AKT*, and cyclin D1.

3.4 Expression level for the selected target gene (*PTEN*) in AH and LC

There were no overlapping target genes between the two miRNAs which are validated by experiments corresponding to strong evidence. Among the 8 target genes listed in Table 3, the further literature review revealed a reported association between *MTOR* and hsa-miR-222-3p in pancreatic cancer (22), *ETS1* and hsa-miR-193a-5p in gastric cancer (23), and *PTEN* and hsa-miR-193a-5p in Alzheimer's disease (24). We selected *PTEN* further to analyze mRNA and miRNA correlations in patient samples. AH and LC samples from a separate cohort (four control subjects and five glaucoma patients) were used for RT-PCR of *PTEN* and qRT-PCR of hsa-miR-193a-5p and hsa-miR-222-3p. Only *PTEN* could be analyzed because of the small amount of RNA in AH samples, whereas *PTEN* and the two miRNAs could be analyzed in LC samples. In one AH sample from the glaucoma group, the RNA quality was unsuitable for the analysis. Consequently, LC samples of four control subjects and five patients with glaucoma, and AH samples of four control subjects and four patients with glaucoma were analyzed. The results showed significant upregulation of the two miRNAs in the LC samples of glaucoma group, concurrently with significant downregulation of *PTEN* in the LC samples of glaucoma group ($p < 0.05$; Figure 4). *PTEN* levels in the AH samples did not differ significantly between the control and glaucoma groups.

3.5 *In vitro* validation of the regulatory roles of the miRNAs (hsa-miR-193a-5p and hsa-miR-222-3p) on the selected target gene (*PTEN*) in a glaucomatous cell model

In RGCs exposed to H_2O_2-induced oxidative injury, the expression levels of hsa-miR-193a-5p and hsa-miR-222-3p significantly increased (Figure 5A), while that of *PTEN* significantly decreased (Figure 5B). Treatment with the hsa-miR-193a-5p inhibitor resulted in a decrease in hsa-miR-193a-5p expression (Figure 5C) and an increase in *PTEN* expression (Figure 5E), a pattern replicated with the hsa-miR-222-3p inhibitor (Figures 5D,E). These findings imply the regulatory roles of these miRNAs on PTEN in RGCs under oxidative stress.

4 Discussion

This study analyzed the apoptosis-related miRNA profiles of both AH and LC samples in patients with glaucoma and control participants. The expression levels of hsa-miR-193a-5p and

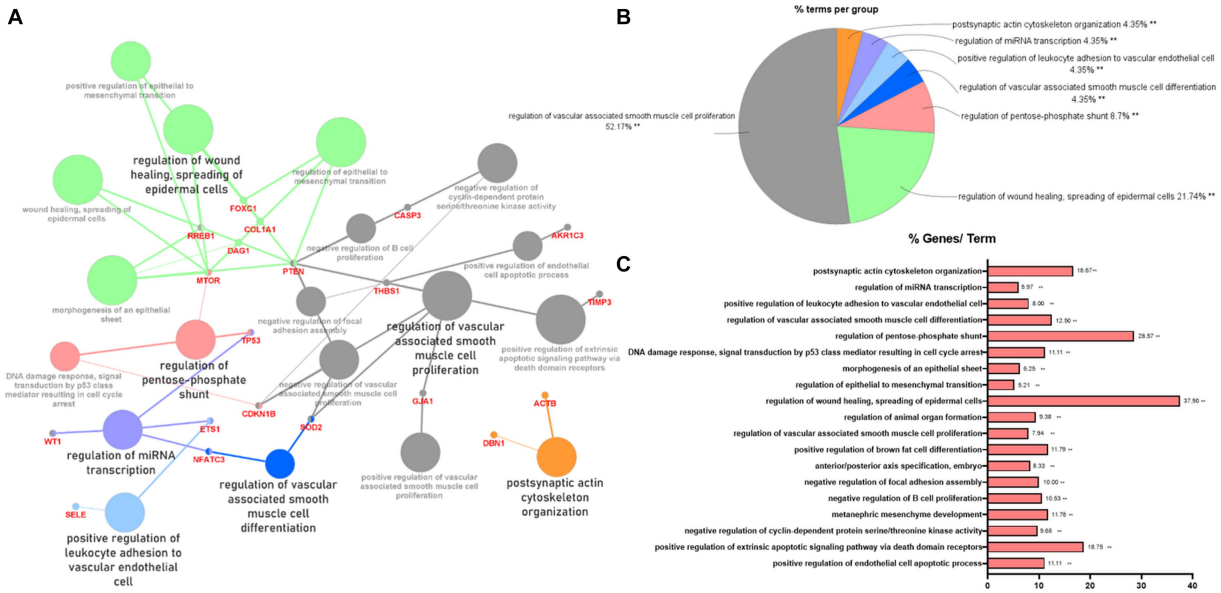

FIGURE 3
Gene ontology enrichment analysis with significant pathways. **(A)** Enrichment analysis showing interactions of target genes of miR-193a-5p and miR-222-3p. All interactions were statistically significant. The color indicates the grouping of the terms. **(B)** A pie chart of biological processes associated with the query genes. Frequency of each group is shown based on percentage. **(C)** Category plot displays GO/pathway terms that were related to target genes. The bars represent the percentage of genes associated with the terms. The number of genes per term is shown as bar label.

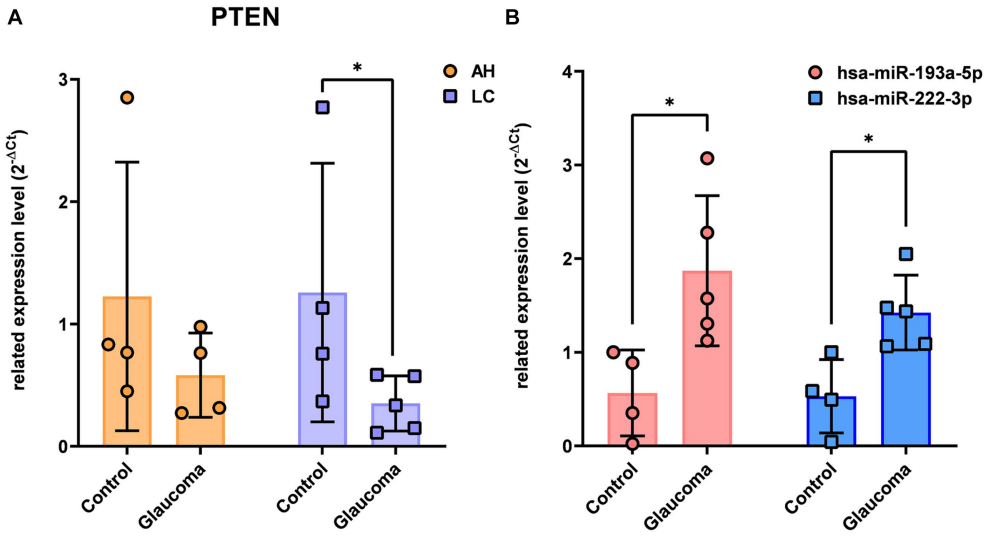

FIGURE 4
The expression level of *PTEN* in the aqueous humor and lens capsule samples of control participants and patients with glaucoma **(A)** and the differential expression of two microRNAs, hsa-miR-193a-5p and hsa-miR-222-3p, in the lens capsule samples of control participants and patients with glaucoma **(B)**. The expression of *PTEN* was analyzed using RT-PCR. Total RNA was isolated, and expression of miRNAs for hsa-miR-193a-5p and has-miR-222-3p were analyzed using qRT-PCR. Each sample was analyzed in a replicate. Values on the y-axis are reported as $2^{-\Delta Ct}$. $*p < 0.05$, $**p < 0.01$ relative to the control group. Data are expressed as mean ± standard deviation. *PTEN*, phosphatase and tensin homolog; miRNA, microRNA; AH, aqueous humor; LC, lens capsule; RT-PCR, Reverse Transcription-PCR; qRT-PCR, quantitative real-time PCR.

hsa-miR-222-3p in both AH and LC samples of patients with glaucoma were upregulated when compared with those in both AH and LC samples of controls. Additionally, this study examined the role of these miRNAs in glaucoma using bioinformatics tools and identified their target genes and associated biological processes (survival and apoptotic signaling pathways). Then, based on a literature review, we selected a putative gene (*PTEN*) to determine its differential expression in AH and LC samples from patients with glaucoma. We further validated the differential expression of the target miRNAs and the target gene through *in vitro* experiments, demonstrating the regulatory role of these miRNAs-*PTEN* axes. This is the first study to use both AH and LC samples for miRNA profiling

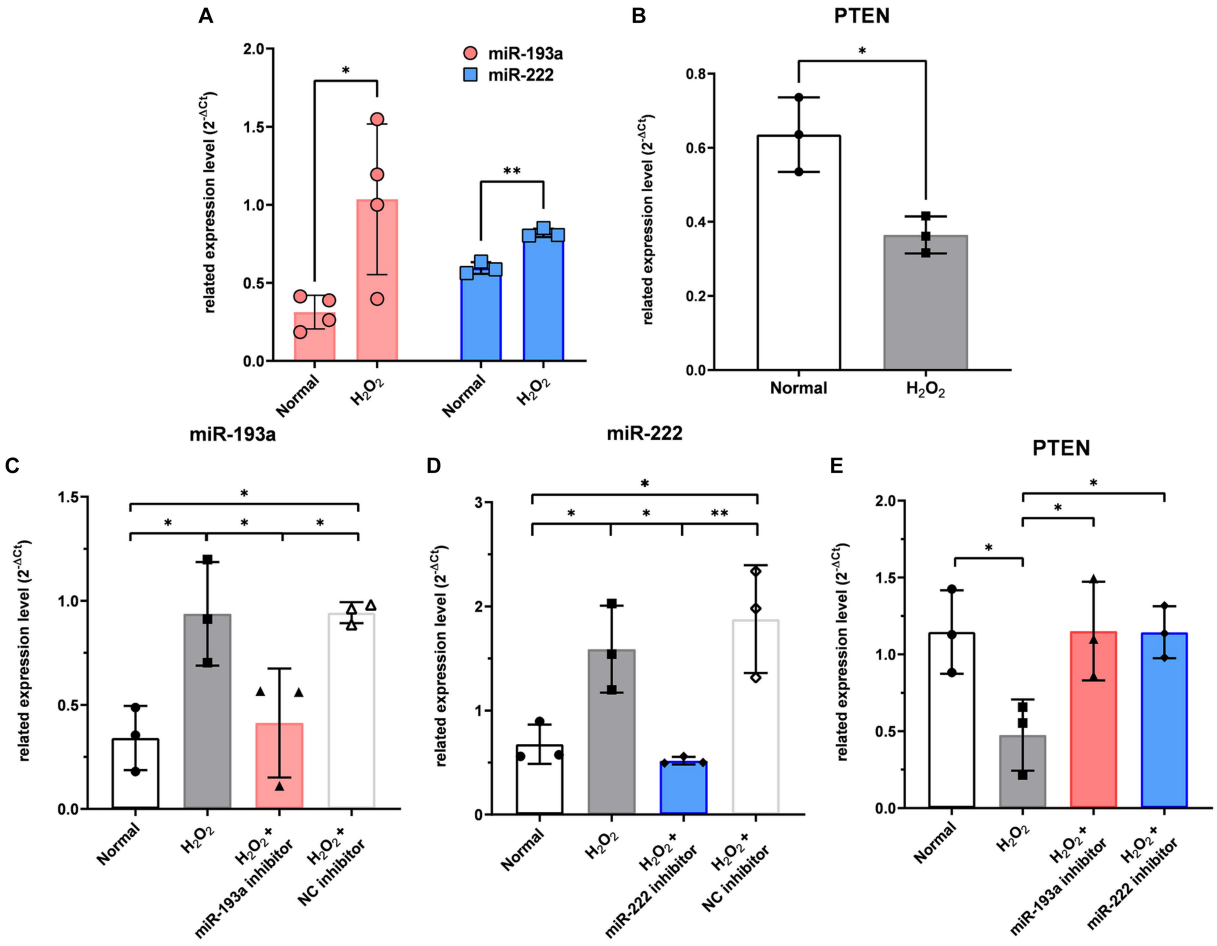

FIGURE 5
The expression level of the two differentially expressed microRNAs (miR-193a-5p and miR-222-3p) **(A)** and *PTEN* **(B)** in the retinal ganglion cell (RGC) model under oxidative stress using H_2O_2. Transfection of miR-193a inhibitor **(C)** and miR-222 inhibitor **(D)** to RGC showed regulation of expression of the miRNAs. Negative control (NC) inhibitor had no effect on the expression of the miRNAs. The two miRNA inhibitors also up-regulated the expression of *PTEN*, which was reduced by H_2O_2 **(E)**. Values on the y-axis are reported as $2^{-\Delta Ct}$. *$p < 0.05$. Data are expressed as mean ± standard deviation.

in patients with glaucoma and reveal the related biological pathways using bioinformatics tools that are experimentally validated.

Several miRNA studies on glaucoma have used experimental animal/cell models and AH or blood samples from patients to elucidate the pathological mechanisms of glaucoma, although no specific consensus has been achieved. Experimental models of glaucoma used in miRNA studies include animal models and damaged RGCs. One study investigated the changes in miRNA expression in RGCs in the laser-induced ocular hypertension rat model and identified potential neuroprotective candidates for RGCs (miR-194 and miR-664-2 inhibitors) (25). Other studies have reported that various miRNAs, such as miR-141-3p, miR-141-5p, miR-21a-5p, and miR-93-5p, which inhibited RGC apoptosis and promoted RGC survival in the N-methyl-D-aspartic acid (NMDA)-induced glaucomatous mouse model, are potential therapeutic targets (26–29). Studies have also been performed to identify potential related biological processes. The overexpression of miR-124b protects RGC function, activates autophagy, and modulates survival signaling pathways, such as *mTOR* and *AKT*, in the surgically-induced glaucomatous neurodegeneration mouse model (30). There have been several studies that analyzed miRNAs expression in patients with glaucoma using samples, such as blood (plasma or serum) or AH. A recent review summarized the findings of various miRNA studies using samples from patients with open-angle glaucoma and suggested that miR-143-3p, miR-125b-5p, and miR-1260b are potential therapeutic targets for glaucoma (31). However, the authors also suggested the lack of overlapping findings among the miRNA profiling studies conducted using the AH (13, 20, 32–38) and other samples, including blood (plasma/serum) and tears of patients with primary open-angle glaucoma (13, 32, 39, 40). The results of miRNA profiling studies using intraocular samples of patients with glaucoma are summarized in Supplementary Table S6. Blood samples can be obtained through minimally invasive procedures and collected at frequent intervals. Recent studies showed that miRNAs in serum samples are biomarkers that serve as valuable indicators of systemic and ocular diseases (41–44). However, AH samples can more directly reflect eye-specific conditions than serum samples. Meanwhile, LC can directly reflect the condition of the anterior chamber, including the TM tissue. miRNA profiling of the LC samples of patients with open-angle glaucoma has not been previously performed. Hence, this

study aimed to analyze the miRNA expression profile in both AH and LC.

This study demonstrated that the two miRNAs hsa-miR-193-5p and hsa-miR-222-3p were upregulated in both AH and LC in patients with open-angle glaucoma. Upregulation of has-miR-222-3p in AH of patients with normal tension glaucoma has recently been reported (33), the dysregulation of hsa-miR-193-5p has not been previously reported in patients with glaucoma. The roles of hsa-miR-193-5p and hsa-miR-222-3p in apoptotic pathways have been extensively studied (40, 45–48). Consistently, Laverne bioinformatics analysis also revealed the association between these two miRNAs and the apoptotic pathway in this study (Supplementary Figure S1). The roles of hsa-miR-193-5p and hsa-miR-222-3p have mostly been studied in the context of cancer biology, including angiogenesis (49, 50) and inflammation (51, 52). miR-193a-5p promotes apoptosis and consequently inhibits colorectal cancer cell survival through the miR-193a-5p/PIK3R3/AKT axis (53). One study reported that miR-193a-5p mimics decrease cancer cell viability and suppress intracellular mechanisms (54). miR-222-3p interacted with circular RNA (circRNA) to inhibit cancer cell development (47). Circ_HIPK3, a circRNA, was reported to protect neuronal cells against apoptosis by inhibiting the miR-222-3p/DUSP19 axis (55). miR-19b/221/222 induces endothelial cell dysfunction and cellular apoptosis through the suppression of proliferator-activated receptor γ coactivator 1α (PGC-1α) (56). Additionally, a previous study examined the roles of miR-222-3p in human lens epithelial cells of the *in vitro* cataract model and reported that the circRNA-mediated inhibition of miR-222-3p mitigates cell damage (57). These previous findings demonstrate that miR-222-3p promotes cell damage by inducing oxidative stress and apoptosis, which are important pathological components of glaucoma (58–61). Previous studies have also reported the association between miRNAs and oxidative stress/apoptosis in glaucoma (12, 40). In summary, our findings are consistent with the previous studies showing that miR-193a and miR-222 tend to induce oxidative stress and apoptosis.

In this study, we selected *PTEN* among the validated target genes to analyze the differences in its expression levels in AH and LC samples between control subjects and patients with glaucoma. Because the amount of AH and LC samples was insufficient to analyze multiple target genes simultaneously with miRNAs, we selected one target gene. Expression of *PTEN* was significantly downregulated in LC samples from patients with glaucoma, whereas it was not statistically significant in AH samples. *PTEN* is involved in multiple cellular processes, including cell proliferation, apoptosis, and migration, and cell-ECM interaction and signaling (62). The beneficial effects of *PTEN* inhibition, including neuroprotective effects, have been reported mainly through the upregulation of the Akt signaling pathway (63); however, beneficial effects of *PTEN* upregulation through treatment with human *PTEN* in neuronal survival have also been reported (64). Analysis of signaling pathway activation using TM tissues obtained from OAG donors revealed significant downregulation of the *PTEN* pathway, which is thought to be associated with apoptosis in the TM (65). In addition, the critical role of *PTEN* in regulating ECM remodeling in tissues is known and a decrease in *PTEN* levels has been reported in many fibrotic diseases (66). It has been reported that a reduction in *PTEN* levels in TM cells contributes to fibrosis of TM by inducing ECM deposition, which may lead to dysfunction of AH drainage (67). In this study, *PTEN* levels were significantly downregulated in LC samples from patients with glaucoma, although this was not significant in AH samples. Since the interactions between *PTEN* and both miRs-193-5p and −222-3p are known (24, 68), it can be hypothesized that the upregulation of miRs-193a and −222 and subsequent downregulation of *PTEN* may have a potential role in OAG. We further validated the differential expression of these miRNAs and *PTEN* in the oxidative-injured RGC model, one of the glaucomatous cell models, and also revealed the regulatory roles of these miRNAs (miRs-193-5p and −222-3p) on *PTEN* for the first time. The exact roles of these miRNAs/*PTEN* axes in the pathogenesis of glaucoma needs to be elucidated through experimental validation in future studies.

In addition to the two miRNAs that were upregulated in both AH and LC samples, we also identified miRNAs with inconsistent upregulation in AH and LC in this study. The upregulated miRNAs in the AH and LC of patients with glaucoma included other 17 miRNAs (hsa-let-7a-5p, hsa-miR-125a-5p, hsa-miR-1285-3p, hsa-miR-181d-5p, hsa-miR-185-5p, hsa-miR-192-5p, hsa-miR-194-5p, hsa-miR-195-5p, hsa-miR-210-3p, hsa-miR-221-3p, hsa-miR-25-3p, hsa-miR-31-5p, hsa-miR-365-3p, hsa-miR-512-5p, hsa-miR-542-3p, hsa-miR-9-5p, and hsa-miR-92a-5p), and hsa-let-7e-5p, respectively. Previous studies have reported the upregulation of hsa-let-7a-5p and hsa-miR-192-5p in the AH of patients with normal tension glaucoma (33, 38), hsa-miR-210-3p in the serum of patients with primary open-angle glaucoma (POAG) (39), hsa-miR-221-3p in the AH of patients with POAG (32), and hsa-miR-9-5p in the peripheral blood mononuclear cells of patients with pseudoexfoliation glaucoma (14). The hsa-miR-125a-5p levels are upregulated in non-glaucomatous human TM cells in response to cyclic mechanical stretch, and this is suggested to be correlated with the pathogenesis of glaucoma (69). On the other hand, the expression of miR-181d-5p in RGC was downregulated in the glaucomatous mouse model (25), and that of miR-25 was downregulated in glaucomatous rat retina (70). These discrepancies can be attributed to differences in the samples used in different studies (animal models in previous studies vs. AH or LC samples of patients in this study). The roles of hsa-miR-185-5p, hsa-miR-194-5p, hsa-miR-195-5p, hsa-miR-31-5p, hsa-miR-92a-5p, and let-7e-5p in glaucoma have not been reported.

This study has some limitations. First, small numbers of participants were included in this study and separate samples were used for each analysis. As the amount of AH was insufficient to be used simultaneously for miRNA PCR array and qRT-PCR analyses, separate samples were used for each analysis. In addition, we initially planned to use the same participants' AH and LC samples for the miRNA PCR array. However, after miRNA extraction and quality control processes, the AH and LC samples available for miRNA PCR array were derived from separate subjects. Consequently, miRNA PCR array was performed using AH and LC samples collected from separate patient groups. Instead, qRT-PCR was performed using AH and LC samples collected from the same eye of the same subject. Second, further studies using animal models were not conducted. Therefore, further research is needed to determine the mechanisms and effects of the identified miRNAs on glaucoma. Additionally, *in vitro* studies using TM tissue will be beneficial to investigate the relationship between these miRNAs and apoptosis of TM cells that could not be conducted in this study.

Finally, it was not possible to assess the association between miRNA expression levels and clinical factors such as the severity of glaucoma owing to the small number of participants in each miRNA analysis. Despite these limitations, this is the first study to report the miRNA profiles of both AH and LC samples in patients with glaucoma. The miRNA profiles found in this study would reflect the intraocular status better than those found in previous studies conducted using only AH of patients with glaucoma. Circulating miRNAs can be considered good potential biomarkers in many diseases (42). We analyzed apoptosis-related miRNAs in AH and LC samples and found two common miRNAs that showed significant differential expression in both AH and LC and were associated with *PTEN*. These miRNAs and *PTEN* have been shown to be associated with apoptosis/survival in other diseases. Therefore, although the role of these miRNAs as biomarkers for glaucoma could not be validated in this study, we propose that these miRNAs and *PTEN*, or their modulation, may represent potential diagnostic biomarkers or therapeutic strategies in glaucoma.

To the best of our knowledge, this is the first study to elucidate the expression profiles of apoptosis-related miRNAs in AH and LC samples of patients with open-angle glaucoma. Two miRNAs, hsa-miR-193a-5p and hsa-miR-222-3p, were upregulated in both AH and LC samples of patients with glaucoma, and their common putative gene was *PTEN*, which was downregulated in both AH and LC samples of patients with glaucoma. The functions of these two miRNAs and *PTEN* are related to apoptosis and oxidative stress, which are involved in the pathogenesis of open-angle glaucoma. Therefore, these miRNAs may serve as novel biomarkers or therapeutic targets in open-angle glaucoma.

Data availability statement

Original datasets are available in a publicly accessible repository: ArrayExpress. The original contributions presented in the study are publicly available. This data can be found here: [https://www.ebi.ac.uk/fg/annotare/edit/18328/] [accession number: E-MTAB-13771].

Ethics statement

The studies involving humans were approved by the institutional review board (IRB) of Hanyang University Guri Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

HY: Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft. EH: Funding acquisition, Investigation, Project administration, Validation, Writing – original draft. JK: Data curation, Software, Writing – review & editing. YL: Validation, Writing – review & editing. WL: Formal analysis, Writing – review & editing, Funding acquisition. MK: Resources, Writing – review & editing. HC: Conceptualization, Resources, Writing – review & editing. YS: Conceptualization, Data curation, Funding acquisition, Supervision, Writing – review & editing. MS: Conceptualization, Data curation, Funding acquisition, Resources, Supervision, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This research was supported by the National Research Foundation of Korea (NRF) grants funded by the Korean government (NRF-2022R1H1A2092110 (MS) and NRF-2021R1I1A1A01059690 (EH)) and the 2023 Cheil-Nammyung Foundation Research Funds (WL).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1288854/full#supplementary-material

References

1. Kuehn MH, Fingert JH, Kwon YH. Retinal ganglion cell death in glaucoma: mechanisms and neuroprotective strategies. *Ophthalmol Clin N Am*. (2005) 18:383–95. doi: 10.1016/j.ohc.2005.04.002

2. Mantravadi AV, Vadhar N. Glaucoma. *Prim Care*. (2015) 42:437–49. doi: 10.1016/j.pop.2015.05.008

3. Vranka JA, Kelley MJ, Acott TS, Keller KE. Extracellular matrix in the trabecular meshwork: intraocular pressure regulation and dysregulation in glaucoma. *Exp Eye Res*. (2015) 133:112–25. doi: 10.1016/j.exer.2014.07.014

4. Alvarado J, Murphy C, Juster R. Trabecular meshwork cellularity in primary open-angle glaucoma and nonglaucomatous normals. *Ophthalmology*. (1984) 91:564–79. doi: 10.1016/S0161-6420(84)34248-8

5. Agarwal R, Talati M, Lambert W, Clark AF, Wilson SE, Agarwal N, et al. Fas-activated apoptosis and apoptosis mediators in human trabecular meshwork cells. *Exp Eye Res*. (1999) 68:583–90. doi: 10.1006/exer.1998.0636

6. Baleriola J, García-Feijoo J, Martínez-de-la-Casa JM, Fernández-Cruz A, de la Rosa EJ, Fernández-Durango R. Apoptosis in the trabecular meshwork of glaucomatous patients. *Mol Vis*. (2008) 14:1513–6.

7. Saccà SC, Gandolfi S, Bagnis A, Manni G, Damonte G, Traverso CE, et al. From DNA damage to functional changes of the trabecular meshwork in aging and glaucoma. *Ageing Res Rev*. (2016) 29:26–41. doi: 10.1016/j.arr.2016.05.012

8. Ha M, Kim VN. Regulation of microrna biogenesis. *Nat Rev Mol Cell Biol*. (2014) 15:509–24. doi: 10.1038/nrm3838

9. Molasy M, Walczak A, Szaflik J, Szaflik JP, Majsterek I. Micrornas in glaucoma and neurodegenerative diseases. *J Hum Genet*. (2017) 62:105–12. doi: 10.1038/jhg.2016.91

10. Wang Y, Niu L, Zhao J, Wang M, Li K, Zheng Y. An update: mechanisms of microrna in primary open-angle glaucoma. *Brief Funct Genomics*. (2021) 20:19–27. doi: 10.1093/bfgp/elaa020

11. Lynam-Lennon N, Maher SG, Reynolds JV. The Roles of microrna in cancer and apoptosis. *Biol Rev Camb Philos Soc*. (2009) 84:55–71. doi: 10.1111/j.1469-185X.2008.00061.x

12. Tabak S, Schreiber-Avissar S, Beit-Yannai E. Crosstalk between microrna and oxidative stress in primary open-angle glaucoma. *Int J Mol Sci*. (2021) 22:2421. doi: 10.3390/ijms22052421

13. Hindle AG, Thoonen R, Jasien JV, Grange RMH, Amin K, Wise J, et al. Identification of candidate mirna biomarkers for glaucoma. *Invest Ophthalmol Vis Sci*. (2019) 60:134–46. doi: 10.1167/iovs.18-24878

14. Rao A, Chakraborty M, Roy A, Sahay P, Pradhan A, Raj N. Differential mirna expression: signature for glaucoma in pseudoexfoliation. *Clin Ophthalmol*. (2020) 14:3025–38. doi: 10.2147/OPTH.S254504

15. Margolis MJ, Martinez M, Valencia J, Lee RK, Bhattacharya SK. Phospholipid secretions of organ cultured ciliary body. *J Cell Biochem*. (2018) 119:2556–66. doi: 10.1002/jcb.26419

16. Freddo TF. a contemporary concept of the blood-aqueous barrier. *Prog Retin Eye Res*. (2013) 32:181–95. doi: 10.1016/j.preteyeres.2012.10.004

17. Delamere NA, Tamiya S. Expression, regulation and function of Na,K-atpase in the lens. *Prog Retin Eye Res*. (2004) 23:593–615. doi: 10.1016/j.preteyeres.2004.06.003

18. Piñero J, Ramírez-Anguita JM, Saüch-Pitarch J, Ronzano F, Centeno E, Sanz F, et al. The disgenet knowledge platform for disease genomics: 2019 update. *Nucleic Acids Res*. (2020) 48:D845–d855. doi: 10.1093/nar/gkz1021

19. Ru Y, Kechris KJ, Tabakoff B, Hoffman P, Radcliffe RA, Bowler R, et al. The Multimir R package and database: integration of microrna-target interactions along with their disease and drug associations. *Nucleic Acids Res*. (2014) 42:e133. doi: 10.1093/nar/gku631

20. Kosior-Jarecka E, Czop M, Gasińska K, Wróbel-Dudzińska D, Zalewski DP, Bogucka-Kocka A, et al. Micrornas in the aqueous humor of patients with different types of glaucoma. *Graefes Arch Clin Exp Ophthalmol*. (2021) 259:2337–49. doi: 10.1007/s00417-021-05214-z

21. Kanehisa M, Goto S. Kegg: kyoto encyclopedia of genes and genomes. *Nucleic Acids Res*. (2000) 28:27–30. doi: 10.1093/nar/28.1.27

22. Guo Y, Wu H, Xiong J, Gou S, Cui J, Peng T. Mir-222-3p-containing macrophage-derived extracellular vesicles confer gemcitabine resistance via Tsc1-mediated Mtor/Akt/Pi3k pathway in pancreatic cancer. *Cell Biol Toxicol*. (2022) 39:1203–14. doi: 10.1007/s10565-022-09736-y

23. Chou NH, Lo YH, Wang KC, Kang CH, Tsai CY, Tsai KW. Mir-193a-5p and -3p Play a distinct role in gastric cancer: Mir-193a-3p suppresses gastric cancer cell growth by targeting Ets1 and Ccnd1. *Anticancer Res*. (2018) 38:3309–18. doi: 10.21873/anticanres.12596

24. Cao F, Liu Z, Sun G. Diagnostic value of Mir-193a-3p in alzheimer's disease and Mir-193a-3p attenuates amyloid-β induced neurotoxicity by targeting Pten. *Exp Gerontol*. (2020) 130:110814. doi: 10.1016/j.exger.2019.110814

25. Mead B, Kerr A, Nakaya N, Tomarev SI. Mirna changes in retinal ganglion cells after optic nerve crush and glaucomatous damage. *Cell*. (2021) 10:1564. doi: 10.3390/cells10071564

26. Zhang LQ, Cui H, Yu YB, Shi HQ, Zhou Y, Liu MJ. Microrna-141-3p inhibits retinal neovascularization and retinal ganglion cell apoptosis in glaucoma mice through the inactivation of docking protein 5-dependent mitogen-activated protein kinase signaling pathway. *J Cell Physiol*. (2019) 234:8873–87. doi: 10.1002/jcp.27549

27. Su W, Li Z, Jia Y, Zhu Y, Cai W, Wan P, et al. Microrna-21a-5p/Pdcd4 axis regulates mesenchymal stem cell-induced neuroprotection in acute glaucoma. *J Mol Cell Biol*. (2017) 9:289–301. doi: 10.1093/jmcb/mjx022

28. Xu K, Li S, Yang Q, Zhou Z, Fu M, Yang X, et al. Microrna-145-5p targeting of Trim2 mediates the apoptosis of retinal ganglion cells via the Pi3k/Akt signaling pathway in glaucoma. *J Gene Med*. (2021) 23:e3378. doi: 10.1002/jgm.3378

29. Li R, Jin Y, Li Q, Sun X, Zhu H, Cui H. Mir-93-5p targeting Pten Regulates the Nmda-induced autophagy of retinal ganglion cells via Akt/Mtor pathway in glaucoma. *Biomed Pharmacother*. (2018) 100:1–7. doi: 10.1016/j.biopha.2018.01.044

30. Guo J, Liu H, Fu L. Microrna-124 ameliorates autophagic dysregulation in glaucoma via regulation of P2x7-mediated Akt/Mtor signaling. *Cutan Ocul Toxicol*. (2022) 41:43–8. doi: 10.1080/15569527.2021.2003378

31. Martinez B, Peplow PV. Micrornas as biomarkers in glaucoma and potential therapeutic targets. *Neural Regen Res*. (2022) 17:2368–75. doi: 10.4103/1673-5374.338989

32. Hubens WHG, Krauskopf J, Beckers HJM, Kleinjans JCS, Webers CAB, Gorgels T. Small RNA sequencing of aqueous humor and plasma in patients with primary open-angle glaucoma. *Invest Ophthalmol Vis Sci*. (2021) 62:24. doi: 10.1167/iovs.62.7.24

33. Cho HK, Seong H, Kee C, Song DH, Kim SJ, Seo SW, et al. Microrna profiles in aqueous humor between pseudoexfoliation glaucoma and normal tension glaucoma patients in a korean population. *Sci Rep*. (2022) 12:6217. doi: 10.1038/s41598-022-09572-4

34. Liu Y, Chen Y, Wang Y, Zhang X, Gao K, Chen S, et al. Microrna profiling in glaucoma eyes with varying degrees of optic neuropathy by using next-generation sequencing. *Invest Ophthalmol Vis Sci*. (2018) 59:2955–66. doi: 10.1167/iovs.17-23599

35. Drewry MD, Challa P, Kuchtey JG, Navarro I, Helwa I, Hu Y, et al. Differentially expressed micrornas in the aqueous humor of patients with exfoliation glaucoma or primary open-angle glaucoma. *Hum Mol Genet*. (2018) 27:1263–75. doi: 10.1093/hmg/ddy040

36. Jayaram H, Phillips JI, Lozano DC, Choe TE, Cepurna WO, Johnson EC, et al. Comparison of microrna expression in aqueous humor of normal and primary open-angle glaucoma patients using pcr arrays: a pilot study. *Invest Ophthalmol Vis Sci*. (2017) 58:2884–90. doi: 10.1167/iovs.17-21844

37. Tanaka Y, Tsuda S, Kunikata H, Sato J, Kokubun T, Yasuda M, et al. Profiles of extracellular mirnas in the aqueous humor of glaucoma patients assessed with a microarray system. *Sci Rep*. (2014) 4:5089. doi: 10.1038/srep05089

38. Seong H, Cho HK, Kee C, Song DH, Cho MC, Kang SS. Profiles of microrna in aqueous humor of normal tension glaucoma patients using rna sequencing. *Sci Rep*. (2021) 11:19024. doi: 10.1038/s41598-021-98278-0

39. Liu Y, Wang Y, Chen Y, Fang X, Wen T, Xiao M, et al. Discovery and validation of circulating Hsa-Mir-210-3p as a potential biomarker for primary open-angle glaucoma. *Invest Ophthalmol Vis Sci*. (2019) 60:2925–34. doi: 10.1167/iovs.19-26663

40. Raga-Cervera J, Bolarin JM, Millan JM, Garcia-Medina JJ, Pedrola L, Abellán-Abenza J, et al. Mirnas and genes involved in the interplay between ocular hypertension and primary open-angle glaucoma. oxidative stress, inflammation, and apoptosis networks. *J Clin Med*. (2021) 10:2227. doi: 10.3390/jcm10112227

41. Barbagallo C, Platania CBM, Drago F, Barbagallo D, Di Pietro C, Purrello M, et al. Do extracellular Rnas provide insight into uveal melanoma biology? *Cancer*. (2021) 13:5919. doi: 10.3390/cancers13235919

42. Trotta MC, Gesualdo C, Platania CBM, De Robertis D, Giordano M, Simonelli F, et al. Circulating mirnas in diabetic retinopathy patients: prognostic markers or pharmacological targets? *Biochem Pharmacol*. (2021) 186:114473. doi: 10.1016/j.bcp.2021.114473

43. Platania CBM, Maisto R, Trotta MC, D'Amico M, Rossi S, Gesualdo C, et al. Retinal and circulating mirna expression patterns in diabetic retinopathy: an in silico and in vivo approach. *Br J Pharmacol*. (2019) 176:2179–94. doi: 10.1111/bph.14665

44. Romano GL, Platania CBM, Drago F, Salomone S, Ragusa M, Barbagallo C, et al. Retinal and circulating mirnas in age-related macular degeneration: an in vivo animal and human study. *Front Pharmacol*. (2017) 8:168. doi: 10.3389/fphar.2017.00168

45. Wang S, Diao YJ, Zhu BB. Mir-193a-5p suppresses cell proliferation and induces cell apoptosis by regulating Hoxa7 in human ovarian cancer. *Neoplasma*. (2020) 67:825–33. doi: 10.4149/neo_2020_190730N687

46. Li P, Xiao Z, Luo J, Zhang Y, Lin L. Mir-139-5p, Mir-940 and Mir-193a-5p inhibit the growth of hepatocellular carcinoma by targeting spock1. *J Cell Mol Med*. (2019) 23:2475–88. doi: 10.1111/jcmm.14121

47. Zheng L, Yan B, Jin G, Han W, Wang H, Wang Z, et al. Circ_0003159 upregulates lifr expression through competitively binding to Mir-221-3p/Mir-222-3p to block gastric cancer development. *J Mol Histol*. (2022) 53:173–86. doi: 10.1007/s10735-021-10044-8

48. Ulhaq ZS, Soraya GV. Aqueous humor interleukin-6 levels in primary open-angle glaucoma (Poag): a systematic review and meta-analysis. *Arch Soc Esp Oftalmol (Engl Ed)*. (2020) 95:315–21. doi: 10.1016/j.oftal.2020.03.018

49. Li J, Wang J, Wang Z. Circ_0006768 upregulation attenuates oxygen-glucose deprivation/reoxygenation-induced human brain microvascular endothelial cell injuries by upregulating Vezf1 via Mir-222-3p inhibition. *Metab Brain Dis*. (2021) 36:2521–34. doi: 10.1007/s11011-021-00775-8

50. Krebs M, Solimando AG, Kalogirou C, Marquardt A, Frank T, Sokolakis I, et al. Mir-221-3p regulates Vegfr2 expression in high-risk prostate cancer and represents an escape mechanism from sunitinib in Vitro. *J Clin Med*. (2020) 9:670. doi: 10.3390/jcm9030670

51. Chen Q, Tong C, Ma S, Zhou L, Zhao L, Zhao X. Involvement of micrornas in probiotics-induced reduction of the cecal inflammation by *Salmonella Typhimurium*. *Front Immunol*. (2017) 8:704. doi: 10.3389/fimmu.2017.00704

52. Wang J, Luo X, Cai S, Sun J, Wang S, Wei X. Blocking hotair protects human chondrocytes against il-1beta-induced cell apoptosis, ecm degradation, inflammatory response and oxidative stress via regulating Mir-222-3p/Adam10 Axis. *Int Immunopharmacol*. (2021) 98:107903. doi: 10.1016/j.intimp.2021.107903

53. Xu H, Liu Y, Cheng P, Wang C, Liu Y, Zhou W, et al. Circrna_0000392 promotes colorectal cancer progression through the Mir-193a-5p/Pik3r3/Akt Axis. *J Exp Clin Cancer Res*. (2020) 39:283. doi: 10.1186/s13046-020-01799-1

54. Polini B, Carpi S, Doccini S, Citi V, Martelli A, Feola S, et al. Tumor suppressor role of Hsa-Mir-193a-3p and -5p in cutaneous melanoma. *Int J Mol Sci*. (2020) 21:183. doi: 10.3390/ijms21176183

55. Liu Y, Ao S, Zhang H, Zhang Y, Wang Y, Yang X, et al. Circ_Hipk3 alleviates Cocl2-induced apoptotic injury in neuronal cells by depending on the regulation of the Mir-222-3p/Dusp19 axis. *Biochem Biophys Res Commun*. (2021) 553:126–33. doi: 10.1016/j.bbrc.2021.03.070

56. Xue Y, Wei Z, Ding H, Wang Q, Zhou Z, Zheng S, et al. Microrna-19b/221/222 induces endothelial cell dysfunction via suppression of pgc-1alpha in the progression of atherosclerosis. *Atherosclerosis*. (2015) 241:671–81. doi: 10.1016/j.atherosclerosis.2015.06.031

57. Xu X, Gao R, Li S, Li N, Jiang K, Sun X, et al. Circular Rna Circznf292 regulates H2 O2 -induced injury in human lens epithelial Hle-B3 cells depending on the regulation of the Mir-222-3p/E2f3 Axis. *Cell Biol Int*. (2021) 45:1757–67. doi: 10.1002/cbin.11615

58. McMonnies C. Reactive oxygen species, oxidative stress, glaucoma and hyperbaric oxygen therapy. *Aust J Optom*. (2018) 11:3–9. doi: 10.1016/j.optom.2017.06.002

59. Chrysostomou V, Rezania F, Trounce IA, Crowston JG. Oxidative stress and mitochondrial dysfunction in glaucoma. *Curr Opin Pharmacol*. (2013) 13:12–5. doi: 10.1016/j.coph.2012.09.008

60. Pinazo-Duran MD, Zanon-Moreno V, Gallego-Pinazo R, Garcia-Medina JJ. Oxidative stress and mitochondrial failure in the pathogenesis of glaucoma neurodegeneration. *Prog Brain Res*. (2015) 220:127–53. doi: 10.1016/bs.pbr.2015.06.001

61. Ahmad A, Ahsan H. Biomarkers of inflammation and oxidative stress in ophthalmic disorders. *J Immunoassay Immunochem*. (2020) 41:257–71. doi: 10.1080/15321819.2020.1726774

62. Shi Y, Paluch BE, Wang X, Jiang X. Pten at a glance. *J Cell Sci*. (2012) 125:4687–92. doi: 10.1242/jcs.093765

63. Franke TF, Hornik CP, Segev L, Shostak GA, Sugimoto C. Pi3k/Akt and apoptosis: size matters. *Oncogene*. (2003) 22:8983–98. doi: 10.1038/sj.onc.1207115

64. Shabanzadeh AP, D'Onofrio PM, Magharious M, Choi KAB, Monnier PP, Koeberle PD. Modifying Pten recruitment promotes neuron survival, regeneration, and functional recovery after Cns injury. *Cell Death Dis*. (2019) 10:567. doi: 10.1038/s41419-019-1802-z

65. Zhavoronkov A, Izumchenko E, Kanherkar RR, Teka M, Cantor C, Manaye K, et al. Pro-fibrotic pathway activation in trabecular meshwork and lamina cribrosa is the main driving force of glaucoma. *Cell Cycle*. (2016) 15:1643–52. doi: 10.1080/15384101.2016.1170261

66. Parapuram SK, Shi-wen X, Elliott C, Welch ID, Jones H, Baron M, et al. Loss of Pten expression by dermal fibroblasts causes skin fibrosis. *J Invest Dermatol*. (2011) 131:1996–2003. doi: 10.1038/jid.2011.156

67. Tellios N, Belrose JC, Tokarewicz AC, Hutnik C, Liu H, Leask A, et al. Tgf-B induces phosphorylation of phosphatase and tensin homolog: implications for fibrosis of the trabecular meshwork tissue in glaucoma. *Sci Rep*. (2017) 7:812. doi: 10.1038/s41598-017-00845-x

68. Gong L, Zhang W, Yuan Y, Xing X, Li H, Zhao G. Mir-222 promotes invasion and migration of ovarian carcinoma by targeting Pten. *Oncol Lett*. (2018) 16:984–90. doi: 10.3892/ol.2018.8743

69. Youngblood H, Cai J, Drewry MD, Helwa I, Hu E, Liu S, et al. Expression of Mrnas, Mirnas, and Lncrnas in human trabecular meshwork cells upon mechanical stretch. *Invest Ophthalmol Vis Sci*. (2020) 61:2. Investigative Ophthalmology & VisualScience. doi: 10.1167/iovs.61.5.2

70. Jayaram H, Cepurna WO, Johnson EC, Morrison JC. Microrna expression in the glaucomatous retina. *Invest Ophthalmol Vis Sci*. (2015) 56:7971–82. doi: 10.1167/iovs.15-18088

frontiers | Frontiers in Genetics

TYPE Original Research
PUBLISHED 07 March 2024
DOI 10.3389/fgene.2024.1349860

OPEN ACCESS

EDITED BY
Rui Medeiros,
Portuguese Oncology Institute of Porto (IPO Porto) / Porto Comprehensive Cancer Centre (Porto.CCC), Portugal

REVIEWED BY
Alessio Martucci,
University of Rome Tor Vergata, Italy
Xi Wu,
Shanghai Jiao Tong University, China

*CORRESPONDENCE
Qianyan Kang,
kangqy@mail.xjtu.edu.cn

RECEIVED 07 December 2023
ACCEPTED 26 February 2024
PUBLISHED 07 March 2024

CITATION
Zhang Y, Fu L, Feng F, Liu B, Lei Y and Kang Q (2024), Mendelian randomization study shows no causal relationship between psychiatric disorders and glaucoma in European and East Asian populations.
Front. Genet. 15:1349860.
doi: 10.3389/fgene.2024.1349860

Mendelian randomization study shows no causal relationship between psychiatric disorders and glaucoma in European and East Asian populations

Yan Zhang[1], Longhui Fu[2], Fang Feng[3], Bo Liu[3], Ying Lei[1] and Qianyan Kang[1]*

[1]Department of Ophthalmology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China, [2]Department of Neurosurgery, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China, [3]Department of Gynecology and Obstetrics, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

Background: Glaucoma is a leading cause of blindness strongly associated with psychiatric disorders, but the causal association between glaucoma and psychiatric disorders remains uncertain because of the susceptibility of observational studies to confounding and reverse causation. This study aims to explore the potential causal association between glaucoma and three highly related psychiatric disorders (Depression, Insomnia, and Schizophrenia) in the European and East Asian populations using a two-sample Mendelian randomization analysis.

Methods: Instrumental variables (IVs) of depression, insomnia, and schizophrenia in the European population were obtained after strict filtering. Summary-level data for glaucoma and glaucoma subtypes (primary open-angle glaucoma and primary closed-angle glaucoma) were obtained as outcomes. The inverse variance weighting (IVW) method was used as the primary method. Additionally, the causal effect was evaluated in the East Asian population using the same methods to validate analysis results. The robustness of these results was confirmed using heterogeneity, pleiotropy, and Steiger directionality test.

Results: The primary MR results indicated that genetically driven psychiatric disorders were not causally associated with glaucoma (Depression: odds ratio (OR): 1.15, 95% confidence interval (CI): 0.93–1.42, $p = 0.20$; Insomnia: OR: 1.14, 95% CI: 0.63–2.05, $p = 0.66$; Schizophrenia: OR: 1.00, 95% CI: 0.93–1.08, $p = 0.95$), either with the risk of glaucoma subtypes in the European population. Meanwhile, results in the East Asian population were consistent with the results among the European population (Depression: OR = 1.38, CI 0.75–2.53, $p = 0.30$; Insomnia: OR = 0.99, CI 0.83–1.18, $p = 0.93$; Schizophrenia: OR = 1.06, CI 0.94–1.20, $p = 0.34$) with similar causal estimates in direction. Consistency was obtained by corroborating with other supporting methods. Besides, the robustness of the results was proved and the directionality test confirmed our estimation of potential causal direction ($p < 0.001$).

Conclusion: This study found a non-causal association between psychiatric disorders and the risk of glaucoma in the European and East Asian

populations, which contradicts many existing observational reports, indicating that increased psychiatric disorders in glaucoma patients were more likely modifiable rather not inheritable.

KEYWORDS

mendelian randomization, depression, insomnia, schizophrenia, glaucoma

1 Introduction

Glaucoma is a group of optic neuropathies characterized by progressive degeneration of retinal ganglion cells, resulting in visual field defects (Quigley, 2011). It has been estimated that the total number of patients would up to 111.8 million by 2040, making glaucoma the most common cause of irreversible blindness worldwide (Tham et al., 2014). Based on the anatomy of anterior chamber angle, glaucoma is categorized as open-angle glaucoma (OAG) and angle-closure glaucoma (ACG). Its pathogenesis is related to various genetic mutations and somatic diseases, indicating that glaucoma is a complicated genetic disorder (Wändell et al., 2022). Specifically, it was found that primary open-angle glaucoma (POAG) is highly heritable with 70% of the variation in risk attributed to genetics (Gharahkhani et al., 2023). To date, clinically, the causing factors contributing to glaucoma progression are still not well characterized. The most significant risk factor is elevated intraocular pressure (IOP). However, despite effective IOP-lowering therapies, visual impairment still progresses in a significant number of patients. Additionally, the most serious concern is that less than 50% of the general population has awareness of their glaucoma status. People who suffer from asymptomatic glaucoma may be significantly higher (Weinreb et al., 2014). Hence, evidence that identifies the risk factors for glaucoma is required urgently for the prevention of visual loss.

Recently, increasing epidemiological reports have illustrated that patients diagnosed with the most common psychiatric disorders such as depression (Jung et al., 2021; Wändell et al., 2022), insomnia (Sun et al., 2022), and schizophrenia (Meer et al., 2022) are more likely to have a higher risk of glaucoma, compared to the general population. It has been suggested that there might be a common underlying pathophysiology between psychiatric disorders and glaucoma, as both involve changes in vascular structures or neurological alterations (Liu et al., 2020). In a recent study, retinal nerve fiber layer thinning and neural cell loss in the ganglion cell layer were observed in the chronic unpredictable mild stress mouse model, indicating that psychological stress could induce glaucoma-like changes (Zhang et al., 2022). While some other epidemiological findings suggested that there was no association between depression and glaucoma (Rezapour et al., 2018; Vidal et al., 2021; Grant et al., 2021), which made this relationship contentious. Establishing a definitive etiological link may be challenging due to the presence of confounding factors and the potential for reverse causation in traditional epidemiological findings. More studies are needed to confirm the causal role of psychiatric disorders in glaucoma.

Mendelian randomization (MR) analysis, simulating the design of randomized control trials, uses genetic instrumental variables (single-nucleotide polymorphisms, SNPs) to assess the causal association between risk factors and outcomes, thereby excluding potential confounders from interfering (Emdin et al., 2017). So far, we found that the MR analysis of causality between psychiatric disorders and glaucoma was still unexplored. Hence, based on the data of genome-wide association studies (GWAS), this study aimed to reveal the causal association between three psychiatric disorders (depression, insomnia, and schizophrenia) and the risk of glaucoma through the two-sample MR analysis. Meanwhile, two main subtypes of glaucoma were explored and the causal effects in two different populations were evaluated respectively (the European and East Asian populations), aiming to contribute robust and novel insights to the field of the association between mental disorders and glaucoma.

2 Methods

2.1 Study design

A flow diagram of the study design is presented in Figure 1. A two-sample MR analysis considering depression, insomnia, and schizophrenia as exposures and glaucoma as the outcome in the European population was conducted in the first step adhering to the three core assumptions (Burgess et al., 2019). Subgroup analysis of cases with POAG and primary angle-closure glaucoma (PACG) were also investigated. Sensitivity analysis was conducted to validate the robustness of the results. Finally, the analysis of individuals in East Asia was conducted for generalization and to provide an additional complement to the conclusion.

In order to adhere to the principle of minimizing duplication between exposure and outcome samples, we comprehensively searched the PubMed dataset and large publicly accessible GWAS data of European and East Asian ancestry samples to select the sample with rigor.

2.2 Data sources

2.2.1 GWAS summary statistics in the European population

Summary statistics of depression in the European population were extracted from the largest European GWAS meta-analysis to date (170,756 cases and 329,443 controls) (Howard et al., 2019). As for insomnia, we obtained available summary data from UKB, which included 462,341 individuals. The GWAS data for schizophrenia were acquired from a dataset in the Psychiatric Genomics Consortium (PGC), which included a sample of 82,315 participants (Ripke et al., 2014).

The European GWAS data for glaucoma were identified from the FinnGen consortium, including three sets of genetic instruments (210,789 to 218,792 individuals): glaucoma, POAG, and PACG.

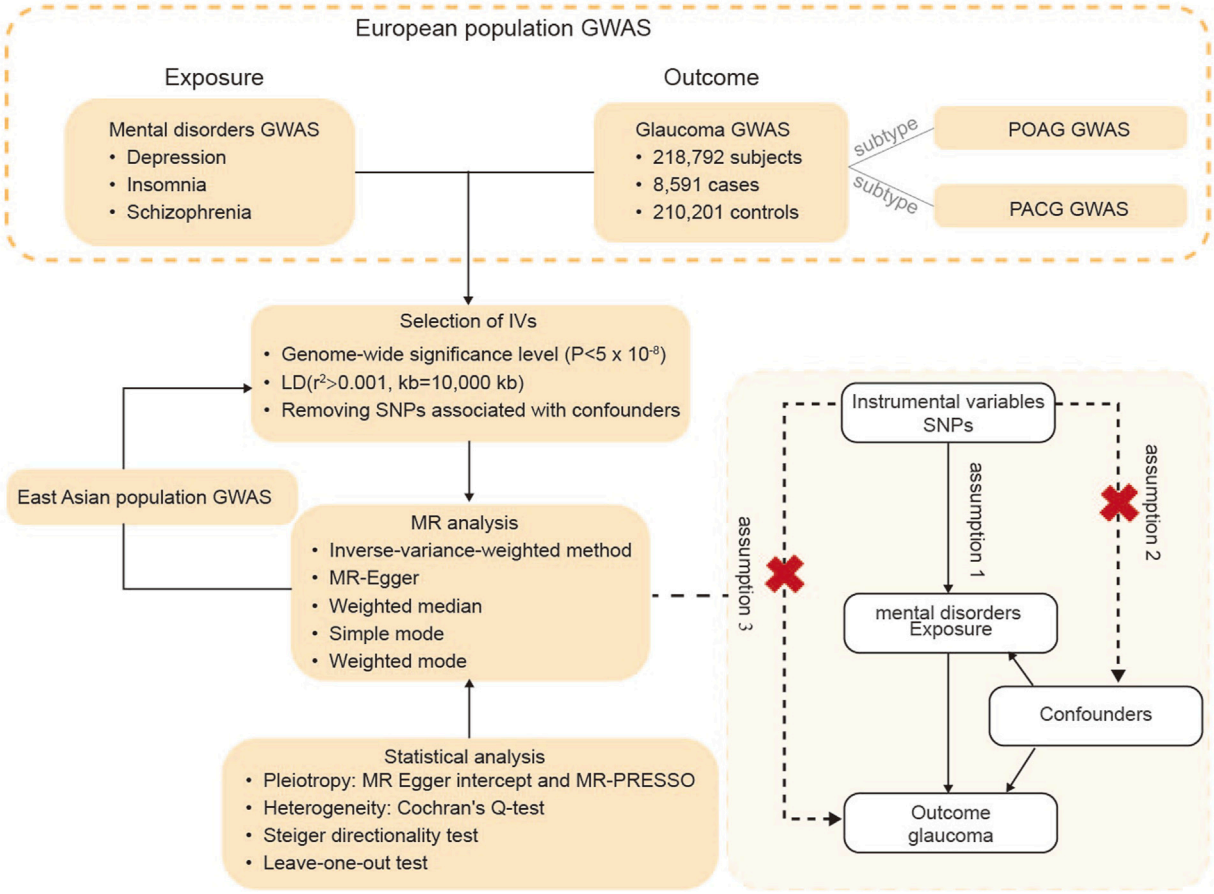

FIGURE 1
Diagram of the study design. The three key assumptions were as follows: (1) The genetic IVs must be associated with exposure (depression, insomnia, and schizophrenia); (2) IVs should not be associated with confounders; (3) IVs must influence glaucoma only via the exposure. Abbreviations: GWAS, genome-wide association studies; SNPs, single nucleotide polymorphisms; IVs, instrumental variables; LD, linkage disequilibrium; MR analysis, Mendelian randomization analysis; POAG, primary open-angle glaucoma; PACG, primary angle-closure glaucoma.

Subtypes were included to further elucidate the causal relationship between genetically predicted psychiatric disorders and glaucoma. This study defined glaucoma by the International Classification of Diseases (ICD)-10: H40/H42.

2.2.2 GWAS summary statistics in the East Asian population

Summary statistics of depression were derived from the hitherto most comprehensive and most up-to-date meta-analysis of depression GWAS among East Asians, comprising 98,502 individuals (12,588 cases and 85,914 controls) (Giannakopoulou et al., 2021). Data for insomnia published by UKB in 2020 that included a sample of 63,732 participants from East Asian populations were obtained from the Open GWAS database (https://gwas.mrcieu.ac.uk/). The East Asian statistics for schizophrenia were found from a large GWAS meta-analysis including 14,004 cases and 16,757 controls, which were open to download from the Psychiatric Genomics Consortium (Kurki et al., 2023).

The GWAS data for glaucoma in East Asian descent were derived from BioBank Japan (BBJ) (Ishigaki et al., 2020). BBJ is the largest East Asian biobank and includes more than 200000 Japanese people ranging in age from 20 to 89 years who were followed up between 2003 and 2018 (Ishigaki et al., 2020). The diagnosis of glaucoma was also defined by ICD-10: H40/H42. Summary-level GWAS data for specific glaucoma subtypes in the East Asian population was not included in the analysis because data was not publicly available. Detailed information of the data sources can be found in Table 1.

2.3 Selection of genetic instrumental variables

In this study, we employed criteria as follows to select the instrumental variables (IVs) (Burgess et al., 2019): (1) Firstly, all SNPs selected as instrumental variables were correlated with the corresponding exposure at a genome-wide significance ($p < 5 \times 10^{-8}$). As for IVs in the East Asian population, since the limitation of sample size, we adopted $p < 5 \times 10^{-6}$ as the threshold as recommended in previous research (Burgess et al., 2013). (2) The clumping process was executed to ensure that all the SNPs were not in linkage disequilibrium (LD) ($r^2 > 0.001$, kb = 10,000) with the clump data function using the 1000 Genomes Project as the

TABLE 1 Characteristics of data sources included in the MR analyses.

Traits	Population	Consortium	Sample size (case/controls)	PubMed ID/Open GWAS ID
Exposures				
Depression	European	UKB,PGC	500,199 (170,756/329,443)	30718901
Insomnia	European	UKB	462,341 (NA/NA)	ukb-b-3957
Schizophrenia	European	PGC	82,315 (35,476/46,839)	25056061
Depression	East Asian	UKB, CKB, etc.	98,502 (12,588/85,914)	34586374
Insomnia	East Asian	UKB	63,732 (2654/61,078)	ukb-e-1200_EAS
Schizophrenia	East Asian	PGC	30,761 (14,004/16,757)	35396580
Outcomes				
Glaucoma	European	Finn	218,792 (8,591/210,201)	finn-b-H7_GLAUCOMA
POAG	European	Finn	214,634 (4,433/210,201)	finn-b-H7_GLAUCPRIMOPEN
PACG	European	Finn	210,789 (588/210,201)	finn-b-H7_GLAUCPRIERM
Glaucoma	East Asian	BBJ	212,453 (5,761/206,692)	32514122

Note: POAG, Primary open-angle glaucoma; PACG, Primary angle-closure glaucoma; UK Biobank, the UK Biobank; PGC, Psychiatric Genomics Consortium; Finn, the FinnGen study; CKB, China Kadoorie Biobank; WHI, Women's Health Initiative. All data was collected on 15 May 2023.

reference panel (Auton et al., 2015). (3) We used the PhenoScanner database (http://www.phenoscanner.medschl.cam.ac.uk/, accessed on 5 July 2023) to rule out SNPs related to confounding factors. (4) SNPs not available in the outcome dataset would also be excluded. (5) Genetic variables of palindromic and incompatible alleles were removed when harmonizing. Finally, F statistics of each SNP were calculated to avoid bias from weak instruments using the formula: $F = BETA^2/SE^2$, in which *BETA* represents the estimated effect size of allele and *SE* is the estimated standard error of *BETA* (Bowden et al., 2016b).

Herein, these SNPs were compliant with the correlation, independence, and statistical intensity requirements of instrumental variables.

2.4 Two sample MR analysis

For MR analysis, the inverse variance weighted (IVW) model which assumed all the IVs were valid was adopted as the main causal evaluation method (Burgess and Thompson, 2017). Different models of IVW were utilized based on the results of heterogeneity test. When the heterogeneity was large ($p > 0.05$), a random effects model would be applied to combine the effects. On the contrary, a fixed effects model would be used. Additionally, we applied MR-Egger, weighted median, and weighted mode as complementary methods. The MR-Egger regression method can also provide robust estimates when horizontal pleiotropy exists (Bowden et al., 2016b). The weighted median method can provide consistent effect estimates when up to 50% of the information comes from invalid instrumental variables (Bowden et al., 2016a). The weighted mode method detects a causal effect smaller compared with the IVW and weighted median methods, with sample size requirements typically smaller than those available from GWAS consortia (Hartwig et al., 2017). Scatter plots were used to visualize analysis results.

2.5 Robust analysis

To further confirm the robustness of the analysis result, heterogeneity was assessed through Cochran's Q test in the IVW approach. We used funnel plots to visualize potential bias, where a symmetrical funnel suggests little bias. We settled MR-Egger regression to examine the existence of horizontal pleiotropy (Burgess and Thompson, 2017) and adopted the MR-pleiotropy residual sum and outlier method (MR-PRESSO) test as a supplement (Verbanck et al., 2018). When the MR PRESSO test showed outliers, the MR PRESSO test examined whether there was significant distortion in the results after removing the outliers. On top of that, a leave-one-out analysis was performed to estimate the stability of the findings, which successively excluded one SNP at a time to check whether the result was biased or driven by a single SNP (Emdin et al., 2017). Furthermore, we performed the MR Steiger directionality test to confirm the causality direction between psychiatric disorders and glaucoma (Hemani et al., 2017).

All statistical analyses were performed with R software 4.3.0 using the "TwoSampleMR" package (version 0.5.7) and "MR PRESSO" (version 1.0) package. The Bonferroni-corrected p-value<0.004 (0.05/12) adjusted for multiple testing was considered statistically significant.

3 Results

3.1 The SNPs used as instrumental variables

We obtained 80 SNPs in depression, 42 SNPs in insomnia, and 83 SNPs in schizophrenia among the European population, which met the generally accepted genome-wide significance threshold ($p < 5 \times 10^{-8}$, $r^2 < 0.001$, kb = 10,000) for exposure. Subsequently, 26 SNPs in depression, 9 SNPs in insomnia, and 45 SNPs in schizophrenia were found available at the significant level ($p <$

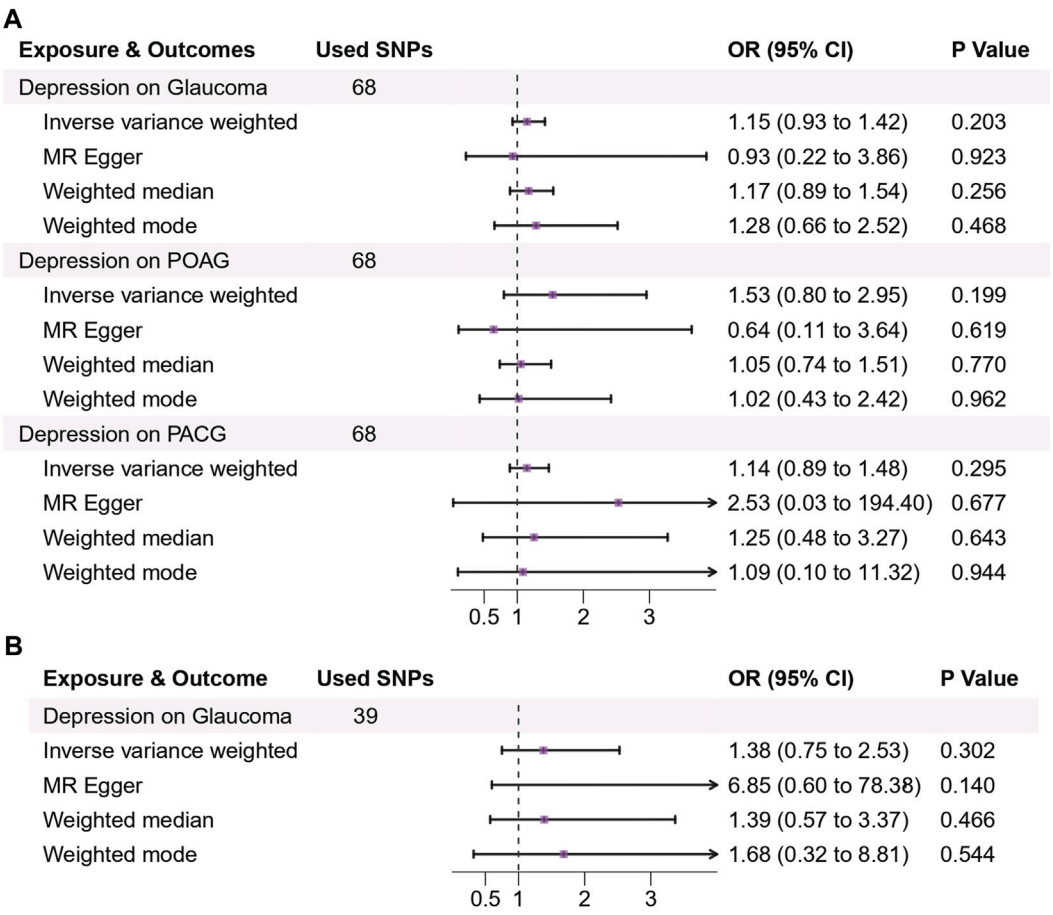

FIGURE 2
Genetic causal associations between depression and the risk of glaucoma in the European **(A)** and East Asian **(B)** populations. **(A)** MR estimates of genetically predicted risk of depression on glaucoma, primary open-angle glaucoma, and primary angle-closure glaucoma in the European population. **(B)** MR estimates of genetically predicted risk of depression on glaucoma in the East Asian population. The inverse variance weighted method is considered the main method. Abbreviations: SNPs, single nucleotide polymorphisms; OR, odds ratio; 95% CI, 95% confidence interval.

5×10^{-6}, $r^2 < 0.001$, kb = 10,000) among East Asian GWAS. Some SNPs significantly correlated with confounding factors such as hypertension (Shukla et al., 2020), diabetes (Choi et al., 2020), body mass index (Leske et al., 1995), waist circumference (Yuan et al., 2022), platelet count (Ma et al., 2019), basophil cell count (Song et al., 2023), lymphocyte count (Yang et al., 2001) were eliminated. The detailed information about eliminated SNPs is listed in Supplementary Table S1. All selected SNPs had F-statistics larger than threshold 10 (ranging from 16.0 to 199.3), indicating no weak instrument bias existed. Detailed information about the used genetic instruments of exposures is presented in Supplementary Tables S2–S4. Scatter plots of different exposures in this study are presented in Supplementary Figures S1–S3.

3.2 MR analysis results in the European population

3.2.1 Depression

In the primary IVW results, depression showed a non-causal association with the risk of glaucoma (OR: 1.15, 95% CI: 0.93–1.42, p = 0.20) and glaucoma subtypes (POAG: OR: 1.53, 95% CI: 0.80–2.95, p = 0.20; PACG: OR:1.14, 95% CI: 0.89–1.48, p = 0.30). The other methods including MR-Egger, weighted median, and weighted mode were consistent with IVW results, indicating that depression had no MR association with the risk of glaucoma through either glaucoma or specific subtypes (POAG and PACG), with all p-values greater than 0.05 (Figure 2).

3.2.2 Insomnia

From the MR analyses between insomnia and glaucoma, the overall causality estimated by the IVW method indicated no potential causal relationship between insomnia and glaucoma (OR: 1.14, 95% CI: 0.63–2.05, p = 0.66). Same as POAG and PACG (OR: 1.08, 95% CI: 0.48–2.42, p = 0.86; OR: 0.49, 95% CI: 0.06–3.91, p = 0.50), no causal relationship between insomnia and glaucoma was detected. The MR Egger and weighted median results also showed no association between insomnia and glaucoma (Figure 3).

3.2.3 Schizophrenia

MR analysis results of schizophrenia did not reveal that schizophrenia could increase the risk of glaucoma (IVW method: OR: 1.00, 95% CI: 0.93–1.08, p = 0.95). The similar results were

Populations	Exposures	Sample size	Outcomes	Methods	OR (95% CI)	P Value
European	Insomnia	386,533	Glaucoma	Inverse variance weighted	1.14 (0.63 to 2.05)	0.661
				MR Egger	1.01 (0.15 to 6.79)	0.994
				Weighted median	1.80 (0.70 to 4.63)	0.224
				Weighted mode	1.96 (0.60 to 6.45)	0.278
			POAG	Inverse variance weighted	1.08 (0.48 to 2.42)	0.855
				MR Egger	0.28 (0.03 to 3.14)	0.313
				Weighted median	0.58 (0.16 to 2.09)	0.409
				Weighted mode	0.45 (0.08 to 2.54)	0.376
			PACG	Inverse variance weighted	0.49 (0.06 to 3.91)	0.503
				MR Egger	0.62 (0.00 to 157.28)	0.868
				Weighted median	1.16 (0.06 to 22.91)	0.924
				Weighted mode	0.72 (0.01 to 40.36)	0.873
	Schizophrenia	82,315	Glaucoma	Inverse variance weighted	1.00 (0.93 to 1.08)	0.946
				MR Egger	1.09 (0.81 to 1.48)	0.563
				Weighted median	1.00 (0.91 to 1.09)	0.929
				Weighted mode	0.98 (0.80 to 1.21)	0.859
			POAG	Inverse variance weighted	1.02 (0.94 to 1.12)	0.582
				MR Egger	1.11 (0.76 to 1.60)	0.601
				Weighted median	1.02 (0.89 to 1.16)	0.817
				Weighted mode	1.13 (0.81 to 1.57)	0.485
			PACG	Inverse variance weighted	0.84 (0.64 to 1.09)	0.189
				MR Egger	1.75 (0.59 to 5.16)	0.314
				Weighted median	0.88 (0.63 to 1.23)	0.463
				Weighted mode	0.88 (0.45 to 1.74)	0.716
East Asian	Insomnia	63,732	Glaucoma	Inverse variance weighted	0.99 (0.83 to 1.18)	0.928
				MR Egger	1.26 (0.73 to 2.19)	0.444
				Weighted median	1.04 (0.83 to 1.31)	0.705
				Weighted mode	1.07 (0.78 to 1.45)	0.701
	Schizophrenia	30,761	Glaucoma	Inverse variance weighted	1.04 (0.94 to 1.15)	0.456
				MR Egger	0.95 (0.65 to 1.40)	0.808
				Weighted median	1.00 (0.88 to 1.13)	0.994
				Weighted mode	0.94 (0.73 to 1.21)	0.613

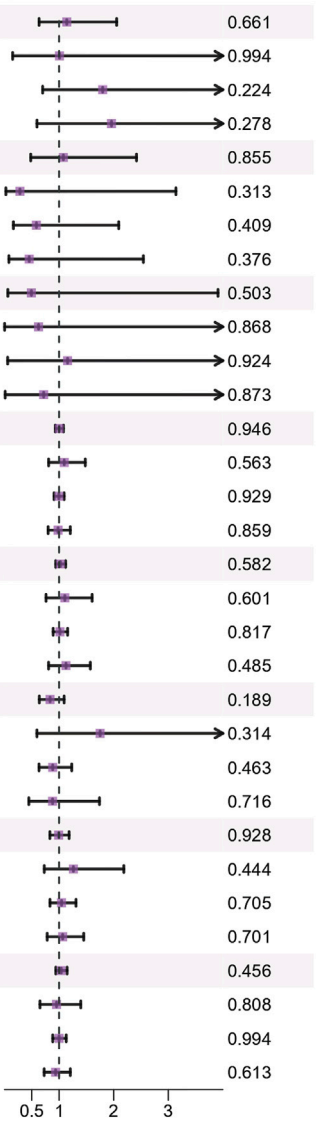

FIGURE 3
Genetic causal associations of insomnia and schizophrenia on the risk of glaucoma in the European and East Asian populations. The inverse variance weighted method is considered the main method. Abbreviations: SNPs, single nucleotide polymorphisms; OR, odds ratio; 95% CI, 95% confidence interval.

found for POAG and PACG (IVW method: OR: 1.02, 95% CI: 0.94–1.12, p = 0.58; OR: 0.84, 95% CI: 0.64–1.09, p = 0.19). These results were corroborated by other methods, indicating that schizophrenia had no MR association with the risk of glaucoma and two subtypes (Figure 3). A brief cartoon describing the result is shown in Figure 4.

3.2.4 MR analysis results in the East Asian population

Replicated analyses in the East Asian population validated the estimation in the European population (all $p > 0.05$). The primary IVW results showed that genetically predicted psychiatric disorders had no causal association with glaucoma (Depression: OR: 1.38, 95% CI: 0.75–2.53, p = 0.30; Insomnia: OR: 0.99, 95% CI: 0.83–1.18, p = 0.93; Schizophrenia: OR: 1.04, 95% CI: 0.94–1.15, p = 0.46), with similar causal estimates in direction in the European population. Consistency was obtained by corroborating with the other methods including MR-Egger, weighted median, and weighted mode (Figures 2, 3).

3.2.5 Robustness of the MR analysis

Potential SNP heterogeneity evaluated by the IVW method was observed in instrumental variables of depression and schizophrenia in the European population (Cochran's Q $p <$ 0.05), in which the random IVW effects model was adopted. In other exposures we analyzed, no evidence of heterogeneity was detected as indicated by the results of Cochran's Q-test (all p-values>0.05). Additionally, the funnel plots that visualized the heterogeneity were presented (Supplementary Figures S4–S6). Regarding pleiotropy, in all analyses we studied in two different

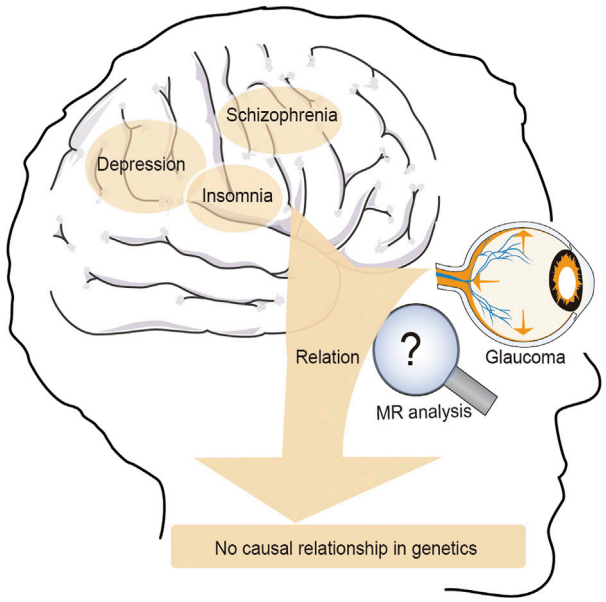

FIGURE 4
Genetic causal associations between psychiatric disorders and glaucoma.

populations, the Egger intercept quantified by the MR-Egger regression method did not differ significantly from zero ($p > 0.05$), which indicated no evidence of horizontal pleiotropic effect. Results remained consistent with IVW results after excluding outliers SNP through the MR-PRESSO distortion test, reconfirming the absence of horizontal pleiotropy ($p > 0.05$) (Supplementary Table S5). The leave-one-out plots demonstrated that the exclusion of any single SNP used in the analysis had no significant impact on the causal association and so draw up the reliability of the causal effect estimates (Supplementary Figures S7–S9). Besides, the results of the MR Steiger directionality test supported our hypothesis regarding the potential causal direction between psychiatric disorders and glaucoma ($p < 0.001$) (Supplementary Table S5).

4 Discussion

This study applied a two-sample MR method to study the causal relationships among three highly related psychiatric disorders and glaucoma, as well as two glaucoma subtypes (POAG and PACG) using large publicly available GWAS summary statistics. Our findings suggested a non-genetic association between depression and glaucoma utilizing the biggest GWAS to date. Meanwhile, there was no evidence indicating that genetically predicted insomnia and schizophrenia were causally related to the risk of glaucoma. Replicated analyses in the East Asian population showed consistency with the results among the European population, with similar causal estimates in amplitude and the same causal estimates in direction. These findings gave us another vision that increasing psychiatric disorders in glaucoma patients observed in previous studies may be more likely to be attributed to modifiable factors rather than inheritable factors.

It is widely known that patients with glaucoma who have irreversible vision impairment often experience continuous mental stress. The worries of losing independence trigger fear with secondary consequences such as depression. A meta-analysis indicated a higher prevalence and severity of depression, anxiety, and sleep disorders in patients with glaucoma (Groff et al., 2023). While prolonged mental stress and psychiatric disorders may not only be a result but also a possible cause (Sabel and Lehnigk, 2021) and a risk factor of glaucoma progression (Shin et al., 2021). Recently, increasing reports from observational studies have found that psychiatric disorders may likely to associated with a higher risk of glaucoma. A study screened all living individuals with specified psychiatric disorders in the years 2010–2019 who resided in Stockholm County, indicating that the risk of POAG was increased in women with depression (Wändell P. E. et al., 2022). A prospective cohort study in the UK investigated the link between sleep behavior and pattern with the risk of glaucoma and found that individuals with insomnia had an excess risk of any glaucoma (Hazard ratio:1.13, 95% CI:1.06–1.20) (Sun et al., 2022). A hospital-based comparative study that comprised 180 patients diagnosed with varying degrees of severity of POAG found that the glaucoma patients showed evidence of poor mental health with 39 (21.7%) of them depressed compared to controls ($p < 0.001$) (Ubochi et al., 2020). Liu et al. observed that glaucoma suspect (OR: 1.88, 95% CI: 1.01–3.49) and OAG (OR: 2.19, 95% CI: 1.13–4.26) showed significant associations with schizophrenia (Liu et al., 2020). However, a prospective cohort research revealed that there was no link between depression and glaucoma, which was inconsistent with findings forementioned (Vidal et al., 2021). Also, a 3-year longitudinal study consisting of 30,097 individuals aged 45–85 years did not find an association between glaucoma and depression (Grant et al., 2021). These contentious findings may be influenced by indissoluble or unidentified risk factors in observational studies.

Several factors may interfere the judgment of causality. Firstly, the causative relationship might be overestimated, considering that psychiatric disorders could be secondary to the glaucoma diagnosis even secondary to the use of antiglaucoma medication. Secondly, some antidepressants such as topiramate (Kocamaz and Karadag, 2019), aripiprazole (Shen et al., 2018), milnacipran (Keks et al., 2018), and duloxetine (Mahmut et al., 2017) have potential eye side effects, such as acute onset angle-closure glaucoma. Chen et al. (2016) found that patients using selective serotonin reuptake inhibitors (SSRIs) have a 5.80-fold increased risk of angle-closure glaucoma in a week. Side effects of antidepressants may affect the accuracy of the findings. Besides, gender was found to have a significant effect on the mental health of glaucoma patients. An institution-based cross-sectional study conducted on 495 glaucoma patients indicated that the female sex (95% CI: 1.66–8.62) ($p = 0.001$) was significantly associated with increased levels of common mental disorders in glaucoma patients (Tilahun et al., 2021). It is in harmony with the study of Lim et al. (2016), reporting higher depression and anxiety in females than in male glaucoma patients. While it is at variance with the report by Ubochi et al. (2020) which revealed that males had higher depression

and anxiety scores than females. As glaucoma and depression are known to be more common among female individuals, the ratio of female patients and the differences in methodology may interfere with the outcome (El-Mogy et al., 2014). In this study, the ratio of female participants is not noted because the ratio cannot be obtained directly from GWAS summary statistics and original articles. Lastly, glaucoma is a group of optic neuropathies that contains different subtypes, overall assessment criteria may misjudge a certain link, and primary glaucoma and secondary glaucoma should be taken into account separately in the investigation. Thus, we employed MR analysis that could exclude the influence of external confounding factors on this contentious relationship so as more likely to draw a reliable genetic causal conclusion. To summarize, rather than the diseases themselves, our non-causal findings indicated that the link between psychiatric problems and glaucoma may emerge through other manageable pathways. This non-causal conclusion has important clinical significance for ophthalmology as further understanding of psychological mechanisms would have to be considered more in the treatment of glaucoma than the development of glaucoma.

This study has several prominent advantages. Firstly, the MR method is the closest approximation to the randomized controlled trial which emulates the random allocation procedure. Theoretically, the influence of external confounding factors can be excluded using MR method, making MR study immune to some limitations of conventional observational studies. Secondly, in our study, the latest and largest publicly accessible GWAS data and strict SNP filtering criteria were used to provide solid evidence for the results. A variety of analytical methods are utilized. Several sensitivity tests were engaged to ensure the robustness of the results. The MR-Egger analysis and MR-PRESSO test suggested no horizontal pleiotropy. Lastly, we performed analysis across two different ancestries (the European and the East Asian populations) and explored subgroup effects (POAG and PACG), which intensified generalizability and validated the adaptation of our results more comprehensively.

Several limitations should be taken into consideration. First and foremost, potential pleiotropy could not be completely voided through the current finite test methods. Secondly, in order to adhere to the principle of minimizing duplication between exposure and outcome samples, the data sources we used are from different institutions. The difference in data collection criteria and diagnosis coding across institutions might affect the estimation of results, especially institutions from different populations. Thirdly, although two different populations had been enrolled in our analysis, it was restricted in other populations due to potential inter-ethnic genetic differences. Additionally, the lack of publicly available GWAS on glaucoma subtypes and other psychiatric disorders like anxiety, disorder, and bipolar disorder in the East Asian population precluded us from exploring the effect in MR analysis. Thus, there is likely to be a need for big sample GWAS and new loci studies of psychiatric disorders and glaucoma across different ancestries.

5 Conclusion

In conclusion, our MR analysis results did not support that genetically predicted psychiatric disorders (including depression, insomnia, and schizophrenia) have any causal effect on the risk of glaucoma, indicating that increased psychiatric disorders in glaucoma patients were more likely not inheritable but modifiable. The findings address an importance of keeping an eye on the mental health of eye disorders and necessitate further research to fully understand this relationship in the future.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The original research of the GWASs used in this study had previously obtained ethical consent, and all analysis was based on publicly accessible summary statistics, which did not exceed the scope of the original ethics committee approval.

Author contributions

YZ: Formal Analysis, Methodology, Resources, Software, Visualization, Writing–original draft. LF: Investigation, Software, Validation, Visualization, Writing–review and editing. FF: Conceptualization, Data curation, Methodology, Project administration, Writing–review and editing. BL: Conceptualization, Data curation, Project administration, Resources, Writing–review and editing. YL: Conceptualization, Data curation, Project administration, Resources, Writing–review and editing. QK: Conceptualization, Funding acquisition, Resources, Validation, Writing–original draft, Writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by the National Science Basic Research Plan in Shaanxi Province of China (Program No. 2021JM-261).

Acknowledgments

We are grateful to the authors of the original genome-wide association studies for accessible statistics.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2024.1349860/full#supplementary-material

References

Auton, A., Durbin, R. M., Garrison, E. P., Kang, H. M., Korbel, J. O., Marchini, J. L., et al. (2015). A global reference for human genetic variation. *Nature* 526, 68–74. doi:10.1038/nature15393

Bowden, J., Davey Smith, G., Haycock, P. C., and Burgess, S. (2016a). Consistent estimation in mendelian randomization with some invalid instruments using a weighted median estimator. *Genet. Epidemiol.* 40, 304–314. doi:10.1002/gepi.21965

Bowden, J., Del Greco, M. F., Minelli, C., Davey Smith, G., Sheehan, N. A., and Thompson, J. R. (2016b). Assessing the suitability of summary data for two-sample Mendelian randomization analyses using MR-Egger regression: the role of the I2 statistic. *Int. J. Epidemiol.* 45, 1961–1974. doi:10.1093/ije/dyw220

Burgess, S., Butterworth, A., and Thompson, S. G. (2013). Mendelian randomization analysis with multiple genetic variants using summarized data. *Genet. Epidemiol.* 37, 658–665. doi:10.1002/gepi.21758

Burgess, S., Davey Smith, G., Davies, N. M., Dudbridge, F., Gill, D., Glymour, M. M., et al. (2019). Guidelines for performing Mendelian randomization investigations. *Wellcome Open Res.* 4, 186. doi:10.12688/wellcomeopenres.15555.2

Burgess, S., and Thompson, S. G. (2017). Interpreting findings from Mendelian randomization using the MR-Egger method. *Eur. J. Epidemiol.* 32, 377–389. doi:10.1007/s10654-017-0255-x

Chen, H.-Y., Lin, C.-L., Lai, S.-W., and Kao, C.-H. (2016). Association of selective serotonin reuptake inhibitor use and acute angle-closure glaucoma. *J. Clin. Psychiatry* 77, e692–e696. doi:10.4088/JCP.15m10038

Choi, J. A., Park, Y.-M., Han, K., Lee, J., Yun, J.-S., and Ko, S.-H. (2020). Fasting plasma glucose level and the risk of open angle glaucoma: nationwide population-based cohort study in Korea. *PLoS One* 15, e0239529. doi:10.1371/journal.pone.0239529

El-Mogy, A., El-Hadidy, M. A., and El-Kaneshy, A. (2014). Comorbid psychiatric disorders with glaucoma. *Middle East Curr. Psychiatry* 21, 252–257. doi:10.1097/01.XME.0000452618.31145.08

Emdin, C. A., Khera, A. V., and Kathiresan, S. (2017). Mendelian randomization. *JAMA* 318, 1925–1926. doi:10.1001/jama.2017.17219

Gharahkhani, P., He, W., Diaz Torres, S., Wu, Y., Ingold, N., Yu, R., et al. (2023). Study profile: the genetics of glaucoma study. *BMJ Open* 13, e068811. doi:10.1136/bmjopen-2022-068811

Giannakopoulou, O., Lin, K., Meng, X., Su, M.-H., Kuo, P.-H., Peterson, R. E., et al. (2021). The genetic architecture of depression in individuals of East Asian ancestry: a genome-wide association study. *JAMA Psychiatry* 78, 1258–1269. doi:10.1001/jamapsychiatry.2021.2099

Grant, A., Aubin, M.-J., Buhrmann, R., Kergoat, M.-J., and Freeman, E. E. (2021). Visual impairment, eye disease, and the 3-year incidence of depressive symptoms: the Canadian longitudinal study on aging. *Ophthalmic Epidemiol.* 28, 77–85. doi:10.1080/09286586.2020.1823425

Groff, M. L., Choi, B., Lin, T., Mcllraith, I., Hutnik, C., and Malvankar-Mehta, M. S. (2023). Anxiety, depression, and sleep-related outcomes of glaucoma patients: systematic review and meta-analysis. *Can. J. Ophthalmol.* 58, 346–355. doi:10.1016/j.jcjo.2022.02.010

Hartwig, F. P., Davey Smith, G., and Bowden, J. (2017). Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. *Int. J. Epidemiol.* 46, 1985–1998. doi:10.1093/ije/dyx102

Hemani, G., Tilling, K., and Davey Smith, G. (2017). Orienting the causal relationship between imprecisely measured traits using GWAS summary data. *PLoS Genet.* 13, e1007081. doi:10.1371/journal.pgen.1007081

Howard, D. M., Adams, M. J., Clarke, T.-K., Hafferty, J. D., Gibson, J., Shirali, M., et al. (2019). Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nat. Neurosci.* 22, 343–352. doi:10.1038/s41593-018-0326-7

Ishigaki, K., Akiyama, M., Kanai, M., Takahashi, A., Kawakami, E., Sugishita, H., et al. (2020). Large-scale genome-wide association study in a Japanese population identifies novel susceptibility loci across different diseases. *Nat. Genet.* 52, 669–679. doi:10.1038/s41588-020-0640-3

Jung, Y., Han, K., Wang, S.-M., Yoon, H. Y., and Moon, J. I. (2021). Effect of depressive symptom and depressive disorder on glaucoma incidence in elderly. *Sci. Rep.* 11, 5888. doi:10.1038/s41598-021-85380-6

Keks, N. A., Hope, J., Keogh, S., and Copolov, D. L. (2018). Milnacipran: serotonin-noradrenaline reuptake inhibitor approved for fibromyalgia may be a useful antidepressant. *Australas. Psychiatry* 26, 537–540. doi:10.1177/1039856218794874

Kocamaz, M., and Karadag, O. (2019). Topiramate-Induced acute myopia, diplopia, and photosensitivity: a case report. *Beyoglu Eye J.* 4, 42–45. doi:10.14744/bej.2019.07379

Kurki, M. I., Karjalainen, J., Palta, P., Sipilä, T. P., Kristiansson, K., Donner, K. M., et al. (2023). FinnGen provides genetic insights from a well-phenotyped isolated population. *Nature* 613, 508–518. doi:10.1038/s41586-022-05473-8

Leske, M. C., Connell, A. M., Wu, S. Y., Hyman, L. G., and Schachat, A. P. (1995). Risk factors for open-angle glaucoma. The Barbados Eye Study. *Arch. Ophthalmol.* 113, 918–924. doi:10.1001/archopht.1995.01100070092031

Lim, N. C. S., Fan, C. H. J., Yong, M. K. H., Wong, E. P. Y., and Yip, L. W. Y. (2016). Assessment of depression, anxiety, and quality of life in Singaporean patients with glaucoma. *J. Glaucoma* 25, 605–612. doi:10.1097/IJG.0000000000000393

Liu, C.-H., Kang, E. Y.-C., Lin, Y.-H., Wu, W.-C., Liu, Z.-H., Kuo, C.-F., et al. (2020). Association of ocular diseases with schizophrenia, bipolar disorder, and major depressive disorder: a retrospective case-control, population-based study. *BMC Psychiatry* 20, 486. doi:10.1186/s12888-020-02881-w

Ma, Y., Han, J., Li, S., Zhang, A., Cao, W., and Sun, X. (2019). Association between platelet parameters and glaucoma severity in primary open-angle glaucoma. *J. Ophthalmol.* 2019, 3425023. doi:10.1155/2019/3425023

Mahmut, A., Tunc, V., Demiryurek, E., and Gursoy, A. (2017). Bilateral acute angle-closure glaucoma induced by duloxetine. *Ideggyogy Sz.* 70, 358–360. doi:10.18071/isz.70.0358

Meer, E. A., Lee, Y. H., Repka, M. X., Borlik, M. F., Velez, F. G., Perez, C., et al. (2022). Association of mood disorders, substance abuse, and anxiety disorders in children and teens with serious structural eye diseases. *Am. J. Ophthalmol.* 240, 135–142. doi:10.1016/j.ajo.2022.03.016

Quigley, H. A. (2011). Glaucoma. *Lancet* 377, 1367–1377. doi:10.1016/S0140-6736(10)61423-7

Rezapour, J., Nickels, S., Schuster, A. K., Michal, M., Münzel, T., Wild, P. S., et al. (2018). Prevalence of depression and anxiety among participants with glaucoma in a population-based cohort study: the Gutenberg Health Study. *BMC Ophthalmol.* 18, 157. doi:10.1186/s12886-018-0831-1

Ripke, S., Neale, B. M., Corvin, A., Walters, J. T., Farh, K.-H., Holmans, P. A., et al. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 511, 421–427. doi:10.1038/nature13595

Sabel, B. A., and Lehnigk, L. (2021). Is mental stress the primary cause of glaucoma? *Klin. Monbl Augenheilkd* 238, 132–145. doi:10.1055/a-1303-8025

Shen, E., Farukhi, S., Schmutz, M., and Mosaed, S. (2018). Acute angle-closure glaucoma associated with aripiprazole in the setting of plateau Iris configuration. *J. Glaucoma* 27, e40–e43. doi:10.1097/IJG.0000000000000836

Shin, D. Y., Jung, K. I., Park, H. Y. L., and Park, C. K. (2021). The effect of anxiety and depression on progression of glaucoma. *Sci. Rep.* 11, 1769. doi:10.1038/s41598-021-81512-0

Shukla, A. G., Razeghinejad, R., and Myers, J. S. (2020). Balancing treatments for patients with systemic hypertension and glaucoma. *Expert Opin. Pharmacother.* 21, 2225–2230. doi:10.1080/14656566.2020.1810235

Song, D.-J., Fan, B., and Li, G.-Y. (2023). Blood cell traits and risk of glaucoma: a two-sample mendelian randomization study. *Front. Genet.* 14, 1142773. doi:10.3389/fgene.2023.1142773

Sun, C., Yang, H., Hu, Y., Qu, Y., Hu, Y., Sun, Y., et al. (2022). Association of sleep behaviour and pattern with the risk of glaucoma: a prospective cohort study in the UK Biobank. *BMJ Open* 12, e063676. doi:10.1136/bmjopen-2022-063676

Tham, Y.-C., Li, X., Wong, T. Y., Quigley, H. A., Aung, T., and Cheng, C.-Y. (2014). Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology* 121, 2081–2090. doi:10.1016/j.ophtha.2014.05.013

Tilahun, M. M., Yibekal, B. T., Kerebih, H., and Ayele, F. A. (2021). Prevalence of common mental disorders and associated factors among adults with Glaucoma attending University of Gondar comprehensive specialized hospital tertiary eye care and training center, Northwest, Ethiopia 2020. *PLoS One* 16, e0252064. doi:10.1371/journal.pone.0252064

Ubochi, C. C., Achigbu, E. O., Nkwogu, F. U., Onyia, O. E., and Okeke, C. J. (2020). The impact of glaucoma on the mental health of primary open-angle glaucoma patients attending a teaching hospital in south East Nigeria. *J. West Afr. Coll. Surg.* 10, 17–22. doi:10.4103/jwas.jwas_59_21

Verbanck, M., Chen, C.-Y., Neale, B., and Do, R. (2018). Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat. Genet.* 50, 693–698. doi:10.1038/s41588-018-0099-7

Vidal, K. S., Suemoto, C. K., Moreno, A. B., Viana, M. C., Lotufo, P. A., Benseñor, I. M., et al. (2021). Association between posterior segment eye diseases, common mental disorders, and depression: cross-sectional and longitudinal analyses of Brazilian longitudinal study of adult health cohort. *J. Acad. Consult Liaison Psychiatry* 62, 70–78. doi:10.1016/j.psym.2020.03.001

Wändell, P., Carlsson, A. C., and Ljunggren, G. (2022a). Systemic diseases and their association with open-angle glaucoma in the population of Stockholm. *Int. Ophthalmol.* 42, 1481–1489. doi:10.1007/s10792-021-02137-w

Wändell, P. E., Ljunggren, G., Wahlström, L., and Carlsson, A. C. (2022b). Psychiatric diseases and dementia and their association with open-angle glaucoma in the total population of Stockholm. *Ann. Med.* 54, 3349–3356. doi:10.1080/07853890.2022.2148735

Weinreb, R. N., Aung, T., and Medeiros, F. A. (2014). The pathophysiology and treatment of glaucoma: a review. *JAMA* 311, 1901–1911. doi:10.1001/jama.2014.3192

Yang, J., Patil, R. V., Yu, H., Gordon, M., and Wax, M. B. (2001). T cell subsets and sIL-2R/IL-2 levels in patients with glaucoma. *Am. J. Ophthalmol.* 131, 421–426. doi:10.1016/s0002-9394(00)00862-x

Yuan, R., Liu, K., Cai, Y., He, F., Xiao, X., and Zou, J. (2022). Body shape and risk of glaucoma: a Mendelian randomization. *Front. Med. (Lausanne)* 9, 999974. doi:10.3389/fmed.2022.999974

Zhang, D., Sun, N., Guo, C., Lee, J. H., Zhang, J., Zhao, Z., et al. (2022). Psychological stress induces moderate pathology in the ganglion cell layer in mice. *Mol. Vis.* 28, 451–459.

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 03 June 2024
DOI 10.3389/fmed.2024.1402604

OPEN ACCESS

EDITED BY
Alessio Martucci,
University of Rome Tor Vergata, Italy

REVIEWED BY
Vicente Zanon-Moreno,
University of Valencia, Spain
Suzana Konjevoda,
General Hospital Zadar, Croatia

*CORRESPONDENCE
Vanja Kopilaš
✉ vkopilas@fhs.unizg.hr

RECEIVED 17 March 2024
ACCEPTED 24 May 2024
PUBLISHED 03 June 2024

CITATION
Kopilaš V and Kopilaš M (2024) Quality of life and mental health status of glaucoma patients.
Front. Med. 11:1402604.
doi: 10.3389/fmed.2024.1402604

Quality of life and mental health status of glaucoma patients

Vanja Kopilaš[1]* and Mirko Kopilaš[2]

[1]Faculty of Croatian Studies, University of Zagreb, Zagreb, Croatia, [2]Private Ophthalmology Clinic, Dubrovnik, Croatia

Introduction: Glaucoma, a leading cause of irreversible blindness worldwide, poses significant challenges to patients' quality of life (QOL) and mental well-being.

Methods: This study aimed to investigate the complex interplay between clinical, demographic, and psychological factors and their impact on QOL among patients diagnosed with glaucoma. A cohort of 201 glaucoma patients, with a mean age of 70 years, participated in the study.

Results: Descriptive analyses revealed that participants reported living with a glaucoma diagnosis for an average of 13.38 years, highlighting the chronic nature of the disease in the cohort. Comorbidity was shown to be in close relationship with QOL, where with additional health problems have lower QOL scores ($M = 34.86$, $SD = 18.25$), as well as higher levels of anxiety ($M = 10.64$, $SD = 5.38$) and depression ($M = 13.42$, $SD = 7.37$). Correlation analyses further unveiled robust associations between clinical characteristics and psychological outcomes, with lower visual acuity strongly correlated with reduced QOL ($rR = -0.74$, $pR < 0.001$; $rL = -0.78$, $pL < 0.001$) and higher levels of anxiety and depression. Additionally, longer duration of glaucoma diagnosis was moderately associated with poorer QOL ($r = 0.56$, $p < 0.001$) and increased psychological distress, highlighting the cumulative burden of living with the disease over time. Mediation analyses indicated that duration of diagnosis partially mediated the relationship between depression and QOL, as well as anxiety and QOL, suggesting that the prolonged experience of living with glaucoma may exacerbate the impact of psychological distress on QOL.

Discussion: These findings underscore the importance of holistic patient care approaches that address both the physical and psychological aspects of glaucoma to improve patient outcomes and enhance overall well-being.

KEYWORDS

glaucoma, quality of life, mental health, depression, anxiety

1 Introduction

Vision is integral to nearly every aspect of daily life, facilitating essential activities such as navigation, communication, and personal independence (1, 2). Thus, any impairment to vision can have profound consequences on an individual's well-being and quality of life (QOL). Glaucoma, a group of progressive optic neuropathies characterized by damage to the optic nerve and visual field loss, represents one such condition that poses significant challenges to affected individuals (3, 4). Despite its asymptomatic nature in the early stages, glaucoma can lead to irreversible vision loss if left untreated, highlighting the critical importance of early detection and intervention in preserving visual function (5). The impact of glaucoma extends beyond its ocular manifestations, permeating various aspects of everyday living (6). As the disease progresses, individuals may experience limitations in performing routine activities, such as driving, reading, and participating in social events (7). These changes can result in

feelings of frustration, dependence, and diminished QOL (8–10). Furthermore, the psychosocial consequences of glaucoma are profound, with vision loss often precipitating emotional distress, anxiety, and depression (7, 11, 12). Symptoms of depression and anxiety are often reported in glaucoma patients, and some research even consider them as potential risk factors for glaucoma development (13–15). Patients diagnosed with open-angle glaucoma frequently encounter challenges in identifying facial expressions and have an increased susceptibility to feelings of depression and anxiety, commonly linked to the deterioration of their vision (16, 17). Nevertheless, the temporal pole, a component of the limbic system in conjunction with the amygdala that is known to be involved in several functions such as such as emotion and behavior, is also involved in the processes of facial recognition and memory storage (18, 19). Understanding the complex interplay between clinical, demographic, and psychological factors and their impact on QOL among glaucoma patients is essential for informing targeted interventions aimed at improving patient outcomes. Previous research has highlighted the significant associations between comorbidity, disease duration, psychological distress, and QOL in this population (8–10, 14, 20–22). However, further investigation is warranted to elucidate the underlying mechanisms driving these relationships and to identify potential modifiable factors that can be targeted in clinical practice. Theoretical framework is provided with biopsychosocial model that is supporting the notion that certain medical conditions can only be understood through the examination of the interaction between physiological, psychological, and sociocultural factors (23, 24). Therefore, the present study aims to comprehensively examine the multifaceted relationship between clinical, demographic, and psychological factors and their impact on QOL among patients diagnosed with glaucoma. Utilizing a different statistical methods including descriptive analyses, correlation analyses, independent sample *t*-tests, and mediation analyses, we seek to address the following objectives:

- Investigate the associations between comorbidity, disease duration, and psychological distress (anxiety and depression) with QOL among glaucoma patients.
- Examine the mediating role of disease duration in the relationship between psychological distress and QOL in glaucoma patients.

By addressing these objectives, our aim is to contribute to a deeper understanding of the determinants of QOL in glaucoma patients and to inform targeted interventions aimed at improving patient outcomes and enhancing overall well-being. Additionally, by elucidating the complex interplay of factors influencing QOL, this study seeks to advance our understanding of the biopsychosocial dimensions of glaucoma and to underscore the importance of holistic approaches to patient care.

2 Materials and methods

2.1 Participants

Two hundred and one participants enrolled in this cross-sectional study were individuals undergoing routine ophthalmological examinations, all of whom had received a diagnosis of primary open-angle glaucoma from their attending ophthalmologist. Ethical approval for this study was obtained by the Ethics Committee at the University of Zagreb Faculty of Croatian Studies (reference number: 053-01/23-2/0001), ensuring that the research complied with all relevant ethical standards and guidelines. These participants were recruited during their visits to the ophthalmology clinic and were invited to participate in the research study. Prior to their involvement, each participant signed informed consent, indicating their understanding of the study's purpose, procedures, and their voluntary participation.

Upon obtaining informed consent, participants were guided through the study protocol by trained research personnel. The procedure involved the completion of a comprehensive battery of questionnaires, designed to assess various psychosocial and demographic factors pertinent to the experience of glaucoma.

2.2 Measures

The battery of questionnaires administered to participants included:

Glaucoma Quality of Life Questionnaire (GQL-15) (25): The GQL-15 is a validated instrument tailored to assess the impact of glaucoma on various aspects of an individual's QOL, covering domains such as vision-related function, mobility, and emotional well-being. The GLQ-15 consists of 15 items. Each question has scores ranging from 0 to 5, where 0 is difficulty to perform the task due to non-visual problems, 1 is no difficulty, and 5 is severe difficulty. The highest score is 75 and the lowest is 15, where higher scores indicate more difficulties with vision-related activities and are associated with lower quality of life as well. The Cronbach alpha for the current study indicates good reliability of the GQL-15 ($\alpha = 0.986$).

Generalized Anxiety Disorder-7 Scale (GAD-7) (26): The GAD-7 is a widely used self-report measure consisting of 7 items designed to assess the severity of anxiety symptoms experienced by individuals over the past 2 weeks, providing valuable insights into the prevalence and intensity of anxiety. Each item has scores ranging from 0 to 3, where 0 is not at all, 1 is several days, and 3 is nearly every day. The GAD-7 total score ranges from 0 to 21. The Cronbach alpha for the current study indicates satisfactory reliability of the GAD-7 ($\alpha = 0.95$).

Patient Health Questionnaire-9 (PHQ-9) (27): The PHQ-9 is a reliable and validated tool for evaluating the severity of depressive symptoms. It consists of 9 items exploring the frequency and intensity of depressive symptoms experienced by participants. Each item explores presentation of certain experiences over the course of the last 2 weeks with scores ranging from 0 to 3, where 0 is not at all, 1 is several days, and 3 is nearly every day. The PHQ-9 total score ranges from 0 to 27. The Cronbach alpha for the current study indicates satisfactory reliability of the PHQ-9 ($\alpha = 0.968$).

Sociodemographic Questionnaire: A structured questionnaire was administered to collect sociodemographic information from participants, including age, gender, educational background, employment status, medical information (duration of diagnosis, visual acuity, comorbidities) and other relevant demographic variables. This information allows for the characterization of the study sample and facilitates the exploration of potential associations between sociodemographic factors and the psychosocial variables under investigation.

The administration of these questionnaires was conducted in a standardized manner, ensuring consistency and reliability across participants. Participants were encouraged to provide accurate and

honest responses to each item, with the assurance of confidentiality and anonymity maintained throughout the data collection process.

2.3 Data analysis

Data was analyzed with IBM SPSS Statistics program (version 26). Before conducting statistical analysis, the normality of the continuous variables was tested. The results of the Shapiro–Wilk test indicated deviations from the normality for all continuous variables. However, it should be noted that all the distributions prove to be symmetrical, except the distribution of quality of life. Descriptive analyses were conducted to compute means, and standard deviation of continuous variables, as well as the median and interquartile range for the variable of quality of life. Additionally, we examined proportions of categorical variables.

In order to examine the differences in observed variables (anxiety, depression, and quality of life) regarding gender and comorbidity, an independent sample *t*-test were performed.

To determine the associations between glaucoma related quality of life, measures of psychological distress (anxiety and depression), and certain aspects of participants' health, the values of the Pearson correlation coefficient were observed. Significance was set at $p < 0.05$.

Mediation analyses were performed to assess whether years of living with glaucoma were significant mediator of the relationship between depression and quality of life, as well as anxiety and quality of life. PROCESS module in SPSS [version 4.0., Model 4, Hayes (28)] was used to conduct the above-mentioned analysis. Significance of the indirect effect was tested with bootstrap method, where confidence interval (CI) was set at 95% and based on 5,000 bootstrap samples. The indirect effect is considered statistically significant if the 95% CI does not contain a value of 0.

3 Results

3.1 Descriptive statistics

This study included 201 patients with glaucoma, of which 125 (62.2%), were women, and 76 (37.8%) were men. Participants were between the ages of 42 and 94, with the average age of 70 years (M = 70.4; SD = 11.52). Most of them marked high school as the highest level of education (42.8%), are retired (64.2%), married (56.7%) and have children (82.6%). On average, our participants live more than 13 years with a diagnosis of glaucoma (M = 13.38; SD = 7.73). Regarding visual acuity, most of them have normal sight on one of the eyes based on the International Classification of Diseases 11 (ICD-11) classification for distance vision impairment (29). Sample characteristics are presented in Table 1.

The mean total score on the GQL-15 was 34.86 (SD = 18.25) indicating somewhat good quality of life of our glaucoma patients. Considering that the quality of life has a positively skewed distribution, it is necessary to consider the values of the median, which is 28 (interquartile range- iqr = 30), and deviates from the previously mentioned mean values. The mean score for depression on PHQ-9 was 13.42 (SD = 7.37), while the mean GAD-7 score was 10.64 (SD = 5.38). Using a cut-off score of ≥ 8 (30, 31), more than two thirds of the sample (68.3%) would be categorized as depressed, and approximately 63% (63.8%) would be considered anxious (30, 31).

TABLE 1 Sociodemographic information of the participants (*N* = 201).

		N (%)
Gender	Female	125 (62.2)
	Male	76 (37.8)
Education	Elementary school	47 (23.4)
	High school	86 (42.8)
	University	68 (33.8)
Work status	Full-time work	55 (27.4)
	Unemployed	17 (8.5)
	Retired	129 (64.2)
Relationship status	Married	114 (56.7)
	Unmarried	24 (11.9)
	Widowed	53 (26.4)
	Divorced	10 (5.0)
Children	Yes	166 (82.6)
	No	35 (17.4)
Comorbidities	Yes	88 (43.8)
	No	113 (56.2)
Visual acuity- R	Blindness	14 (7.0)
	Severe	5 (2.5)
	Moderate	20 (9.95)
	Mild	17 (8.45)
	Normal	145 (72.1)
Visual acuity- L	Blindness	14 (7.0)
	Severe	7 (3.5)
	Moderate	19 (9.45)
	Mild	20 (9.95)
	Normal	141 (70.1)

	M (SD)
Age	70.4 (11.5)
Duration of diagnosis	13.38 (7.73)

3.2 Differences in the observed variables

The results of *t*-test (Table 2) indicated a statistically significant difference in quality of life, depression and anxiety regarding comorbidity, but not gender. Glaucoma patients with additional health problems reported greater difficulties in performing daily activities (GQL-15), and higher levels of anxiety and depression. Due to the positively skewed distribution of the quality of life, a Mann Whitney U test was performed (U = 7,143, z = 5.31, $p < 0.001$) which confirmed a significant difference in quality of life with respect to the comorbidity. In addition, measures of psychological distress (anxiety and depression) and quality of life differed significantly based on comorbidity, even after controlling for age. There were no statistically significant gender differences in observed variables, i.e., the GQL-15 scores, PHQ-9 scores and GAD-7 scores were similar for both groups. Additionally, observed variables did not differ significantly in regard to gender, after controlling for the age of participants.

TABLE 2 Differences in observed variables regarding gender and comorbidity.

Dependent variable	Group		*M* (SD)	*t* (df)	*p*-value	95% CI
GQL-15	Gender	Female	33.18 (17.35)	−1.686 (199)	0.093	[−9.667, 0.756]
		Male	37.63 (19.45)			
	Comorbidity	Yes	40.77 (15.95)	−4.219 (199)	**<0.001**	[−15.431, −5.601]
		No	30.26 (18.67)			
PHQ-9	Gender	Female	13.21 (7.38)	−0.517 (199)	0.606	[−2.672, 1.561]
		Male	13.76 (7.38)			
	Comorbidity	Yes	15.60 (6.43)	−3.835 (199)	**<0.001**	[−5.883, −1.888]
		No	11.72 (7.62)			
GAD-7	Gender	Female	10.53 (5.4)	−0.367 (199)	0.714	[−1.836, 1.260]
		Male	10.82 (5.39)			
	Comorbidity	Yes	12.26 (4.69)	−3.907 (199)	**<0.001**	[−4.348, −1.431]
		No	9.37 (5.56)			

Significant values bolded. M, mean; SD, standard deviation; t, t-statistic; df, degrees of freedom; 95% CI, 95% confidence interval; GQL-15, Glaucoma Quality of Life Questionnaire; PHQ-9, Patient Health Questionnaire-9; GAD-7, Generalized Anxiety Disorder-7 Scale.

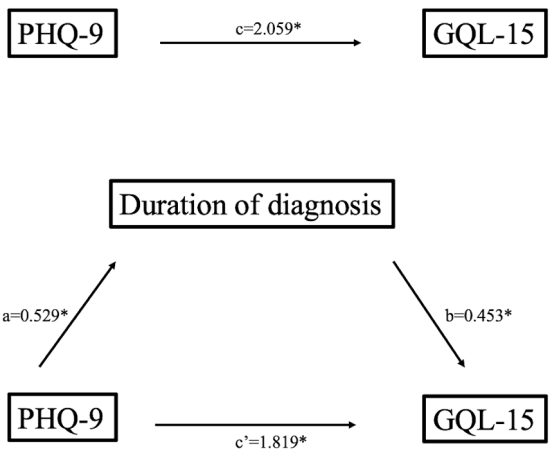

FIGURE 1
Mediation model of depression on quality of life through duration of diagnosis (unstandardized coefficients); *$p < 0.001$.

3.3 Correlation analysis

To determine the association between certain aspects of participants' health (visual acuity, duration of diagnosis), and quality of life, anxiety and depression, Pearson's correlation analysis was conducted. Quality of life was significantly negatively associated with observed clinical characteristics. Visual acuity in both eyes was significantly negatively associated with GQL-15 (Pearson's correlation coefficient of the right eye- $r_R = -0.74$, corresponding *p*-value of the right eye- $p_R < 0.001$; Pearson's correlation coefficient of the left eye $r_L = -0.78$, corresponding *p*-value of the left eye- $p_L < 0.001$), indicating that glaucoma patients with lower visual acuity tend to experience greater difficulties in performing daily activities. Furthermore, visual acuity exhibited significant negative correlation with depression ($r_R = -0.59$, $p_R < 0.001$; $r_L = -0.75$, $p_L < 0.001$) and anxiety ($r_R = -0.6$, $p_R < 0.001$; $r_L = -0.71$, $p_L < 0.001$). Duration of glaucoma diagnosis was moderately and positively associated with GQL-15 ($r = 0.56$, $p < 0.001$), PHQ-9 ($r = 0.5$, $p < 0.001$), and GAD-7 ($r = 0.48$, $p < 0.001$), implying that longer coexistence with glaucoma is linked to greater perception of difficulties in everyday functioning and higher levels of depression and anxiety. Additionally, decrease in performance-related quality of life (GQL-15) was significantly positively correlated with depression ($r = 0.83$, $p < 0.001$) and anxiety ($r = 0.8$, $p < 0.001$).

3.4 Mediation analysis

To assess the possible mediating role of duration of diagnosis in the relationship between anxiety and quality of life, as well as depression and quality of life, simple mediation analyses were performed. Regarding the first mediation model (Figure 1), the path coefficients from depression to duration of diagnosis (b = 0.53, $p < 0.001$; 95% CI [0.402, 0.655]), and from depression to quality of life (path c) were significant (b = 2.06, $p < 0.001$, 95% CI [1.866, 2.251]). As shown in Table 3, duration of the diagnosis made a significant contribution to quality of life (b = 0.45, $p < 0.001$). Considering the bootstrap 95% confidence interval, the significant indirect effect from depression to quality of life through duration of diagnosis was confirmed (b = 0.24, 95% CI [0.112, 0.401]). Finally, the direct effect of depression on quality of life remained significant, but the effect value was somewhat lower (b = 1.82, $p < 0.001$).

Regarding the second mediation model (Table 3; Figure 2), anxiety made significant contribution to duration of the diagnosis (b = 0.69, $p < 0.001$, 95% CI [0.515, 0.866]), and to quality of life (path c, b = 2.72, $p < 0.001$, 95% CI [2.44, 3.01]). Duration of diagnosis positively predicted vision related quality of life (b = 0.54, $p < 0.001$). Moreover, the indirect effect of anxiety on quality of life through duration of diagnosis (b = 0.37, $p < 0.001$) was also significant. After accounting for duration of diagnosis as mediator, the direct effect of anxiety on quality of life remained significant (b = 2.35, $p < 0.001$), indicating that years living with diagnosis partially mediates the

TABLE 3 Path estimates of mediation models.

Outcome	Predictors	B	SE	β	95% CI	R^2	F	p-value
GQL-15	PHQ-9	1.82	0.11	0.73	[1.61, 2.03]	0.718	251.94	**<0.001**
	DD	0.45	0.1	0.19	[0.25, 0.65]			
	PHQ-9 x DD	0.24	0.07	0.097	[0.11, 0.401]			
GQL-15	GAD-7	2.35	0.15	0.69	[2.05, 2.65]	0.685	215.18	**<0.001**
	DD	0.54	0.11	0.23	[0.33, 0.75]			
	GAD-7 x DD	0.37	0.11	0.11	[0.19, 0.59]			

Significant values bolded; B, unstandardized coefficient; SE, Standard Error; β, standardized (beta) coefficient; 95% CI, 95% confidence interval; R^2, coefficient of determination; F, F- statistic; DD, duration of diagnosis; GQL-15, Glaucoma Quality of Life Questionnaire; PHQ-9, Patient Health Questionnaire-9; GAD-7, Generalized Anxiety Disorder-7 Scale.

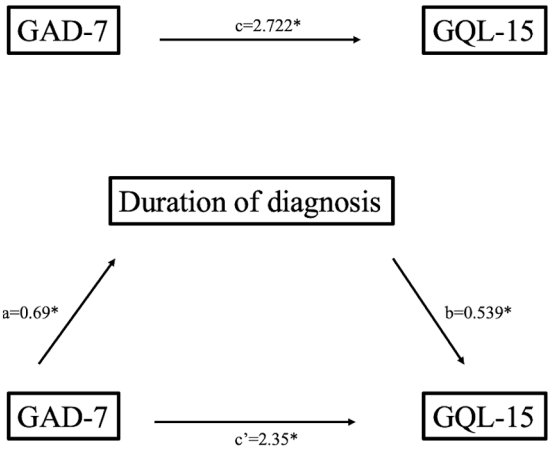

FIGURE 2
Mediation model of anxiety on quality of life through duration of diagnosis (unstandardized coefficients); *$p < 0.001$.

relationship between level of anxiety and vision related quality of life in glaucoma patients.

4 Discussion

Our study employed an analytical approach to investigate the complex interplay between clinical, demographic, and psychological factors and their impact on the QOL among patients diagnosed with glaucoma. Series of analyses was conducted, including descriptive statistics, correlation analyses, independent sample *t*-tests, and mediation analyses with specific aim of exploring the underlying mechanisms behind the observed relationships.

Descriptive analyses revealed important demographic characteristics of our sample, comprising 201 glaucoma patients, with 62.2% being women and 37.8% men. The average age of participants was 70 years, with the majority having completed high school education (42.8%), being retired (64.2%), married (56.7%), and having children (82.6%). Furthermore, the participants reported living with a glaucoma diagnosis for an average of 13.38 years, highlighting the chronic nature of the disease in our cohort.

Our analysis of clinical measures revealed significant associations between comorbidity and QOL among glaucoma patients. Those with additional health problems reported significantly lower QOL scores (M = 34.86, SD = 18.25), as well as higher levels of anxiety (M = 10.64, SD = 5.38) and depression (M = 13.42, SD = 7.37). Notably, more than two-thirds of the sample would be categorized as depressed, and approximately 63% would be considered anxious, indicating a high prevalence of mental distress in this population.

While our study did not find statistically significant gender differences in QOL, anxiety, or depression among glaucoma patients, both male and female participants exhibited similar scores on these measures. This suggests that gender may not be a significant predictor of psychological well-being in this population. Contrary, previous research found that women with glaucoma were more likely to experience depression and stress (22). However, research is not quite clear about the role of gender suggesting that this area has yet to be explored. Our findings are in line with other research showing no significant gender difference among glaucoma patients (32).

Correlation analyses unveiled robust associations between clinical characteristics and psychological outcomes. Lower visual acuity was strongly correlated with reduced QOL ($r_R = -0.74$, $p_R < 0.001$; $r_L = -0.78$, $p_L < 0.001$) and higher levels of anxiety ($r_R = -0.6$, $p_R < 0.001$; $r_L = -0.71$, $p_L < 0.001$) and depression ($r_R = -0.59$, $p_R < 0.001$; $r_L = -0.75$, $p_L < 0.001$), emphasizing the profound impact of visual impairment on psychosocial functioning. This is in line with previous research confirming significant decrease in social functioning and mental health due to the lower visual acuity (33, 34). Additionally, longer duration of glaucoma diagnosis was moderately associated with poorer QOL ($r = 0.56$, $p < 0.001$) and increased psychological distress, highlighting the cumulative burden of living with the disease over time. These results are expected. Progression of glaucoma symptoms is expected to have an effect on the psychological well-being and everyday functioning (14, 35). Changes imposed by the lower vision quality can lead to the higher prevalence of anxious and depressive symptoms, and then consequently to the lower QOL.

Our mediation analyses provided further insights into the underlying mechanisms linking anxiety, depression, and QOL in glaucoma patients. Duration of diagnosis emerged as a significant mediator, partially mediating the relationship between anxiety and QOL, as well as depression and QOL. Specifically, the indirect effect of anxiety on QOL through duration of diagnosis was significant (b = 0.37, $p < 0.001$), suggesting that the prolonged experience of living with glaucoma may exacerbate the impact of anxiety on QOL. These findings confirm previous research showing existent triad of factors impacting QOL (14, 36, 37). As such, it becomes imperative for healthcare systems to prioritize interventions targeting these areas to enhance QOL for individuals living with glaucoma. By addressing the

complex interactions between anxiety, depression, and duration of diagnosis, healthcare providers can implement more effective strategies to improve the well-being of glaucoma patients.

Our study has several practical significances. Based on the empirical evidence, new prevention and curation programs can be developed in order to improve relationships between clinical, demographic, and psychological factors in glaucoma patients. By identifying key determinants of QOL and psychological distress, our findings underscore the importance of holistic patient care in managing this complex condition. Future research employing longitudinal designs and objective assessments could provide further insights into the dynamic interplay between these factors, ultimately informing targeted interventions to improve the well-being of individuals living with glaucoma.

4.1 Limitations

There are certain limitations related to this study. Due to the cross-sectional design, our findings have to be carefully interpreted. In order to have more generable conclusions, it would be beneficial to run longitudinal study looking at how these variables may change over time, and whether that change is related to the interplay between observed variables, or some other factors. One of the potential limitations is definitely gender ratio of our sample, and that majority of participants were older. Future research should make sure that sample is fair representative of the population in terms of gender and age. Finally, differences between various glaucoma types were not observed. Rather, we were interested if one has diagnosis of glaucoma or not. In order to see if different glaucoma types differ in the relationship with observed variables, future studies should incorporate this in the study design.

5 Conclusion

Our study explored notable impacts of comorbidity on the quality of life (QOL) among glaucoma patients, accompanied by increased levels of anxiety and depression. Although gender disparities in QOL were not notable, strong associations were discovered between clinical factors such as visual acuity and duration of diagnosis with QOL and psychological distress. These findings emphasize the significance of comprehensive patient care and propose the necessity for targeted interventions to relieve the mental burden experienced by glaucoma patients. Future exploration employing longitudinal designs could provide further insights into effective management strategies for this intricate condition.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee at the University of Zagreb Faculty of Croatian Studies. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

VK: Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. MK: Investigation, Methodology, Resources, Supervision, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Hutmacher F. Why is there so much more research on vision than on any other sensory modality? *Front Psychol*. (2019) 10:2246. doi: 10.3389/fpsyg.2019.02246

2. Kuriakose B, Shrestha R, Sandnes FE. Tools and Technologies for Blind and Visually Impaired Navigation Support: a review. *IETE Tech Rev*. (2022) 39:3–18. doi: 10.1080/02564602.2020.1819893

3. Bolton E, Miller C, Huang R, Kang JM. Glaucoma. In: Li E, Bacorn C. editors *Ophthalmology Clerkship. Contemporary Surgical Clerkships* Cham: Springer (2023). p. 73–92.

4. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of Glaucoma. *JAMA*. (2014) 311:1901. doi: 10.1001/jama.2014.3192

5. Liu H, Chen C, Chen Z, Li Q, Li Q, Liu W. Factors associated with delayed first ophthalmological consultation for primary glaucoma: a qualitative interview study. *Front Med (Lausanne)*. (2023) 10:1161980. doi: 10.3389/fmed.2023.1161980

6. Martucci A, Cesareo M, Toschi N, Garaci F, Bagetta G, Nucci C. Brain networks reorganization and functional disability in glaucoma (2020) 257:65–76. doi: 10.1016/bs.pbr.2020.07.007.

7. Huang W, Gao K, Liu Y, Liang M, Zhang X. The adverse impact of Glaucoma on psychological function and daily physical activity. *J Ophthalmol*. (2020) 2020:1–8. doi: 10.1155/2020/9606420

8. Zhang Q, Zhou W, Song D, Xie Y, Lin H, Liang Y, et al. Vision-related quality of life in patients with glaucoma: the role of illness perceptions. *Health Qual Life Outcomes*. (2022) 20:78. doi: 10.1186/s12955-022-01979-x

9. Quaranta L, Riva I, Gerardi C, Oddone F, Floriano I, Konstas AGP. Quality of life in Glaucoma: a review of the literature. *Adv Ther*. (2016) 33:959–81. doi: 10.1007/s12325-016-0333-6

10. Wang Y, Zhao Y, Xie S, Wang X, Chen Q, Xia X. Resilience mediates the relationship between social support and quality of life in patients with primary Glaucoma. *Front Psych*. (2019) 10:22. doi: 10.3389/fpsyt.2019.00022

11. Shin DY, Jung KI, Park HYL, Park CK. The effect of anxiety and depression on progression of glaucoma. *Sci Rep*. (2021) 11:1769. doi: 10.1038/s41598-021-81512-0

12. Sabel BA, Wang J, Cárdenas-Morales L, Faiq M, Heim C. Mental stress as consequence and cause of vision loss: the dawn of psychosomatic ophthalmology for preventive and personalized medicine. *EPMA J*. (2018) 9:133–60. doi: 10.1007/s13167-018-0136-8

13. Jung Y, Han K, Wang S, Yoon HY, Moon JI. Effect of depressive symptom and depressive disorder on glaucoma incidence in elderly. *Sci Rep*. (2021) 11:5888. doi: 10.1038/s41598-021-85380-6

14. Zhang X, Olson DJ, Le P, Lin F-C, Fleischman D, Davis RM. The association between Glaucoma, anxiety, and depression in a large population. *Am J Ophthalmol*. (2017) 183:37–41. doi: 10.1016/j.ajo.2017.07.021

15. Thau AJ, Rohn MCH, Biron ME, Rahmatnejad K, Mayro EL, Gentile PM, et al. Depression and quality of life in a community-based glaucoma-screening project. *Can J Ophthalmol*. (2018) 53:354–60. doi: 10.1016/j.jcjo.2017.10.009

16. Di Ciò F, Garaci F, Minosse S, Passamonti L, Martucci A, Lanzafame S, et al. Reorganization of the structural connectome in primary open angle Glaucoma. *Neuroimage Clin*. (2020) 28:102419. doi: 10.1016/j.nicl.2020.102419

17. Schafer A, Rouland JF, Peyrin C, Szaffarczyk S, Boucart M. Glaucoma affects viewing distance for recognition of sex and facial expression. *Invest Opthalmol Vis Sci*. (2018) 59:4921–8. doi: 10.1167/iovs.18-24875

18. Olson IR, Plotzker A, Ezzyat Y. The enigmatic temporal pole: a review of findings on social and emotional processing. *Brain*. (2007) 130:1718–31. doi: 10.1093/brain/awm052

19. Von Der Heide RJ, Skipper LM, Olson IR. Anterior temporal face patches: a meta-analysis and empirical study. *Front Hum Neurosci*. (2013) 7:17. doi: 10.3389/fnhum.2013.00017

20. Kong XM, Zhu WQ, Hong JX, Sun XH. Is glaucoma comprehension associated with psychological disturbance and vision-related quality of life for patients with glaucoma? A cross-sectional study. *BMJ Open*. (2014) 4:e004632. doi: 10.1136/bmjopen-2013-004632

21. Arrigo A, Aragona E, Saladino A, Arrigo D, Fantaguzzi F, Battaglia Parodi M, et al. Cognitive dysfunctions in Glaucoma: an overview of Morpho-functional mechanisms and the impact on higher-order visual function. *Front Aging Neurosci*. (2021) 13:747050. doi: 10.3389/fnagi.2021.747050

22. Delavar A, Bu JJ, Radha Saseendrakumar B, Weinreb RN, Baxter SL. Gender disparities in depression, stress, and social support among Glaucoma patients. *Transl Vis Sci Technol*. (2023) 12:23. doi: 10.1167/tvst.12.12.23

23. Engel GL. The need for a new medical model: a challenge for biomedicine. *Science (1979)*. (1977) 196:129–36. doi: 10.1126/science.847460

24. Miles E. Biopsychosocial Model In: Gellman MD, Turner JR. editors *Encyclopedia of behavioral medicine*. New York, NY: Springer (2013). 227–8.

25. Nelson P, Aspinall P, Papasouliotis O, Worton B, O'Brien C. Quality of life in Glaucoma and its relationship with visual function. *J Glaucoma*. (2003) 12:139–50. doi: 10.1097/00061198-200304000-00009

26. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder. *Arch Intern Med*. (2006) 166:1092. doi: 10.1001/archinte.166.10.1092

27. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. *J Gen Intern Med*. (2001) 16:606–13. doi: 10.1046/j.1525-1497.2001.016009606.x

28. Hayes AF. *Introduction to mediation, moderation, and conditional process analysis: a regression-based approach*. *2nd* ed. New York: The Guilford Press (2018).

29. World Health Organization. Vision impairment including blindness. *International Classification of Diseases Eleventh Revision (ICD-11)* (2021). Available at: https://icd.who.int/browse/2024-01/mms/en#1103667651 (Accessed February 10, 2024).

30. Manea L, Gilbody S, McMillan D. Optimal cut-off score for diagnosing depression with the patient health questionnaire (PHQ-9): a meta-analysis. *Can Med Assoc J*. (2012) 184:E191–6. doi: 10.1503/cmaj.110829

31. Plummer F, Manea L, Trepel D, McMillan D. Screening for anxiety disorders with the GAD-7 and GAD-2: a systematic review and diagnostic metaanalysis. *Gen Hosp Psychiatry*. (2016) 39:24–31. doi: 10.1016/j.genhosppsych.2015.11.005

32. Ajith B, Najeeb N, John A, Anima V. Cross sectional study of depression, anxiety and quality of life in glaucoma patients at a tertiary Centre in North Kerala. *Indian J Ophthalmol*. (2022) 70:546. doi: 10.4103/ijo.IJO_1389_21

33. Gkioka M, Almpanidou S, Lioti N, Almaliotis D, Karampatakis V. Daily functionality of people with low vision: the impact of visual acuity, depression, and life orientation—a cross-sectional study. *Behav Neurol*. (2024) 2024:1–10. doi: 10.1155/2024/4366572

34. Klauke S, Sondocie C, Fine I. The impact of low vision on social function: the potential importance of lost visual social cues. *J Optom*. (2023) 16:3–11. doi: 10.1016/j.optom.2022.03.003

35. Berchuck S, Jammal A, Mukherjee S, Somers T, Medeiros FA. Impact of anxiety and depression on progression to glaucoma among glaucoma suspects. *Br J Ophthalmol*. (2021) 105:1244–9. doi: 10.1136/bjophthalmol-2020-316617

36. Wang SY, Singh K, Lin SC. Prevalence and predictors of depression among participants with Glaucoma in a nationally representative population sample. *Am J Ophthalmol*. (2012) 154:436–444.e2. doi: 10.1016/j.ajo.2012.03.039

37. Kong X, Yan M, Sun X, Xiao Z. Anxiety and depression are more prevalent in primary angle closure Glaucoma than in primary open-angle Glaucoma. *J Glaucoma*. (2015) 24:e57–63. doi: 10.1097/IJG.0000000000000025

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 13 June 2024
DOI 10.3389/fmed.2024.1269332

OPEN ACCESS

EDITED BY
Alessio Martucci,
University of Rome Tor Vergata, Italy

REVIEWED BY
Christophe Orssaud,
Georges Pompidou European, France
Ferdinando Cione,
University of Salerno, Italy

*CORRESPONDENCE
Shamira Perera
✉ shamiraperera@gmail.com

RECEIVED 29 July 2023
ACCEPTED 03 June 2024
PUBLISHED 13 June 2024

CITATION
Chaung JQ, Sangapillai T, Quilat KK and Perera S (2024) A comparison of intraocular pressure measurement using SUOER SW-500 rebound tonometer and conventional reusable Goldmann prisms.
Front. Med. 11:1269332.
doi: 10.3389/fmed.2024.1269332

A comparison of intraocular pressure measurement using SUOER SW-500 rebound tonometer and conventional reusable Goldmann prisms

Jia Quan Chaung[1,2], Thanendthire Sangapillai[1], Karen Kate Quilat[1] and Shamira Perera[1,2,3]*

[1]Singapore National Eye Centre, Singapore, Singapore, [2]Singapore Eye Research Institute, Singapore, Singapore, [3]Duke-NUS Medical School, Singapore, Singapore

Introduction: To determine the agreement between intraocular pressure (IOP) measurements using conventional Goldmann applanation tonometry (GA[1,2]T) and SUOER SW-500 Rebound Tonometer.

Methods: This was a retrospective observational study where 205 eyes of 106 glaucoma patients had their IOPs measured by 2 fellowship trained ophthalmologists. Data were analyzed using the Bland–Altman method of differences. Correlation was measured using the Pearson coefficient.

Results: Most of our patients were Chinese (88.7%) and female (51.9%). The average age was 66.9years. The range of IOPs as measured by GAT was 2 to 58mm Hg. Using the Bland–Altman method to compare GAT and SUOER SW-500 Rebound Tonometer. The tonometer overestimated the IOP by 0.5mm Hg in the right eye and underestimated it by 0.1mm Hg in the left eye. Overall, the tonometer overestimated the IOP by 0.2mmHg. The Tonometer IOP correlated well with GAT, with a Pearson coefficient of correlation(r) of 0.89 (p<0.001) for the right eye and 0.86 (p<0.001) for the left eye, respectively. In patients with GAT IOP ≥ 21mm Hg (n=25), the Tonometer underestimated the IOP by 2.96mm Hg.

Discussion: The IOP measurements from the SUOER SW-500 Rebound Tonometer correlates well with the conventional GAT in measuring the IOP within normal ranges of IOP. SUOER SW-500 Rebound Tonometer may be of use, especially if the risk of transmission of infection is high considering that the probes are disposable. It is easy to use and its small size and portability makes it useful in situations where the patient is unable to be examined at the slit lamp.

KEYWORDS

glaucoma, rebound tonometer, IOP, intraocular pressure, Goldmann applanation tonometry

Introduction

Goldmann applanation tonometry (GAT) has been the gold standard for measuring intraocular pressure (IOP) for decades. IOP is the major modifiable risk factor for glaucoma and its measurement is integral for appropriate management. Treatment of glaucoma is mainly directed at lowering IOP. However, not all patients are able to

be examined under a slit lamp and hence may not be suitable for GAT.

The SUOER Rebound Tonometer (RBT; model SW-500) is a hand-held, lightweight and contact tonometer that measures IOP with the help of a disposable probe. The motion parameters of the probe is recorded through an induction based coil system. The deceleration of the probe is analysed. The deceleration speed correlates with IOP. For example, the higher the IOP, the faster the deceleration of the probe and the shorter is the duration of impact.

A number of studies have compared the accuracy of different portable RBT, in particular between the GAT and versions of the Icare (e.g. IC100, IC200, Care Pro, TA01i) which are similar in design to the SUOER SW-500 Tonometer. However, these studies have published rather inconsistent results. Some studies reported under measurement of IOP by the Icare in comparison to GAT (1, 2). Other studies found Icare overestimates IOPs when compared to GAT (3–5). While other studies have also reported no significant differences in mean IOP measured by Icare compared to GAT when the IOP measured was in the normal ranges (6, 7) and even at extremes of IOP (8). The cause of these differences are uncertain, it is likely that there may be a multiple factors contributing to this difference. This includes the variability in the patients' age range, sample size of study, study bias, ethnicity, previous glaucoma filtration surgery, whether they were healthy subjects or subjects with pre-existing glaucoma. Moreover, external factors such as central corneal thickness, corneal astigmatism and even altitude can affect the reliability of IOP measurement (9, 10).

The advantage of RBT over GAT is its portability and that it does not require topical anesthetics or fluorescein staining. Its portability allows IOP measurements in situations that the GAT may be difficult to use such as in young children, in the operating room, bed-bound patients. The disposable probes also reduces cross contamination. As IOP measurements with the RBT does not require topical anesthetics, it also reduces the risks of damaging the corneal surface while measuring IOP.

To this date, it is our understanding that there are no published studies that compares the performance of the SUOER SW-500 Rebound tonometer against the gold standard GAT. As the SUOER SW-500 rebound tonometer may be a potential portable screening tool for IOP, we have decided to compare its accuracy in IOP measurements against the GAT.

Materials and methods

Patient selection

One hundred and six patients that underwent follow-up visits at the Singapore National Eye Centre Glaucoma Clinic were included in our study. The principles of the declaration of Helsinki were adhered to and approval from the Singapore Eye Research Institute's Institutional Review Board was obtained for a retrospective review of these prospectively collected cases. Patients were excluded if they were under 21 years of age, had corneal abnormalities that might render IOP measurements inaccurate (severe epithelial/stromal edema, large central scars), patients with corneal dystrophies, previous corneal refractive surgery or corneal transplantation, active ocular infection, poor cooperation, or refused to participate. Prior corneal refractive surgery as well as corneal transplants affects the overall reliability of IOP measurements (11–13). Furthermore, since corneal thickness was not measured, these patients were excluded.

IOP measurement

After instillation of proparacaine hydrochloride 0.5% and application of sterile fluorescein 10% strips, IOP was measured on a slit lamp biomicroscope for both eyes of each participant. The IOP of the right eye was measured first using conventional GAT followed by SUOER SW-500 rebound tonometry. Subsequently, the IOP of the left eye was measured using SUOER SW-500 rebound tonometry followed by GAT. These measurements were taken at the same clinic setting and at the same time. IOP measurement was performed by 2 fellowship trained ophthalmologists. As previous research has reported that repeat tonometry induces a decrease in IOP and that there is a consensual decrease in IOP in the other eye (14) our methodology eliminated this bias by not using GAT readings more than once per eye.

The study used a separate IOP measurer and reader and by having the tonometer reset to 10 mm Hg before each reading. One person adjusted the dial in a masked manner, and a second person recorded the value.

Statistical analysis

In terms of sample size calculation, a sample of 64 patients was needed ($\alpha = 0.05$, $\beta = 0.80$ and S.D. 2.0 mmHg). Sample size was estimated with the G*Power program (version 3.1.9.6, University Dusseldorf, Germany). All statistical analyses were performed using Statistical Package for the Social Sciences version 29.0 (SPSS Inc., Chicago, IL). Normality check of data was performed with Kolmogorov–Smirnov and Shapiro–Wilk Tests. Both IOP measured by GAT and SW-500 Rebound tonometer were not normally distributed ($p < 0.001$). We plotted the differences between the 2 methods against their average (the Bland–Altman method of differences). The Pearson coefficient of correlation was calculated for each eye.

Results

There were 106 (205 eyes) participants of which 51 were male and 45 were female (Table 1). The race proportion was 88.7% Chinese, 3.8% Malay, 5.7% Indian, 1.9% Other Ethnicities. The average age was 66.9 years (range, 26 to 89 years).

The mean IOP of the right eye was 15.1 mm Hg (95% CI, 14.0–16.3 mm Hg) using conventional prisms and 15.6 mm Hg (95% CI, 14.8–16.5 mm Hg) with the SUOER SW-500 rebound tonometer. The mean IOP of the left eye was 16.3 mm Hg (95% CI, 14.9–17.8 mm Hg) using conventional prisms and 16.2 mm Hg (95% CI, 15.2–17.2 mm

TABLE 1 Demographics of glaucoma clinic patients.

Female Sex (%)	51.9
Mean age (*y*) (range)	66.9 (26–89)
Race (% Chinese, % Malay, % Indians, % others)	88.7, 3.8, 5.7, 1.9

Hg) with the SUOER SW-500 rebound tonometer. The range of IOP was 2 to 58 mm Hg. Using the Bland–Altman method of differences, the SW-500 Tonometer overestimated the IOP by 0.5 mm Hg in the right eye (Figure 1) and underestimated it by 0.1 mm Hg in the left eye (Figure 2). The limits of agreement were from −6.07 to 5.08 for the right and from −7.41 to 7.65 for the left eye.

The SUOER SW-500 rebound tonometer correlated well with GAT, with a Pearson coefficient of correlation(r) of 0.89 ($p < 0.001$) for the right eye (Figure 3) and 0.86 ($p < 0.001$) for the left eye (Figure 4). In our cohort of 25 eyes with IOP ≥ 21 mm Hg (Figure 5), we found that the SUOER tonometer underestimated the IOP by 2.96 mm Hg with limits of agreement being from −9.51 to 15.43. Based on the SW500 product information page, the precision of this device is ±1.5 mmHg for IOPs in the range of 3 mmHg to 25 mmHg, and ± 2.5 mmHg for IOPs in the range of 25 mmHg to 70 mmHg. In our study, for patients in the IOP ≥21 group, 6 out of 10 right eyes fell within a range of ±1.5 mmHg of the GAT measurement; while 3 out of 15 left eyes, fell within the range of ±1.5 mmHg of the GAT measurement.

Discussion

In our study of 205 eyes of 106 patients who attended glaucoma subspecialty clinics, we found that the mean difference in GAT- and SUOER SW-500 Rebound tonometry IOP measurements was between −0.1 to +0.5 mmHg. IOP correlated well with the GAT-measured IOP across a wide range of IOPs, however, the results were not interchangeable.

The SUOER RBT overmeasured IOP compared to GAT in the right and undermeasured IOP in the left eye. Of note, the right eye was measured first with GAT then RBT and then inversed for the left eye. The mean difference was +0.5 mmHg in the right eye and −0.1 mmHg in the left eye. The largest difference in IOPs occurred in eyes with IOPs at extreme ends of the spectrum. The difference in each eye could have been a result of inaccuracies of the RBT for IOPs that were very high and IOPs that were very low. For example, in one eye the GAT measured 58 mmHg but the RBT measured 33 mmHg, underestimating the IOP. At the other end of the IOP spectrum, the GAT measured 2 mmHg but the RBT measured 9 mmHg, overestimating the IOP in this case. Additionally, the right-handed operator may find it more difficult to position the device when measuring the IOP from the right eye and the patient's nose may have been in the way resulting in less consistent measurements in the right eye compared to left eye.

There are various models of Icare in the market. The TA01i, Icare Pro, Icare ic100 and Icare ic-200 are similar in design to the SUOER RBT. However, each tonometer have different characteristics and comparative IOP value measurements. The mean difference in IOP with the SUOER RBT is smaller than those obtained in earlier studies with the Icare ic100. In a large study of 1,000 eyes reported by Subramaniam et al., the Icare consistently underestimated IOP by −4.2 mmHg (SD 4.3) (15). Other studies reported differences in mean IOP measured. In a study of 45 eyes Nakakura et al. reported a mean difference of −2.5 mmHg (SD 2.8); the same author subsequently did a larger study of 106 eyes and reported a difference of −4.2 mmHg (SD 3.0) (16, 17). This may suggest that the SUOER RBT may produce IOP measurements that are more consistent with GAT measurements as compared to the ICare ic100.

In a study of 65 eyes using the Icare TA01i by Salim et al., they reported a mean difference of +2.45 mmHg (SD 4.24). Previous studies with the Icare TA01i have also shown that it records a higher mean IOP

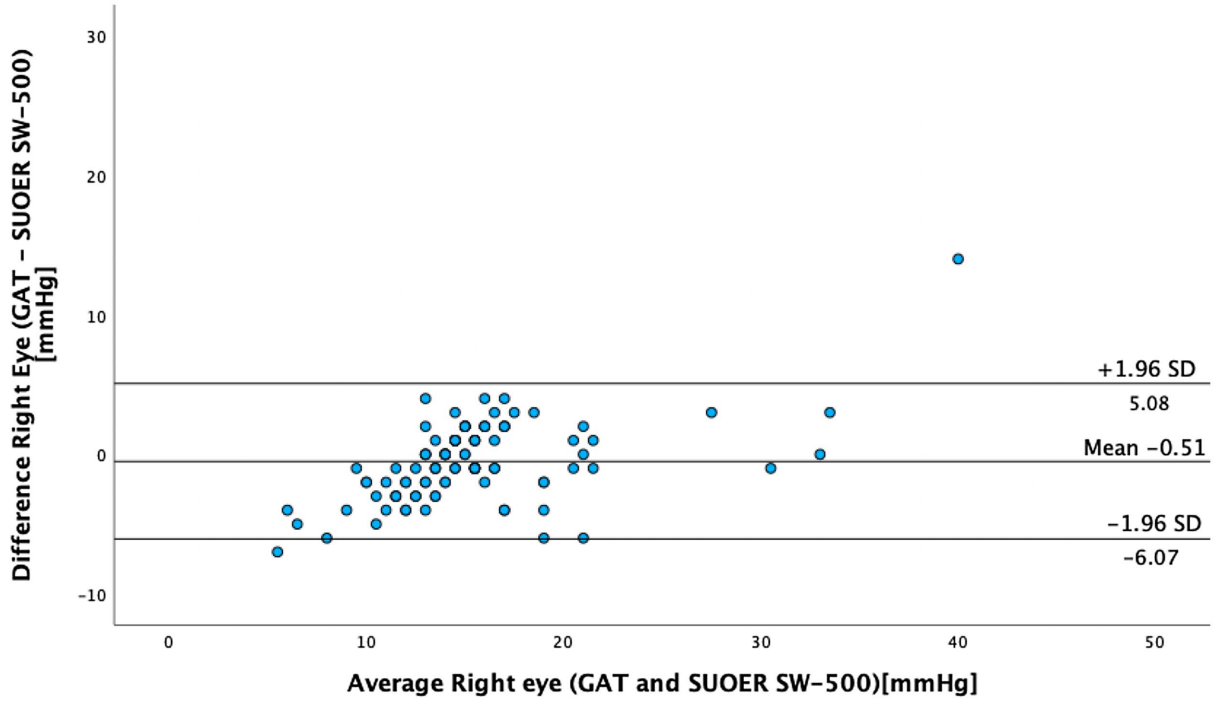

FIGURE 1
The Bland–Altman test of GAT versus SUOER SW-500 right eye.

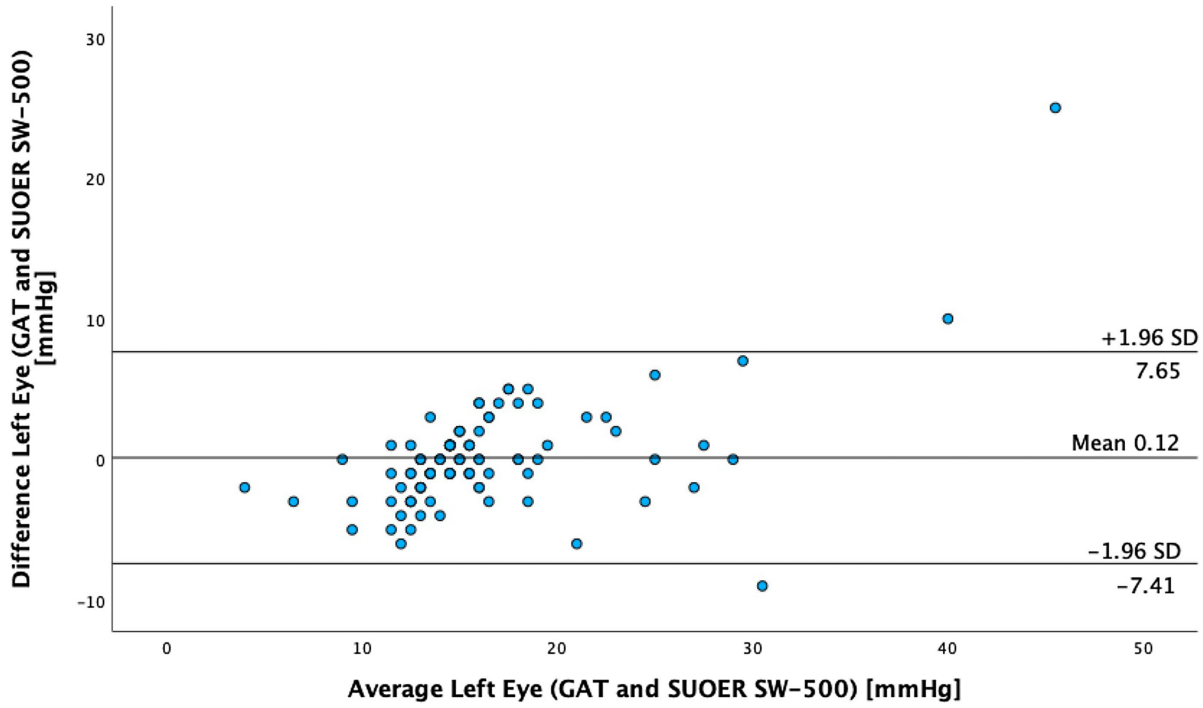

FIGURE 2
The Bland–Altman test of GAT versus SUOER SW-500 left eye.

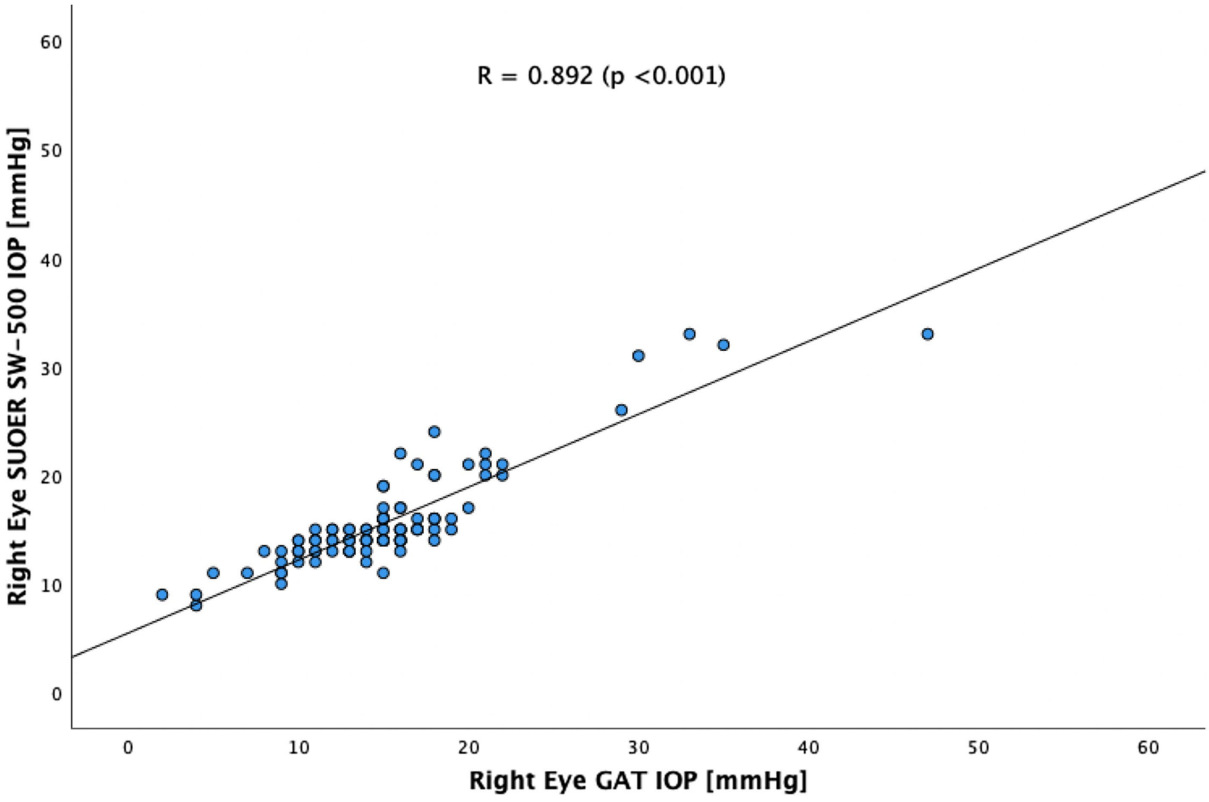

FIGURE 3
Scatter plot of the right eye SUOER SW-500 IOP against the GAT IOP.

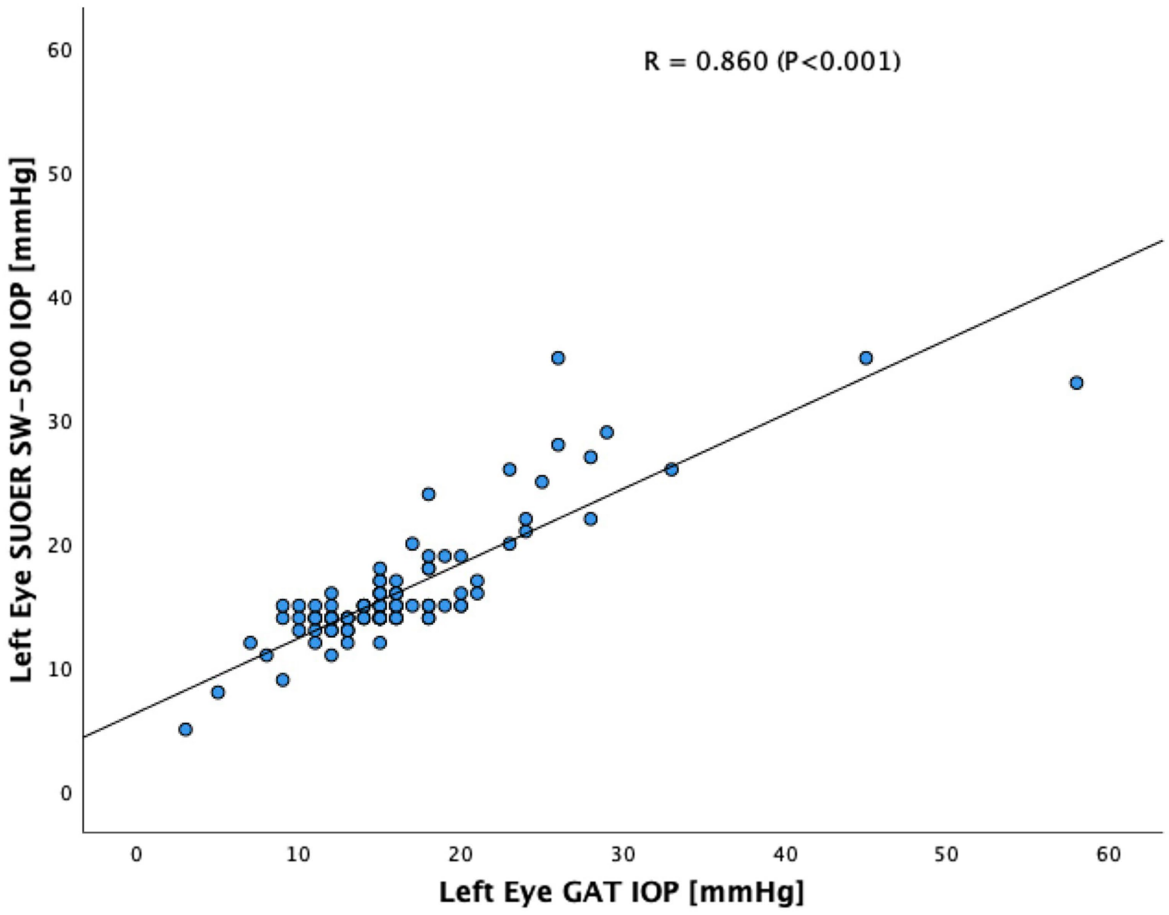

FIGURE 4
Scatter plot of the left eye SUOER SW-500 IOP against the GAT IOP.

than GAT: 3.35 ± 2.28 mmHg (18), 1.40 ± 2.19 mmHg (19), 0.6 ± 3.27 mmHg (20), and 1.49 ± 2.90 mmHg (21). The ICare Pro is the updated version of the Icare TA01i and reportedly gives a mean IOP that is closer to the GAT value. Previous studies showed that the mean IOP difference between Icare PRO and GAT was between −0.38 mmHg to 0.43 mmHg (22, 23). As for the newest model of Icare the IC200, the mean IOP was approximately 3 mmHg lower than that of GAT IOP in a recent study by Nakamura et al. (24). However, 2 other studies comparing the IC200 showed that the IC200 measured a higher IOP than the GAT (18, 25). In a study of 96 Glaucoma and 60 healthy subjects Badakere et al. reported a mean difference of +1.27 mmHg (25). Additionally, Perez-Garcia et al. (18) reported that IC200 measured 0.82 mmHg higher than GAT in a study of 40 patients with congenital glaucoma and 42 healthy subjects. There variations in IOP measurements between the Icare and GAT in previous studies described above, could have been a result of the vastly difference sample size of each study and the extremes of IOP values included. Additionally, IOP measurements by both devices could have been affected by biomechanical properties of the cornea, such as corneal thickness, curvature, underlying corneal pathologies and rigidity which were not evaluated as it was not the focus of these studies.

The SUOER SW-500 Rebound tonometry seemed more inconsistent in measuring higher IOP ≥21 mm Hg. This may limit the scope of the SUOER RBT in routine glaucoma clinics when higher IOPs are encountered. The Early Manifest Glaucoma Trial suggested that a 1 mm increase in IOP is associated with an 11% increase in the hazard ratio in the development of glaucoma (26). Similarly, previous studies on the Icare also suggest poor correlation with GAT at high IOP ranges (≥23 mmHg) (27, 28).

Although the study was conducted in glaucoma clinics, most of the IOPs measured were within the normal range. Our study cannot be applied to eyes with corneal disease or where surgery has been performed (e.g., Fuchs endothelial dystrophy, excimer laser surgery, lamellar or penetrating keratoplasty), as these patients were excluded. Additionally, the 2 groups could have been randomized to have either the right or the left eye measured first with our set protocol of IOP measurement. Other limitations of this study was the relatively small sample size of our subgroup of 25 eyes with IOP ≥ 21 mm Hg. A larger sample size of glaucoma patients with both low and high IOP values would have been ideal. We acknowledge that bilateral eyes were included but Bootstrap or generalized estimating equations were not used to account for inter-eye correlation this may have led to smaller *p*-values with eyes in the same group (29). However, we decided that our study's primary focus is on comparing the performance of the SW500 tonometer against the GAT, rather than assessing individual patient-level variations in IOP and hence decided that the correlation between eyes of the sample patient is less relevant to our research question. Ocular parameters such as corneal thickness and axial length were not included. Additionally, our study did not test

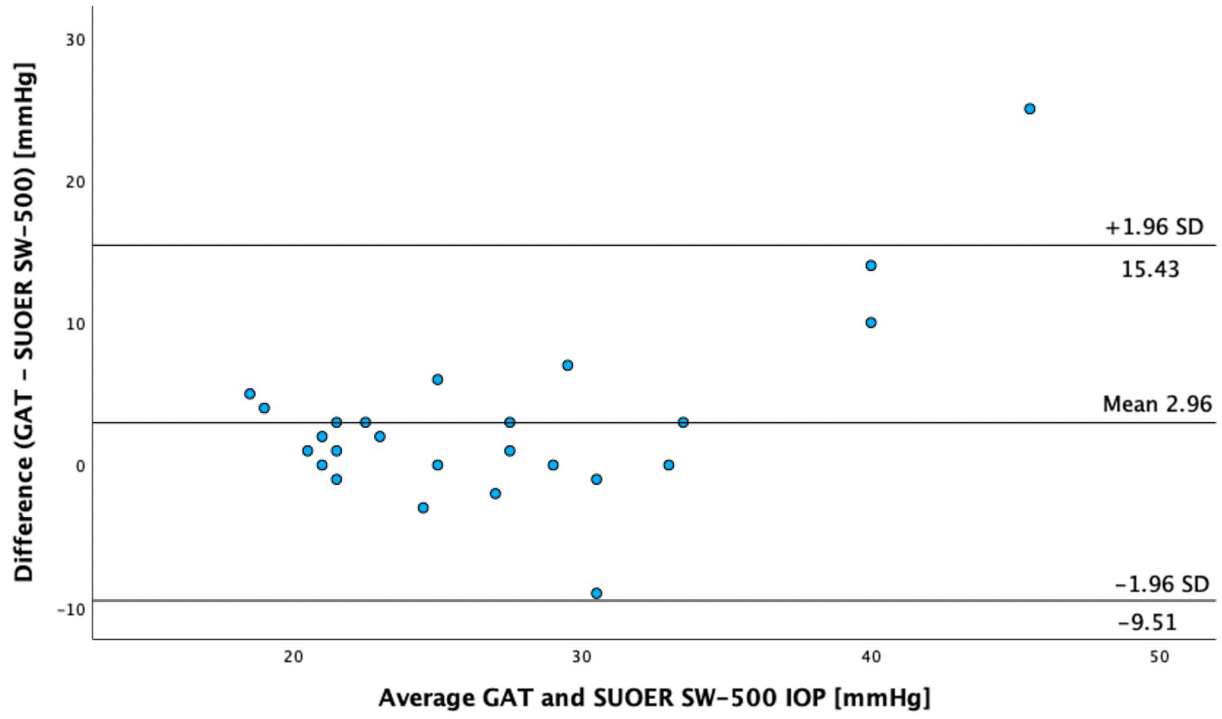

FIGURE 5
The Bland–Altman test GAT versus SUOER SW-500 (for intraocular pressure ≥21 mm Hg).

IOP with patients in the supine position which may be relevant to its future use in bedbound patients. De Bernado et al. evaluated IOP in sitting, supine, prone, and standing positions and again 5 minutes after standing, utilizing an Icare Pro (ICP) and a Tono-Pen Avia (TPA). They reported an agreement between the 2 devices which both confirmed the increase in IOP in the supine position, and also an increase after prolonged standing (30). In a study by Avitabile et al. (28) on the effects of refractive errors on IOP measurements obtained with RBT and GAT, they reported RBT readings to be >2 mm Hg in 17.9% (emmetropic), 13.3% (hyperopic), 34.5% (myopic), and 7.6% (astigmatic) eyes. Given our high prevalence of Myopia in Singapore, underlying myopia and other forms of refractive efforts may have had an effect on IOP readings by RBT.

The portability and ease of use of the SUOER Rebound tonometer makes it a potential alternative in mass eye screenings and for patient that otherwise are unable to be examined on the slit lamp. The disposable tips may help with the prevention of spread of infectious organisms. Besides adenovirus, more destructive organisms commonly implicated in contact lens-related microbial keratitis such as Pseudomonas, Staphyloccocus, and Acanthamoeba may also be spread by tonometer tips. Additionally, the SUOER SW-500 Rebound tonometer may be a good potential tool for home screening of IOP by a patient's caregiver. Its inbuild software is able to store the last 999 IOP readings and may provide the reviewing clinician a good understanding of the IOP trend of the patient across an extended period. The Bluetooth capability of the tonometer also allows IOP measurements to be fed to the patient or caregiver's smart phone. This may allow the patient to be more present with their management of glaucoma. In developing countries where more infectious eye diseases prevail, disposable rebound tonometer tips would confer a major advantage. The cost is also much lower than the iCare and the device is powered by 2AA batteries. In comparison to the iCare, it can also be used vertically as well as horizontally as it has an electromagnet that holds the probe in place. Additionally, it also connects to an infrared pocket printer to make hard copies of measured IOP data.

In conclusion, we have shown that the SUOER SW-500 Rebound tonometer-measured IOP correlates well with the GAT-measured IOP especially when IOP is in the normal range, but the results are not interchangeable during any transition period or from site to site. We acknowledge the SUOER SW-500 Rebound tonometer is not a substitute for GAT in the glaucoma clinic where general IOP measurements may higher. However, the SUOER SW-500 rebound tonometer presents a viable alternative to GAT in several circumstances such as where GAT measurements cannot be done, where spread of ocular infection is of concern or in the setting of mass health screenings.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Singapore Eye Research Institute Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

JC: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. TS: Data Curation, Writing – review & editing. KQ: Data Curation, Writing – review & editing. SP: Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Salim S, Du H, Wan J. Comparison of intraocular pressure measurements and assessment of intraobserver and interobserver reproducibility with the portable ICare rebound tonometer and Goldmann applanation tonometer in glaucoma patients. *J Glaucoma*. (2013) 22:325–9. doi: 10.1097/IJG.0b013e318237caa2

2. Hladíková E, Pluháček F, Marešová K. Comparison of measurement of intraocular pressure by ICARE PRO® tonometer and Goldman applanation tonometer. *Cesk Slov Oftalmol*. (2014) 70:90–3.

3. Rehnman JB, Martin L. Comparison of rebound and applanation tonometry in the management of patients treated for glaucoma or ocular hypertension. *Ophthalmic Physiol Opt*. (2008) 28:382–6. doi: 10.1111/j.1475-1313.2008.00571.x

4. Motolko MA, Feldman F, Hyde M, Hudy D. Sources of variability in the results of applanation tonometry. *Can J Ophthalmol*. (1982) 17:93–5.

5. López-Caballero C, Contreras I, Muñoz-Negrete FJ, Rebolleda G, Cabrejas L, Marcelo P. Rebound tonometry in a clinical setting. Comparison with applanation tonometry. *Arch Soc Esp Oftalmol*. (2007) 82:273–8.

6. Chen M, Zhang L, Xu J, Chen X, Gu Y, Ren Y, et al. Comparability of three intraocular pressure measurement: iCare pro rebound, non-contact and Goldmann applanation tonometry in different IOP group. *BMC Ophthalmol*. (2019) 19:225. doi: 10.1186/s12886-019-1236-5

7. Pahlitzsch M, Brünner J, Gonnermann J, Maier AKB, Torun N, Bertelmann E, et al. Comparison of ICare and IOPen vs Goldmann applanation tonometry according to international standards 8612 in glaucoma patients. *Int J Ophthalmol*. (2016) 9:1624–8.

8. Pakrou N, Gray T, Mills R, Landers J, Craig J. Clinical comparison of the Icare tonometer and Goldmann applanation tonometry. *J Glaucoma*. (2008) 17:43–7. doi: 10.1097/IJG.0b013e318133fb32

9. De Bernardo M, Casaburi C, De Pascale I, Capasso L, Cione F, Rosa N. Comparison between dynamic contour tonometry and Goldmann applanation tonometry correcting equations. *Sci Rep*. (2022) 12:20190. doi: 10.1038/s41598-022-24318-y

10. Albis-Donado O, Ramirez-Neria P, Rios-Acosta N, Stalmans I. The influence of altitude on the differences between Goldmann tonometry and Pascal dynamic contour tonometry: an ecological meta-analysis. *Indian J Ophthalmol*. (2024) 72:S398–403. doi: 10.4103/IJO.IJO_907_23

11. Ajazaj V, Kaçaniku G, Asani M, Shabani A, Dida E. Intraocular pressure after corneal refractive surgery. *Med Arch*. (2018) 72:341–3. doi: 10.5455/medarh.2018.72.341-343

12. Saini C, Davies EC, Chodosh J, Shen LQ. Glaucoma in patients with endothelial Keratoplasty. *Cornea*. (2022) 41:1584–99. doi: 10.1097/ICO.0000000000003122

13. Shrivastava A, Madu A, Schultz J. Refractive surgery and the glaucoma patient. *Curr Opin Ophthalmol*. (2011) 22:215–21. doi: 10.1097/ICU.0b013e3283477c73

14. Whitacre MM, Stein R. Sources of error with use of Goldmann-type tonometers. *Surv Ophthalmol*. (1993) 38:1–30. doi: 10.1016/0039-6257(93)90053-A

15. Subramaniam AG, Allen P, Toh T. Comparison of the Icare ic100 rebound tonometer and the Goldmann Applanation tonometer in 1,000 eyes. *Ophthalmic Res*. (2021) 64:321–6. doi: 10.1159/000511455

16. Nakakura S. Icare® rebound tonometers: review of their characteristics and ease of use. *Clin Ophthalmol*. (2018) 12:1245–53. doi: 10.2147/OPTH.S163092

17. Nakakura S, Mori E, Fujio Y, Fujisawa Y, Matsuya K, Kobayashi Y, et al. Comparison of the intraocular pressure measured using the new rebound tonometer Icare ic100 and Icare TA01i or Goldmann Applanation tonometer. *J Glaucoma*. (2019) 28:172–7. doi: 10.1097/IJG.0000000000001138

18. Perez-Garcia P, Morales-Fernandez L, Saenz-Frances F, Mendez-Hernandez CD, Garcia-Feijoo J, Santos-Bueso E, et al. Comparison of intraocular pressure measured using the new Icare 200™ rebound tonometer and the Perkins™ applanation tonometer in healthy subjects and in patients with primary congenital glaucoma. *Arch Soc Esp Oftalmol*. (2021) 96:175–80. doi: 10.1016/j.oftal.2020.06.007

19. Nakamura M, Darhad U, Tatsumi Y, Fujioka M, Kusuhara A, Maeda H, et al. Agreement of rebound tonometer in measuring intraocular pressure with three types of applanation tonometers. *Am J Ophthalmol*. (2006) 142:332–4. doi: 10.1016/j.ajo.2006.02.035

20. van der Jagt LH, Jansonius NM. Three portable tonometers, the TGDc-01, the ICARE and the Tonopen XL, compared with each other and with Goldmann applanation tonometry. *Ophthalmic Physiol Opt*. (2005) 25:429–35. doi: 10.1111/j.1475-1313.2005.00318.x

21. Nakakura S, Mori E, Yamamoto M, Tsushima Y, Tabuchi H, Kiuchi Y. Intraocular pressure of supine patients using four portable tonometers. *Optom Vis Sci*. (2013) 90:700–6. doi: 10.1097/OPX.0b013e3182972df4

22. Güler M, Bilak Ş, Bilgin B, Şimşek A, Çapkin M, Hakim RA. Comparison of intraocular pressure measurements obtained by Icare PRO rebound tonometer, Tomey FT-1000 noncontact tonometer, and Goldmann applanation tonometer in healthy subjects. *J Glaucoma*. (2015) 24:613–8. doi: 10.1097/IJG.0000000000000132

23. Jablonski KS, Rosentreter A, Gaki S, Lappas A, Dietlein TS. Clinical use of a new position-independent rebound tonometer. *J Glaucoma*. (2013) 22:763–7. doi: 10.1097/IJG.0b013e318259aa47

24. Nakakura S, Asaoka R, Terao E, Nagata Y, Fukuma Y, Oogi S, et al. Evaluation of rebound tonometer iCare IC200 as compared with IcarePRO and Goldmann applanation tonometer in patients with glaucoma. *Eye Vis*. (2021) 8:25. doi: 10.1186/s40662-021-00249-z

25. Badakere SV, Chary R, Choudhari NS, Rao HL, Garudadri C, Senthil S. Agreement of intraocular pressure measurement of Icare ic200 with Goldmann Applanation tonometer in adult eyes with Normal cornea. *Ophthalmol Glaucoma*. (2021) 4:89–94. doi: 10.1016/j.ogla.2020.08.004

26. Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M, et al. Reduction of intraocular pressure and glaucoma progression: results from the early manifest Glaucoma trial. *Arch Ophthalmol*. (2002) 120:1268–79. doi: 10.1001/archopht.120.10.1268

27. Munkwitz S, Elkarmouty A, Hoffmann EM, Pfeiffer N, Thieme H. Comparison of the iCare rebound tonometer and the Goldmann applanation tonometer over a wide IOP range. *Graefes Arch Clin Exp Ophthalmol*. (2008) 246:875–9. doi: 10.1007/s00417-007-0758-3

28. Avitabile T, Longo A, Rocca D, Amato R, Gagliano C, Castaing M. The influence of refractive errors on IOP measurement by rebound tonometry (ICare) and Goldmann applanation tonometry. *Graefes Arch Clin Exp Ophthalmol*. (2010) 248:585–91. doi: 10.1007/s00417-009-1176-5

29. Hoffer KJ, Aramberri J, Haigis W, Olsen T, Savini G, Shammas HJ, et al. Protocols for studies of intraocular lens formula accuracy. *Am J Ophthalmol*. (2015) 160:403–405.e1. doi: 10.1016/j.ajo.2015.05.029

30. De Bernardo M, Abbinante G, Borrelli M, Di Stasi M, Cione F, Rosa N. Intraocular pressure measurements in standing, sitting, and supine position: comparison between Tono-pen Avia and Icare pro Tonometers. *J Clin Med*. (2022) 11:6234. doi: 10.3390/jcm11216234

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 23 July 2024
DOI 10.3389/fmed.2024.1402606

OPEN ACCESS

EDITED BY
Alessio Martucci,
University of Rome Tor Vergata, Italy

REVIEWED BY
Haoyu Wang,
Sheffield Teaching Hospitals NHS Foundation Trust, United Kingdom
Massimo Cesareo,
University of Rome Tor Vergata, Italy

*CORRESPONDENCE
Julio González-Martín-Moro
julio.gonzalez@salud.madrid.org

RECEIVED 17 March 2024
ACCEPTED 21 June 2024
PUBLISHED 23 July 2024

CITATION
González-Martín-Moro J, Fernández Miguel Y, Castro-Rebollo M, Izquierdo-Rodríguez C, Prieto-Garrido FL, Padeira Iranzo V, Mittendrein V, Miralles Pechuan V, Ruiz-Pomeda A and Cobo-Soriano R (2024) Ocular hypertension after EyeCee One preload lens implantation: a retrospective cohort study.
Front. Med. 11:1402606.
doi: 10.3389/fmed.2024.1402606

Ocular hypertension after EyeCee One preload lens implantation: a retrospective cohort study

Julio González-Martín-Moro[1,2]*, Yolanda Fernández Miguel[1], María Castro-Rebollo[1], Carlos Izquierdo-Rodríguez[1], Francisco Luis Prieto-Garrido[1], Victoria Padeira Iranzo[1], Vanesa Mittendrein[1], Vicente Miralles Pechuan[1], Alicia Ruiz-Pomeda[3] and Rosario Cobo-Soriano[1,2]

[1]Department of Ophthalmology; Hospital Universitario del Henares, Fundación para la Investigación e Innovación Biomédica del Hospital Universitario Infanta Sofía y del Hospital Universitario del Henares (FIIB HUIS HHEN), Madrid, Spain, [2]Department of Health Sciences; Universidad Francisco de Vitoria, Madrid, Spain, [3]Department of Optometry and Vision, Faculty of Optics and Optometry, Universidad Complutense de Madrid, Madrid, Spain

Objective: In 2022, several cases of ocular hypertension (OHT) related to EyeCee One preloaded IOLs were reported. The aim of this study was to determine the presurgical and surgical variables associated with this response.

Methods and analysis: An analysis was conducted on patients who underwent isolated cataract surgery between September 2022 and December 2022 at the Hospital Universitario del Henares. The influence of potential factors was studied using the Kruskal–Wallis test and multiple regression analysis.

Results: A total of 353 cataract surgeries were included in the study. No significant differences between the different IOLs were found related to a change in the IOP on the first postoperative day (p=0.395), but the change in the IOP after 1month was higher in the EyeCee One group (p=0.016). Approximately 6.1% of the patients who received EyeCee One had an IOP increase greater than 10mmHg, compared to only 0.8% of the patients who received other IOLs. The odds ratio (OR) of experiencing an IOP increase greater than 10mmHg in the EyeCee One group at the 1-month visit was 7.99 (1.52–41.99). The multiple regression analysis showed that receiving the EyeCee One lens was associated with a 2-mmHg increase in IOP. A previous history of glaucoma or OHT was not associated with greater IOP. Two patients in the EyeCee One group developed severe visual loss.

Conclusion: Patients who received the EyeCee One IOL experienced significant increases in IOP at the 1-month visit. A small number of patients might suffer visual loss secondary to the rise in IOP.

KEYWORDS

cataract surgery, EyeCee One, intraocular lens, glaucoma, intraocular pressure

1 Introduction

During the last months of 2022, a number of cases of ocular hypertension (OHT) following uncomplicated cataract surgery were reported in Spain and other countries (1). These cases of unexplained postoperative OHT were later associated with the EyeCee One preloaded and the

EyeCee One Crystal preloaded IOLs, manufactured by NIDEK and distributed by Bausch&Lomb. An internal investigation at NIDEK identified the coating agent used in the nozzle portion of the injector, polyvinylpyrrolidone (PVP), as the reason why the drainage pathway of aqueous humor was obstructed, leading to an increased intraocular pressure (IOP). These cases prompted the laboratory to halt distribution and issue a recall of these lenses (1). The EyeCee One IOLs used in our study were confirmed to be part of the affected batch identified by NIDEK (NIDEK, July 2023).

Various risk factors for acute OHT on the first day after cataract surgery have been suggested, such as incomplete removal of viscoelastic material, surgery performed by a resident, male patients, a prior history of glaucoma or pseudoexfoliation, axial length greater than 25 mm, poor pupillary dilation, tamsulosin use, or corticosteroid response (2, 3). However, to date, only one study has linked one model of intraocular lens (IOL) to changes in postoperative IOP values (1, 4).

Very few articles have been published on this topic, as these cases constitute a recently discovered condition (1). OHT is often asymptomatic and not always accompanied by pain, ocular inflammation, or significant corneal edema. While elevated IOP can sometimes lead to symptoms such as pain or visual disturbances, it may be detected during routine eye exams without any obvious clinical signs.

In the ophthalmology department of the Hospital Universitario del Henares, six different models of IOLs were implanted in 2022. We analyzed the postoperative IOP of the entire cohort of patients undergoing cataract surgery at our center during the 3 months prior to the withdrawal of the lens. The objective of this study is to determine whether the observed increase in IOP is an idiosyncratic response or if the entire cohort of patients receiving the EyeCee One lens experienced higher IOP after surgery. Additionally, the study aims to identify preoperative characteristics of patients and intraoperative variables that could be related to this atypical outcome.

2 Materials and methods

This study was conducted with the entire cohort of patients undergoing cataract surgery at the Ophthalmology Department of the Hospital Universitario del Henares from 1 September 2022 to 12 December 2022. This timeframe coincided with the period of higher incidence of this side effect in Spain, just before Bausch&Lomb and NIDEK decided to discontinue the commercialization of the IOL and to withdraw supplies from hospitals. The sample was created using convenience sampling, focusing on November, when the first cases were detected in our center. The Hospital Universitario del Henares is a level 1 hospital serving a population of approximately 200,000 inhabitants. Eleven experienced surgeons and two residents performed cataract surgery during the study period. Only isolated cataract surgery was considered in the study. Combined cataract surgery with vitrectomy or glaucoma was considered an exclusion criterion. Rupture of the posterior capsule with sulcus IOL implantation was also an exclusion criterion, as it involves the implantation of a different IOL model. Other complications, including the rupture of the posterior capsule, were not considered exclusion criteria, provided one of the usual in-the-bag-IOLs was implanted.

In our center, patients undergoing uncomplicated cataract surgery are typically seen the day after surgery and between 4 and 6 weeks later (1-month post-cataract surgery visit). If deemed necessary, the surgeon schedules intermediate visits. The first visit includes a slit lamp examination and IOP measurement using an air tonometer. The patient follows a treatment regime combining topical ofloxacin every 4 h during the daytime for the first week and topical dexamethasone, 1 drop every 4 h for the first week, gradually decreasing over 5 weeks. Additional medications, such as bromfenac, anti-edema ointment, or ocular hypotensives, may be added at the surgeon's discretion. The 1-month visit, prior to discharge, includes IOP measurement, patient visual acuity, automated refraction, and a fundus examination. Goldman tonometry is only performed in cases where IOP is high, or the patient has a history of glaucoma.

To conduct the study, information from the digital surgical formularies was transferred into an Excel database. These surgical questionnaires capture all intraoperative information minutes after the surgical procedure has been completed, including epidemiological variables (age and gender), clinical variables (alpha-adrenergic blockers intake, drug allergies, and comorbidities), and variables related to the surgical procedure (type of anesthesia, surgical complications, use of trypan blue, intracameral use of phenylephrine or acetylcholine, type of intracameral antibiotic, IOL power, axial length, and anterior chamber depth). To complete the database, the electronic clinical charts of the patients were reviewed to add information regarding the presence of glaucoma, the number of antiglaucoma drugs, presurgical visual acuity, and postsurgical visual acuity in the previous month. Since most patients are not refracted before or after cataract surgery (if the visual result has been optimal), pinhole visual acuity was used as an approximate measure of the best-corrected distance visual acuity. IOP at the pre-cataract surgery appointment was considered baseline IOP. If this information was not available on the last visit before surgery, it was obtained from the nearest visit that included it. IOP was also measured on the first day and at the 1-month post-cataract surgery visit. Since IOP after cataract surgery in our center is usually measured using air tonometry, air tonometry data were preferred if both air tonometry and applanation tonometry records were available. Nuclear cataract grade (assessed using the LOCS III classification) was also recorded and considered a surrogate variable of cataract severity.

During the study period, in addition to the EyeCee One, other five models of IOL were implanted: PhysIOL® 123 Micropure IOL, J&J® Tecnis Eyhance DIB00, the Alcon® ACU00T0, Alcon® SN6CWS, and Alcon® AcrySof Toric SN6ATx.

The information, along with data obtained from surgical protocols, was entered into an Excel database and analyzed using SPSS (SPSS 22, IBM Corporation). The main variables were the change in IOP on the first day after surgery (first day IOP - baseline IOP) and the change of IOP at the 1-month visit (1-month visit IOP - baseline IOP). The normality of the variables was assessed using the Kolmogorov–Smirnov test. The three IOLs marketed by Alcon (ACU00T0, SN6CWS Alcon®, and AcrySof Toric SN6ATx Alcon®), which share the same platform and material, were grouped for statistical analysis and optimization. There were two main dependent variables: the change in IOP compared to preoperative IOP on the first postoperative day and at the 1-month visit. The

Kolmogorov–Smirnov test showed that neither of the two variables followed a normal distribution, so a non-parametric approach was carried out.

Demographic variables were expressed in terms of means and standard deviations, except for visual acuity, which, as measured using a decimal scale, is non-parametric and therefore was expressed as median and interquartile range. Changes in IOP were expressed both ways. The Kruskal–Wallis test was used to initially compare the four IOL models. In a second approach to increase statistical power, the change in pressure experienced by the eyes that received the EyeCee One implant was compared to a group containing eyes that received any of the other IOLs.

The influence of potential confounding variables in the association between the studied IOL model and IOP was studied using multiple regression analysis. The possible association of the change in IOP with the IOL model was also graphically analyzed using box plots. The number of patients that experienced IOP elevations exceeding 5 and 10 mmHg from baseline was determined, and tables were created to assess the risk of peak IOP exceeding 5 and 10 mmHg associated with the EyeCee One implant.

The study was conducted in accordance with the Declaration of Helsinki after obtaining approval from the clinical research committee of the University Hospital of La Princesa. (Study Number: 5237).

3 Results

During the 15 weeks of the study, 355 cataract surgeries were performed on 349 patients. Only six patients underwent cataract surgery on both eyes during the period of study. In these six cases, cataract surgery was performed on different days. Two eyes were excluded from the study due to posterior capsule rupture that required the implantation of a three-piece IOL in the sulcus and thus the final number of patients included in the analysis was 353. Table 1 shows the presurgical characteristics and intraoperative variables of the eyes included in the study. The average age of the patients was lower in the group that received the J&J® Tecnis Eyhance DIB00 and PhysIOL® Micropure 123 IOLs. Preoperative visual acuity, nuclear cataract grade, and biometric values were similar in all four groups. All patients, except 8, underwent surgery with topical anesthesia and 1% intracameral lidocaine (Table 1). The proportion of patients on whom trypan blue, intracameral phenylephrine, or intracameral acetylcholine were used was also similar in the four groups (Table 1). Cefuroxime was predominantly used as an intracameral antibiotic in all four groups (Table 1). The proportion of patients experiencing zonular dehiscence and intraoperative floppy iris syndrome (IFIS) was similar in all four groups (Table 1). The proportion of patients with glaucoma or OHT before surgery ranged between 8 and 9% in three of the groups, but it was lower for the Tecnis Eyhance IOL. These patients were younger, with glaucoma present in only 3.8% of the cases. Consequently, the number of antiglaucoma drugs used in this group was lower than in the other three groups.

No significant differences were found in the change in IOP associated with the use of the four IOLs on the first postoperative day ($p = 0.395$), but differences were observed in the change in IOP after 1 month ($p = 0.016$). Contrasts between pairs of IOLs in the IOP change after 1 month showed statistically significant differences between the EyeCee One and the Eyhance IOL ($p = 0.03$) and between the EyeCee One IOL and the Alcon IOL group (ACU00T0 or SN6CWS Alcon® or AcrySof Toric SN6ATx) ($p = 0.017$). However, after applying the Bonferroni correction for multiple comparisons, only the first comparison remained statistically significant ($p = 0.016$).

To achieve greater statistical power, the EyeCee One IOL was compared to the rest of the IOLs. In this analysis, no differences were found on the first postoperative day between the group receiving the EyeCee One implant and those receiving other IOLs. However, differences were observed after 1 month of surgery ($p = 0.005$).

These groups include patients with higher values of IOP at both postoperative visits (Figures 1, 2). The distribution of IOPS was not symmetrical. The box plot showed the median IOP is higher, the interquartile range is asymmetrical, skewed toward higher values of IOP, and there were several outliers. There was a small group of patients who exhibited a very noticeable hypertensive response, which mostly accounted for the observed differences. (Figures 1, 2). The OR of having at the 1-month visit an IOP elevation higher than 5 mmHg in the EyeCee One patients was 4.44 (1.92–10.22), and the OR of having an IOP elevation higher than 10 mmHg was 7.99 (1.52–41.99) (Table 2).

The increase in IOP on the first day does not predict the rise in IOP after 1 month; a total of 57 patients had an IOP greater than 10 mmHg the day after surgery; of these, only 2 presented an IOP increase greater than 10 mmHg after 1 month. The OR of showing an increase in IOP greater than 10 mmHg on the first postoperative day and after 1 month was 1.91 (0.36–10.11). Therefore, in our sample, the hypertensive peak on the first postoperative day did not have predictive value for the presence of an elevated IOP after 1 month.

A total of 14 preoperative and intraoperative variables, potentially related to the increase in IOP, were included in a multiple regression model using the backward method, with significance levels of 0.05 for variable inclusion in the model and 0.1 for variable exclusion from the model. The variables included in the model were: age, gender, medical history of glaucoma or intraocular hypertension, nuclear cataract degree, axial length, anterior chamber depth, IOL power, subjective perception of the surgeon of complicated surgery, intraoperative complications, occurrence of IFIS, use of trypan blue, phenylephrine, or acetylcholine, and the use of antibiotic prophylaxis other than the usual (intracameral cefuroxime). The final model included only two variables: the type of IOL (EyeCee One vs. non-EyeCee One), which would be responsible for an increase in IOP between 2 and 3 mmHg; and axial length, which was also associated with higher postoperative IOPs (Table 3).

Patients who experienced this IOL-related hypertensive response did not show intraocular inflammation or corneal edema, and gonioscopy revealed no abnormalities. However, two patients suffered severe visual loss among the patients of the EyeCee One group who developed high postoperative IOP. One suffered post-cataract surgery non-arteritic ischemic optic neuropathy (PCSNAION). In the other case, no optic disk swelling was identified, although severe visual loss and severe thinning of the retina's fiber layer took place over the course of 2 months. No similar cases were observed among the patients who received any of the other IOLs.

10.3389/fmed.2024.1402606

TABLE 1 Presurgical characteristics and intraoperative variables of the eyes included in the study.

		B&L® EyeCee One (*n* = 88)	ACU00T0 or SN6CWS Alcon® or AcrySof Toric SN6ATx (*n* = 113)	J&J® Tecnis Eyhance DIB00 (*n* = 106)	PhysIOL® Micropure 123 (*n* = 46)	Total (*n* = 353)
Preoperative characteristics						
Mean age (SD)		74.7 years (6.6 years)	74.5 years (8.6 years)	68.7 years (9.1 years)	69.6 years (8.7 years)	72.5 years (8.7 years)
Male percentage		44 (50%)	35 (31%)	56 (53%)	17 (37%)	152 (43.2%)
Glaucoma/OHT		8 (9.1%)	9 (8%)	4 (3.8%)	4 (8.7%)	25 (7.1%)
Type of glaucoma						
	OHT	1 (1.1%)	3(2.7%)	1 (0.9%)	0	5(1.4%)
	POAG	5 (5.7%)	1 (0.9%)	1 (0.9%)	1 (2.2%)	8 (2.3%)
	PG	0	2 (1.8%)	0	1 (2.2%)	3 (0.8%)
	PEXG	0	2 (1.8%)	1 (0.9%)	0	3 (0.8%)
	Other	2 (2.3%)	1 (0.9%)	1 (0.9%)	2 (4.3%)	6 (1.8%)
	No	80 (90.9%)	104 (92%)	102 (96.2%)	42 (91.3%)	327 (92.9%)
Number of glaucoma drugs (SD)		0.11 (0.03)	0.13 (0.05)	0.05 (0.02)	0.2 (0.1)	0.11 (0.02)
IOL power (SD)		22.56 D (2.83 D)	21.45 D (3.98 D)	21.01 D (4.58 D)	20.37 D (7.46 D)	21.46 D (4.58 D)
Axial length (SD)		23.13 mm (0.96 mm)	23.41 mm (1.47 mm)	23.65 mm (1.52 mm)	23.95 mm (2.75 mm)	23.48 mm (1.63 mm)
Anterior chamber Depth (SD)		3.11 mm (0.38 mm)	3.10 mm (0.34 mm)	3.21 mm (0.34 mm)	3.12 mm (0.37 mm)	3.14 mm (0.36 mm)
Presurgical VA (median (IQR))		0.5 (0.33–0.60)	0.33 (0.33–0.50)	0.50 (0.33–0.67)	0.50 (0.33–0.51)	0.46 (0.33–0.6)
VA 1 month after cataract surgery (median (IQR))		0.67 (0.5–1)	0.67 (0.60–0.9)	0.67 (0.6–1)	0.67 (0.5–1)	0.67 (0.5–1)
Nuclear cataract grade [median (IQR)]		3 (3–4)	3 (2.5–3.5)	3 (2.1–3.5)	3 (3–3.5)	3 (2.5–3.5)
Surgical variables:						
Anesthesia	General	1 (1.1%)	2 (1.8%)			3 (0.9%)
	Subtenon	1 (1.1%)	1 (0.9%)	1 (0.9%)		3 (0.9%)
	Topical	86 (98%)	110 (97.3%)	105 (99.1%)	46 (100%)	347 (98.2%)
Trypan blue		12 (13.6%)	18 (16.1%)	15 (14.2%)	2 (4.3%)	47 (13.4%)
Intracameral phenylephrine		39 (44%)	39 (35%)	32 (30%)	19 (41%)	129 (36.7%)
Intracameral acetylcholine		4 (4.5%)	5 (4.5%)	4 (3.8%)	2 (4.3%)	15 (4.3%)
Antibiotic prophylaxis	Cefuroxime	80 (91%)	109 (97%)	99 (93%)	43 (97%)	331 (94%)
	Moxifloxacin	8 (9%)	2 (2%)	6 (6%)	3 (7%)	19 (5.4%)
	Vancomycin	-	1 (1%)	1 (1%)		2 (0.6%)
Zonular disinsertion		2 (2%)	0	1 (1%)	1 (2%)	4 (1.1%)
IFIS		8 (9%)	10 (9%)	5 (4.7%)	3 (6.5%)	26 (7.4%)
Postoperative change in IOP:						
First day	Mean (SD)	7.57 mmHg(8.59 mmHg)	5.13 mmHg (6.28 mmHg)	5.47 mmHg (6.15 mmHg)	5.58 mmHg (6.53 mmHg)	5.83 mmHg (6.87 mmHg)
	Median (IQR)	5 mmHg (2–8.5 mmHg)	4 mmHg (1.75–8 mmHg)	5 mmHg (2–9 mmHg)	5 mmHg (0–10 mmHg)	5 mmHg (2–8.5 mmHg)

(Continued)

TABLE 1 (Continued)

		B&L® EyeCee One (*n* = 88)	ACU00T0 or SN6CWS Alcon® or AcrySof Toric SN6ATx (*n* = 113)	J&J® Tecnis Eyhance DIB00 (*n* = 106)	PhysIOL® Micropure 123 (*n* = 46)	Total (*n* = 353)
	Eyes with IOP rise>5 mmHg	42 (48.3%)	43 (39.8%)	39 (37.5%)	23 (50%)	147 (42.6%)
	Eyes with IOP rise>10 mmHg	18 (20.7%)	15 (13.9%)	15 (14.4%)	11 (23.9%)	59 (17.1%)
1 month	Mean (SD)	1.56 mmHg (5.88 mmHg)	−0.53 mmHg (3.89 mmHg)	−1.16 mmHg (3.66 mmHg)	−0.24 mmHg (3.53 mmHg)	−0.18 mmHg (4.48 mmHg)
	Median (IQR)	0 mmHg (−2–3.5 mmHg)	−1 mmHg (−3–2 mmHg)	−1 mmHg (−3–1 mmHg)	0 mmHg (−3–2 mmHg)	0 (−3-2)mmHg
	Eyes with IOP > 5 mmHg	14 (17.1%)	7 (6.7%)	3 (3%)	1 (2.2%)	25 (7.6%)
	Eyes with IOP > 10 mmHg	5 (6.1%)	2 (1.9%)	0	0	7 (2.1%)
Cases of NAION		2	0	0	0	2

SD, standard deviation; IQR, interquartile range; OHT, ocular hypertension, VA, visual acuity. AV was measured using a decimal scale.

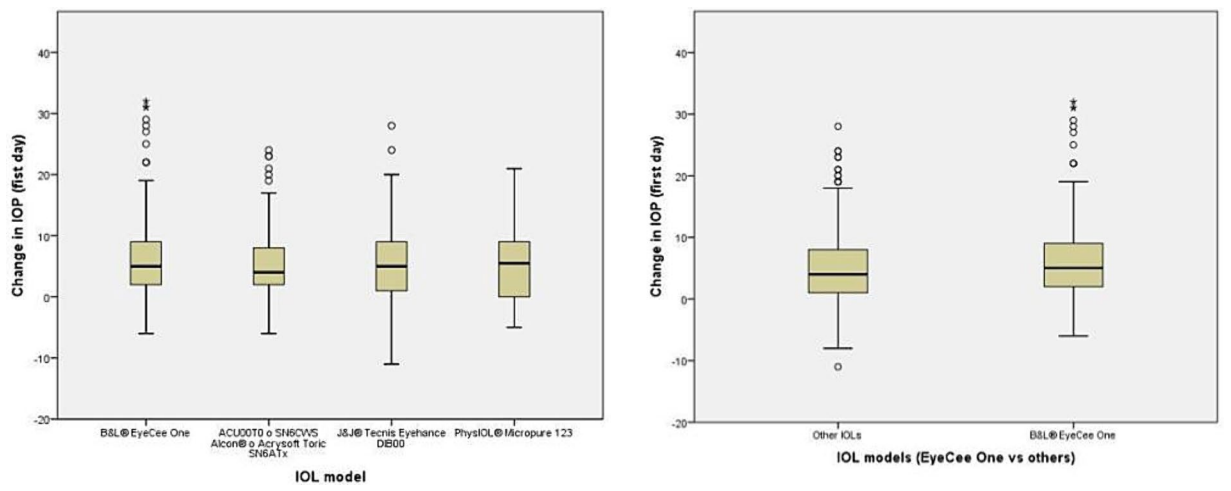

FIGURE 1
Box plot represents the change in IOP on the first day after the cataract surgery.

4 Discussion

In our sample, the implantation of the B&L® EyeCee One IOL was associated with a higher IOP in the postoperative period compared to the other IOLs, both on the first postoperative day and after 1 month. While these differences did not reach statistical significance on the first postoperative day, it is possible that the effect was not observed due to a required incubation period or because the IOL's effect may have been diluted by various intraoperative factors. These factors include incomplete removal of viscoelastic, surgeries performed by residents, male gender, a history of glaucoma or pseudoexfoliation, axial length greater than 25 mm, poor pupil dilation, and the use of tamsulosin. In the case of the change in IOP at the 1-month visit, the association was statistically significant, although IOP elevation was mild in most cases and the change in IOP was severe in only a few patients. As can be appreciated in the box plots, the majority of patients who received the B&L® EyeCee One IOL exhibited pressure changes similar to those who received other prostheses, with the observed differences being attributed to a small group of patients who displayed an anomalous response. It is challenging to determine whether this variability is due to a true idiosyncratic response or if some unidentified variable is involved.

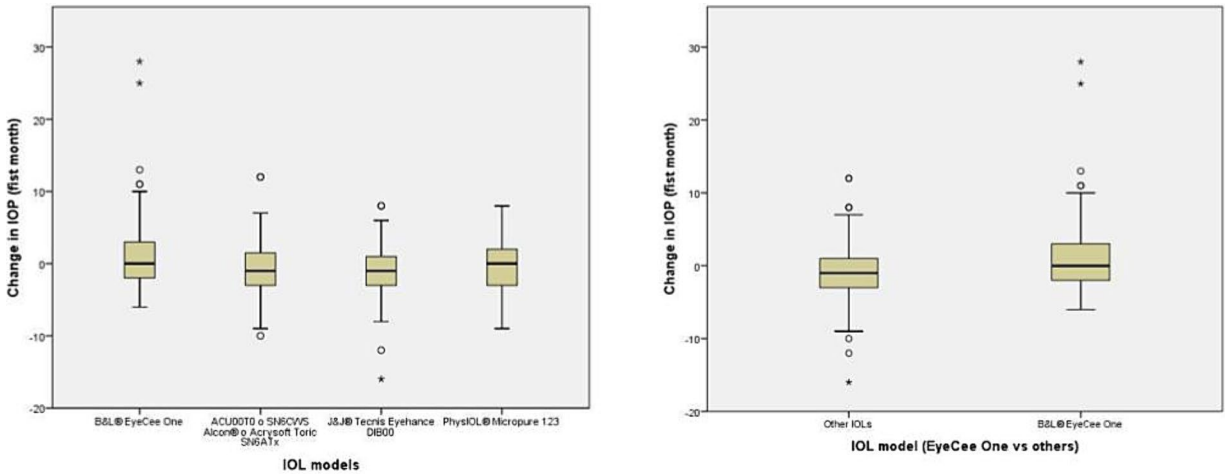

FIGURE 2
Box plot represents the change in IOP during the first month after cataract surgery.

TABLE 2 Association between IOP rise greater than 5 mmHg and 10 mmHg in the EyeCee One at the first-month visit.

		Change in IOP first day				
		<5 mmHg	>5 mmHg		OR	Range
IOL model	Non-B&L® EyeCee One	237 (95.6%)	11 (4.4%)	248	4.44	(1.92–10.22)
	B&L® EyeCee One	68 (82.9%)	14 (17.1%)	82		
		305 (92.4%)	25 (7.6%)	330		
		Change in IOP first month				
		<10 mmHg	>10 mmHg			
IOL model	Non-B&L® EyeCee One	246 (99.2%)	2 (0.8%)	248	7.99	(1.52–41.99)
	B&L® EyeCee One	77 (93.9%)	5 (6.1%)	82		
		323 (97.9%)	7 (2.1%)	330		

TABLE 3 Multiple regression model.

Factor	Coefficient (95% CI)	*p*-value
Axial length	0.55 (0.21–0.89)	0.002
IOL model (EyeCee One vs. non-EyeCee One)	2.39 (1.28–3.50)	0.00006

The most significant variable was the type of intraocular lens.

To determine the type of interaction responsible for this association, preoperative and intraoperative variables were introduced into a multiple regression equation. Two variables were significant: EyeCee One IOL and the axial length. In the logistic regression equation, assuming a linear behavior, each 1 mm increase in axial length would be responsible for a 0.55 mmHg increase in IOP; therefore, it is a small effect from a biological standpoint. This would mean that, after 1 month, an eye with a length of 30 mm would have an IOP approximately 5.5 mmHg higher than an eye with an AL of 20 mm. This effect could be explained by a greater steroid response in myopic patients. Implanting the EyeCee One IOL would result in an increase of almost 2.5 mmHg in IOP, assuming linear behavior, compared to the implantation of other IOLs.

It is interesting to note that neither the perceived subjective complexity of cataract surgery by the surgeon nor the four other variables that could be considered surrogated variables for complexity (nuclear cataract degree, use of trypan blue, phenylephrine, or acetylcholine) were associated with a greater hypertensive response. Furthermore, the hypertensive response does not appear to be related to the use of an intraocular antibiotic other than cefuroxime. Contrary to what was recently published by Jones et al. (1) in our sample, the previous diagnosis of glaucoma or OHT was not associated with a higher risk of developing OHT.

TABLE 4 Summary of the two patients that suffered severe visual loss.

	Patient 1 (Figure 3)	Patient 2 (Figure 4)
	Male, 72 years old, right eye	Female, 71 years old, left eye
Past medical history	Psoriasis, HBP	HBP
Glaucoma or family history of glaucoma	No	No
Surgery	Uneventful. Ultrasound time: 2.35 s. Intracameral lidocaine, no intracameral mydriatics, no capsular staining. IOL power 23 (EyeCee One preloaded)	Uneventful. Ultrasound time: 4.01 s. Intracameral lidocaine, no intracameral mydriatics, no capsular staining. IOL power 23.5 (EyeCee One preloaded)
VA	Presurgical: 0.15 Postsrugical: 0.66	Presurgical: 0.65 Postsurgical: 0.95
Cataract grade	NO2	C3NO4
Postsurgical evolution	Visual loss 7 days after surgery. IOP 42 and optic disk edema. Optic disk atrophy 2 months later.	Intense pain did not make possible IOP measurement on the first day visit. Anterior chamber aqueous tap was performed. After aqueous tap IOP was 25. In the first month visit, she referred to visual field loss.
Endothelial count	Presurgical: 1589 Postsurgical: 1552	Presurgical: 2660 Postsurgical: 2043
Postsurgical gonioscopy	Shaffer grade IV, minimum pigmentation of the trabecular meshwork. No synechiae.	Shaffer grade IV, minimum pigmentation of the trabecular meshwork. No synechiae.

HBP-High blood pressure; RE-right eye; LE-left eye.

Two patients developed severe visual loss among the group that received the EyeCee One IOL (Table 4). One of them was a clear case of PCSNAION (Figure 3). In the other case (Figure 4), the diagnosis was not so clear (it may have been PCSNAION or just a post-cataract surgery acute glaucoma). It is not possible to test the statistical significance of this finding since, among the 264 patients who received other IOLs, no cases of PCSNAION were detected. However, it is possible to compare these figures with historical data from our center and with data from the literature (5). Prior to these cases, we had only diagnosed four cases of PCSNAION, two of which were reported in a previous article on the morphology of disk at-risk patients (6). Considering that cataract surgery has been performed at our center since 2008 and that we operate 1,500 cataracts each year, the previous incidence of PCSNAION among our patients would be 16.7 PCSNAION per 100,000 cataract surgeries.

The incidence of PCSNAION among the 88 patients who were implanted with the EyeCee One would be 2,272 cases in 100,000 (considering both cases as true PCSNAION) or 1,136 in 100,000 (considering only the first case as a true PCSNAION). These incidences are several times higher than the estimated incidence of PCSNAION in our hospital in previous years (16,7 in 100,000), the incidence of PCSNAION in the general population (51.8 in 100,000), and the reported incidence of PCSNAION (7.8 in 100,000) (5) or (10.9 in 100,000) (7). The causal relationship between the IOL and this ischemic event seems plausible, given that the most accepted theories consider that PCSNAION is caused by increased intraoperative or perioperative IOP.

It is notable that the examination of patients who experienced this complication was otherwise normal. Patients who experienced this IOL-related hypertensive response did not show intraocular inflammation or corneal edema, and gonioscopy revealed no abnormalities. Thus, a better understanding of this new form of OHT may be useful in the future in two ways. First, the injection of a high dose of PVP or a related molecule in the anterior chamber may allow for the development of better animal models of glaucoma. Second, it may be useful for the treatment of ocular hypotony.

Animal models of glaucoma are based on genetic selection of individuals with the condition, transgenic animals, obstruction of the trabecular meshwork with particles, or destruction of the trabecular meshwork or episcleral veins (8). Although these models have evolved in recent years, they remain imperfect and unpredictable (8).

Currently, we have an arsenal of drugs and surgical techniques that, with limitations, allow for the treatment of OHT. However, the management of ocular hypotony remains an unresolved issue (9, 10). Serendipity is a very important part of many scientific discoveries. In the history of pharmacology, situations where the identification of a side effect has led to the development of a new drug, potentially useful for treating the opposite condition, are not uncommon. The most well-known case is that of sildenafil in the 1980s (11) but the history of pharmacology is full of similar examples. For instance, the anti-abuse effect of disulfiram was also identified by chance as a side effect when this substance was being researched in the 1940s as a potential anti-scabies drug (12). At present, apart from corticosteroids, ibopamine (13) is the only available drug to treat ocular hypotony, with a very limited effect. A better understanding of the dose-response effect of the substance involved in these increases in IOP may contribute to filling in this gap.

The value of this study is based on the detailed information available for each operated patient and the inclusion of eyes with four different IOL models. The limitations of this study stem from its observational design and the small sample size. In the sample, the distribution of independent variables was similar in all four IOL models (except for age, which was lower in the Tecnis Eyhance DIB00 IOL). However, the choice of IOL could be related to certain clinical or surgical variables that we have not been able to identify and which might be responsible for this atypical evolution. Nevertheless,

10.3389/fmed.2024.1402606

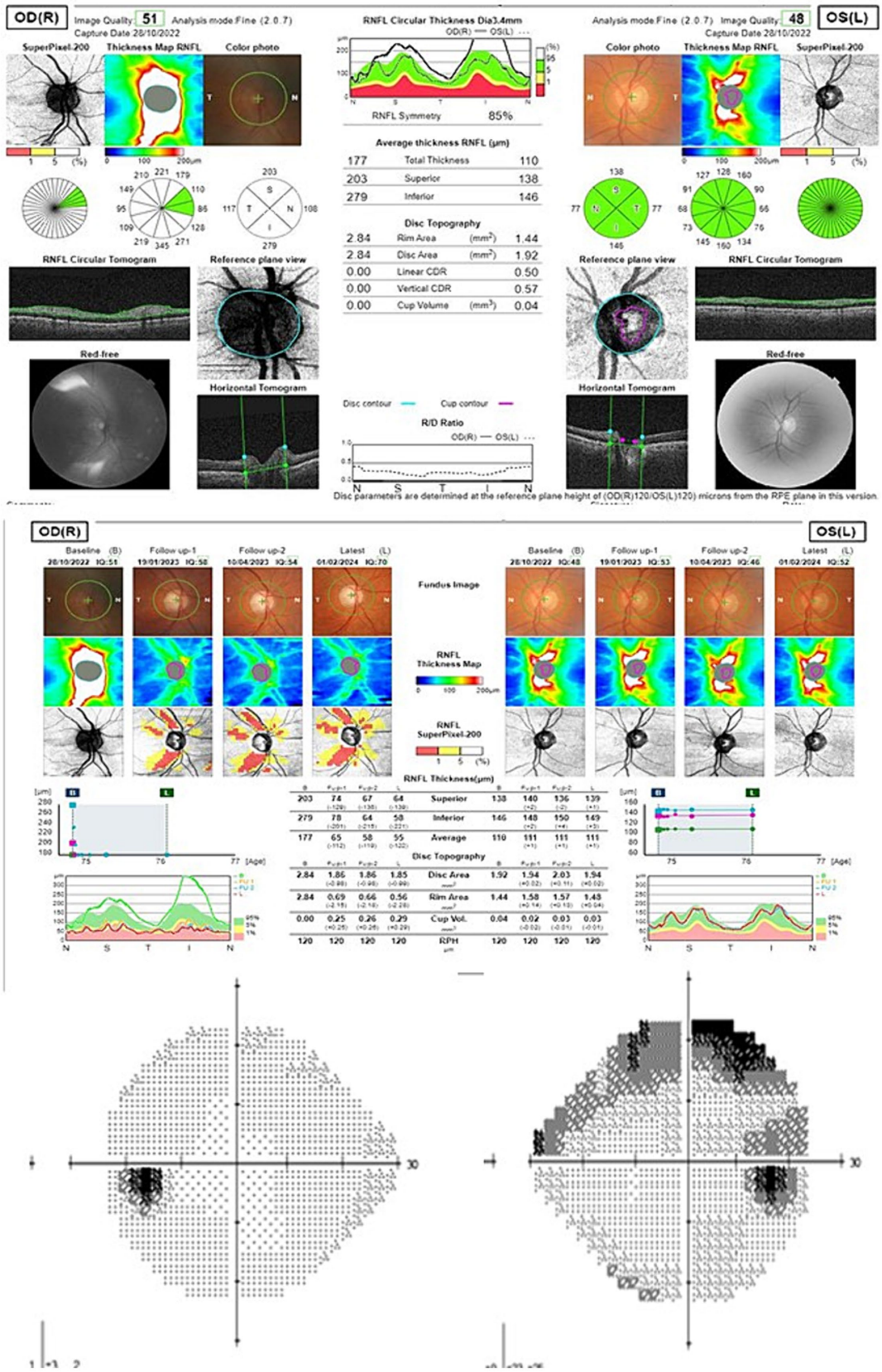

FIGURE 3
Peripapillary retinal nerve fiber layer OCT and 24–2 Visual field of patient 1 (upper scan at onset, middle evolution over the follow-up time; down: final visual field).

10.3389/fmed.2024.1402606

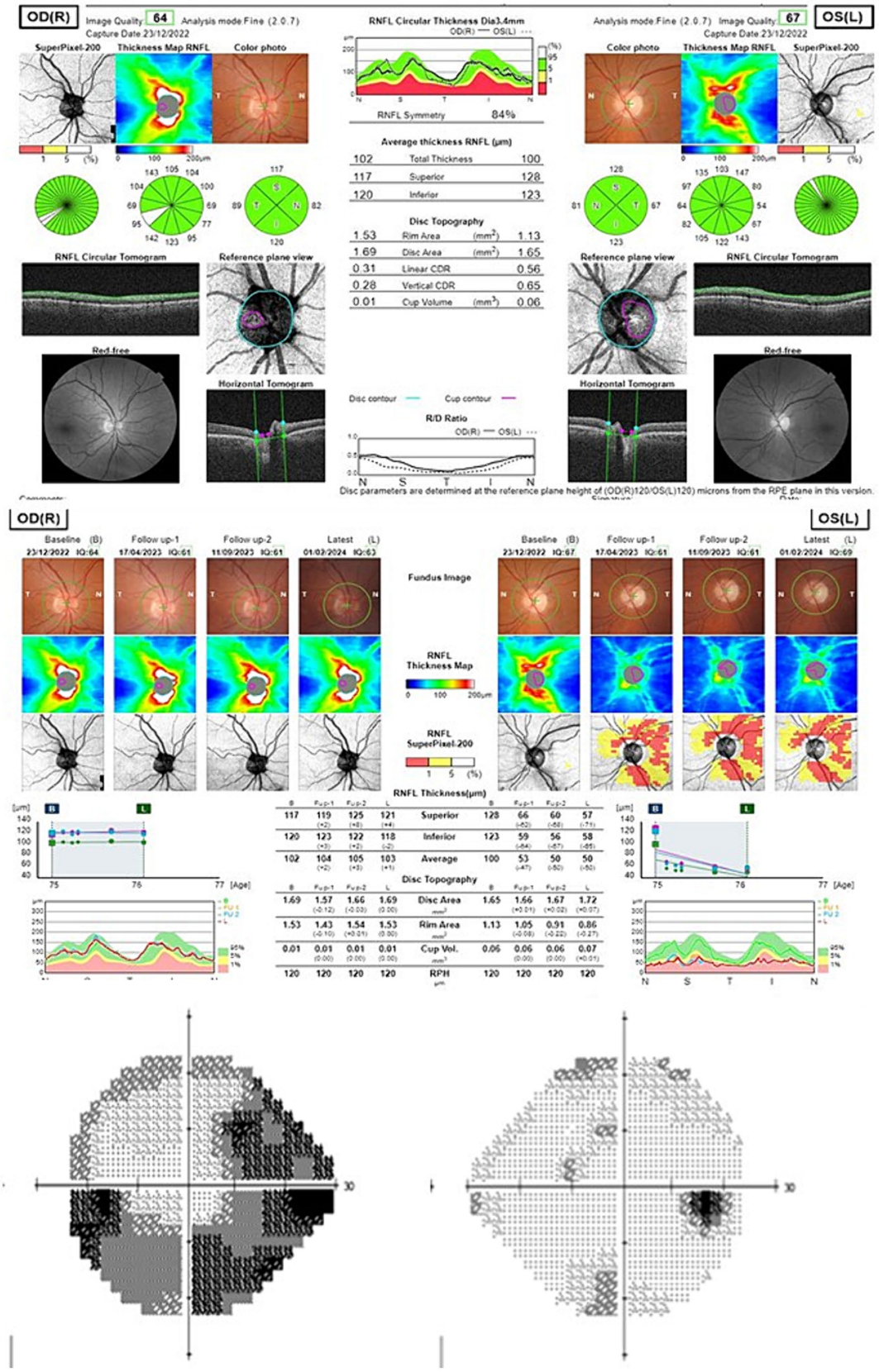

FIGURE 4
Peripapillary retinal nerve fiber layer OCT and 24–2 Visual field of patient 2 (upper scan at onset, middle evolution over the follow-up time; down: final visual field).

intraoperative variables are usually associated more with IOP levels on the first postoperative day, and it is more challenging to understand their relationship with IOP levels in the longer term. Studies using larger samples offering greater statistical power are needed to help understand this perplexing response.

In summary, we can conclude that some of the patients who received the B&L® EyeCee One IOL exhibited a more frequent hypertensive response than those who received other IOLs. At this moment, this response could be considered idiosyncratic, as we have not been able to correlate any of the studied variables with this outcome. In our sample, glaucoma patients did not experience greater IOP change.

In the long run, it would be very interesting to identify the mechanism by which the molecule induces OHT and to determine the dose–response curve of this side effect, which in the future could become a therapeutic effect in certain clinical situations.

State of the question

EyeCee One preloaded IOL-induced ocular hypertension (OHT) in some patients.

There are many drugs and surgical techniques available to reduce intraocular pressure; however, the therapeutic options for treating ocular hypotony are very limited.

How this study might affect research, practice, or policy

The identification of polyvinylpyrrolidone (PVP) as a contributing factor to increased IOP underscores the need for thorough material evaluation and monitoring in IOL manufacturing.

A better understanding of polyvinylpyrrolidone (PVP) induced ocular hypertension could be useful for developing new animal models of glaucoma and new drugs for treating ocular hypotony.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study was approved by the Ethics and Clinical Research Committee of the University Hospital of La Princesa (Study Number: 5237) and conducted in accordance with local legislation and institutional requirements. Since this study is retrospective and reports mostly aggregated data, written informed consent was obtained only from the two participants whose data are shown in Table 4 and Figures 3 and 4.

Author contributions

JGMM: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. YFM: Data curation, Writing – original draft, Writing – review & editing. MCR: Data curation, Writing – original draft, Writing – review & editing. FPG: Data curation, Writing – original draft, Writing – review & editing. VI: Data curation, Writing – original draft, Writing – review & editing. VM: Data curation, Writing – original draft, Writing – review & editing. VPI: Data curation, Writing – original draft, Writing – review & editing. ARP: Data curation, Writing – original draft, Writing – review & editing. RS: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This study was funded by Fundación para la Investigación e Innovación Biomédica del Hospital Universitario Infanta Sofía y del Hospital Universitario del Henares (FIIB HUIS HHEN), Program 312D "Investigación, Docencia y Documentación."

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Jones RK, Jong JLZ, Ramjiani V, Tan JHY. EyeCee one preloaded intraocular lens: are patients with glaucoma more at risk? *BMJ Open Ophthalmol.* (2023) 8:e001433. doi: 10.1136/bmjophth-2023-001433

2. Grzybowski A, Kanclerz P. Early postoperative intraocular pressure elevation following cataract surgery. *Curr Opin Ophthalmol.* (2019) 30:56–62. doi: 10.1097/ICU.0000000000000545

3. Oku H, Mori K, Watanabe M, Aoki T, Wakimasu K, Yamamura K, et al. Risk factors for intraocular pressure elevation during the early period post cataract surgery. *Jpn J Ophthalmol.* (2022) 66:373–8. doi: 10.1007/s10384-022-00918-z

4. Wang H, Jong JLZ, Chiu SJ, Kay WL, Tan JHY. Evaluation of raised intraocular pressure post EyeCee one preloaded intraocular lenses implantation. *Eye (Lond).* (2023) 37:3293–4. doi: 10.1038/s41433-023-02487-y

5. Bhatti MT, Miller NR. Post-cataract surgery optic neuropathy: a chronological narrative review of the literature and speculation on pathogenesis. *Curr Opin Ophthalmol.* (2022) 33:485–93. doi: 10.1097/ICU.0000000000000898

6. Martín-Moro JG, Gutiérrez-Ortiz C, Gómez-Sanz FJ, Contreras I. Disc configuration is also a prognostic factor in non-arteritic ischaemic optic neuropathy. *Neuro-Ophthalmology*. (2015) 39:S66. Available at: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L72282712

7. Moradi A, Kanagalingam S, Diener-West M, Miller NR. Post-cataract surgery optic neuropathy: prevalence, incidence, temporal relationship, and fellow eye involvement. *Am J Ophthalmol*. (2017) 175:183–93. doi: 10.1016/j.ajo.2016.10.008

8. Bouhenni RA, Dunmire J, Sewell A, Edward DP. Animal models of glaucoma. *J Biomed Biotechnol*. (2012) 2012:692609:1–11. doi: 10.1155/2012/692609

9. González-Martín-Moro J, Contreras-Martín I, Muñoz-Negrete FJ, Gómez-Sanz F, Zarallo-Gallardo J. Cyclodialysis: an update. *Int Ophthalmol*. (2017) 37:441–57. doi: 10.1007/s10792-016-0282-8

10. Wang Q, Thau A, Levin AV, Lee D. Ocular hypotony: A comprehensive review. *Surv Ophthalmol*. (2019) 64:619–38. doi: 10.1016/j.survophthal.2019.04.006

11. Andersson K-E. PDE5 inhibitors - pharmacology and clinical applications 20 years after sildenafil discovery. *Br J Pharmacol*. (2018) 175:2554–65. doi: 10.1111/bph.14205

12. Lanz J, Biniaz-Harris N, Kuvaldina M, Jain S, Lewis K, Fallon BA. Disulfiram: mechanisms, applications, and challenges. *Antibiotics*. (2023) 12. doi: 10.3390/antibiotics12030524

13. Ugahary LC, Ganteris E, Veckeneer M, Cohen AC, Jansen J, Mulder PGH, et al. Topical ibopamine in the treatment of chronic ocular hypotony attributable to vitreoretinal surgery, uveitis, or penetrating trauma. *Am J Ophthalmol*. (2006) 141:571–3. doi: 10.1016/j.ajo.2005.09.034

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 07 August 2024
DOI 10.3389/fmed.2024.1410607

OPEN ACCESS

EDITED BY
Alessio Martucci,
University of Rome Tor Vergata, Italy

REVIEWED BY
Ferdinando Cione,
University of Salerno, Italy
Vanja Kopilaš,
University of Zagreb, Croatia

*CORRESPONDENCE
Dong-kan Li
✉ xmecldk@163.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 01 April 2024
ACCEPTED 29 July 2024
PUBLISHED 07 August 2024

CITATION
Lin B, Xu M, Chen L-l and Li D-k (2024) A study exploring the causal relationship between glaucoma and anxiety disorders. *Front. Med.* 11:1410607. doi: 10.3389/fmed.2024.1410607

A study exploring the causal relationship between glaucoma and anxiety disorders

Bin Lin[1,2,3,4,5,6†], Meng Xu[1,2,3,4,5,6†], Long-long Chen[1,2,3,4,5,6] and Dong-kan Li[1,2,3,4,5,6*]

[1]Xiamen Eye Center and Eye Institute of Xiamen University, Xiamen, China, [2]Xiamen Clinical Research Center for Eye Diseases, Xiamen, Fujian, China, [3]Xiamen Key Laboratory of Ophthalmology, Xiamen, Fujian, China, [4]Fujian Key Laboratory of Corneal and Ocular Surface Diseases, Xiamen, Fujian, China, [5]Xiamen Key Laboratory of Corneal and Ocular Surface Diseases, Xiamen, Fujian, China, [6]Translational Medicine Institute of Xiamen Eye Center of Xiamen University, Xiamen, Fujian, China

Background: Glaucoma, a leading cause of global blindness, is characterized by optic nerve damage and visual field loss. Previous studies have suggested a potential association between glaucoma and anxiety disorders. However, the causal relationship between these two conditions remains unclear.

Methods: In this study, we conducted a Mendelian Randomization analysis to investigate the causal relationship between glaucoma and anxiety disorders. We sourced Genome-Wide Association Study (GWAS) datasets for glaucoma and anxiety with the largest sample sizes from the Integrative Epidemiology Unit OpenGWAS (IEU OpenGWAS) project website. Instrumental variables were selected based on specific criteria, and statistical analyses were performed using the R programming language.

Results: After filtering and merging the datasets, a total of 60 Single Nucleotide Polymorphisms (SNPs) were obtained for analysis. Regression models were applied to assess the causal relationship between glaucoma and anxiety disorders. The results from all four methods indicated that glaucoma does not cause anxiety disorders ($p > 0.05$).

Conclusion: Through rigorous Mendelian Randomization analysis, our findings indicate that glaucoma is not a causative factor for anxiety, with minimal influence from confounding factors in this study. These findings enhance our understanding of the relationship between glaucoma and anxiety.

KEYWORDS

glaucoma, anxiety disorders, causal relationship, Mendelian Randomization, GWAS datasets

1 Background

Glaucoma, a leading cause of global blindness, is characterized by optic nerve damage and visual field loss, often culminating in blindness (1). With multifactorial etiology, it affects approximately 5.2 million individuals worldwide, constituting 15% of the global burden of blindness (2). Moreover, due to population aging, its prevalence is expected to rise, projected to affect approximately 112 million people by 2040 (3).

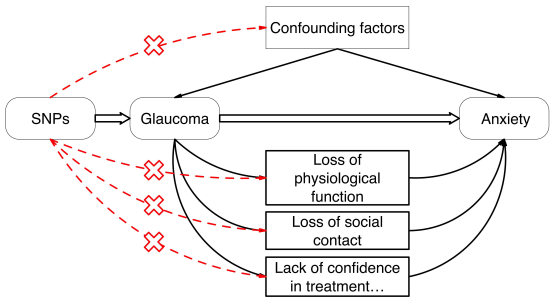

FIGURE 1
The causal relationship between Glaucoma and anxiety can be further confirmed by Mendelian Randomization studies and the effect of confounding factors can be excluded.

Anxiety disorders represent the most prevalent mental health issues globally, significantly impacting individuals' quality of life, work productivity, and societal well-being. Despite being distinct diagnostic entities, anxiety often coexist clinically, demonstrating high comorbidity (4). Globally, it is estimated that 3.7% of individuals will experience Generalized Anxiety Disorder (GAD) at some point in their lives (5). The impact of GAD on functioning and quality of life is comparable to, or even greater than, the effects associated with severe depression and substance abuse disorders (6).

In recent years, increasing attention has been directed toward the high prevalence of anxiety among individuals with glaucoma. These studies suggest that glaucoma is not solely a visually impairing ocular condition but may also be linked to patients' psychological well-being, indicating a close interplay between the two (7–10).

In our research, we employed the two-sample Mendelian Randomization (MR) approach, leveraging Single Nucleotide Polymorphisms (SNPs) as instrumental variables derived from Genome-Wide Association Study (GWAS) summary statistics. This methodology was utilized to explore the potential causal linkage between Glaucoma and Anxiety. By conducting this gene-centric analysis, our goal was to surpass the constraints associated with conventional research methodologies, thereby furnishing more robust evidence in favor of a causal connection between Glaucoma and anxiety, as depicted in Figure 1.

2 Materials and methods

We conducted a Mendelian Randomization investigation to elucidate the potential causal association between Glaucoma and the susceptibility to anxiety. The MR methodology employs genetic variants as instrumental variables to estimate the causal impact of the exposure (Glaucoma) on the outcome (risk of anxiety), while mitigating the influence of confounding factors. All statistical analyses were executed using the R programming language, employing specialized software packages tailored for MR studies such as TwoSampleMR and Mendelian Randomization.

2.1 Data source

We sourced GWAS datasets for Glaucoma (Pubmed ID: GCST90011766) and anxiety (Pubmed ID: GCST007710) with the largest sample sizes from the Integrative Epidemiology Unit OpenGWAS (IEU OpenGWAS) project website.[1] Raw data can be accessed via the respective publications on the Pubmed website. Data retrieval occurred on March 21, 2024. Both datasets comprised European populations without gender restrictions. The Glaucoma dataset encompassed 14,219,919 SNPs, while the anxiety dataset comprised 18,485,882 SNPs.

2.2 Instrumental variable criteria

Criteria for selecting SNPs as instrumental variables were as follows:

(1) The instrumental variables exhibited high correlation with the exposure, with an F-statistic exceeding 10 indicating substantial correlation (11).
(2) Instrumental variables were not directly associated with the outcome but influenced it solely through the exposure, indicating absence of genetic pleiotropy. A pleiotropy test was conducted, with a result of $P \geq 0.05$ signifying no genetic pleiotropy.
(3) Instrumental variables were unrelated to unmeasured confounding factors. Since MR-selected SNPs adhere to the genetic principle of random allele allocation from parents to offspring, their susceptibility to environmental and postnatal factors is minimal. Thus, it was theoretically assumed that instrumental variables remained independent of environmental factors such as socioeconomic and cultural influences (12).

2.3 SNP selection

Meaningful SNPs were selected from the GWAS summary data of Glaucoma based on a screening criterion of $P < 5 \times 10^{-8}$. Each SNP's independence was ensured by setting a linkage disequilibrium coefficient (r^2) of 0.001 and a linkage disequilibrium region width of 10,000 kb, thereby mitigating the potential influence of genetic pleiotropy (13). Glaucoma-associated SNPs were then extracted from the anxiety GWAS summary data, with a minimum $r^2 > 0.8$ to ensure result accuracy. Missing SNPs were directly excluded. The datasets were integrated, and SNPs directly associated with anxiety ($P < 5 \times 10^{-8}$) were filtered out.

2.4 Causal relationship verification

To verify the causal relationship between Glaucoma exposure and anxiety outcome using SNPs as instrumental variables, we

1 https://gwas.mrcieu.ac.uk

TABLE 1 Summary of the selected SNP information.

Number	SNP	CHR	BP	A1	Beta	SE
1	rs10151220	14	34715465	T	−0.0019	0.0015
2	rs10230941	7	117636111	C	0.0013	0.0015
3	rs10248136	7	39077397	T	−0.0022	0.0015
4	rs10517281	4	54027595	A	9.00E−04	0.0015
5	rs10739689	9	129914147	C	6.00E−04	0.0015
6	rs111439095	13	76254433	A	0.0014	0.0015
7	rs1139795	22	19867771	T	0.0013	0.0016
8	rs11658334	17	58830188	A	6.00E−04	0.0017
9	rs11968883	6	158971411	T	0.0022	0.0015
10	rs12208086	6	36586070	A	−0.0026	0.0015
11	rs12540035	7	116159526	A	−0.004	0.0015
12	rs1336980	9	129377855	C	3.00E−04	0.0015
13	rs1649068	10	60304864	A	0.0036	0.0015
14	rs17125973	14	53415359	A	0.0014	0.0015
15	rs17527016	4	111963719	T	−4.00E−04	0.0015
16	rs1972459	7	83287607	A	−0.0021	0.0015
17	rs2113818	2	12890860	T	−0.0016	0.0015
18	rs2472494	9	107695539	T	−0.0022	0.0015
19	rs2514885	8	108277130	T	0.0014	0.0015
20	rs257336	16	65055840	T	0.0054	0.0015
21	rs2579989	6	51460154	T	0	0.0015
22	rs2627761	2	55933014	T	8.00E−04	0.0016
23	rs2667477	12	84023388	T	0.0022	0.0015
24	rs2735114	6	29910034	A	0.001	0.0015
25	rs2745572	6	1548369	A	0.0018	0.0015
26	rs2790049	1	165743523	A	0.0018	0.0015
27	rs2811688	6	134372150	C	−6.00E−04	0.0015
28	rs31916	5	14814883	A	0.0024	0.0015
29	rs33912345	14	60976537	A	9.00E−04	0.0016
30	rs36039219	7	11704538	A	2.00E−04	0.0015
31	rs3753841	1	103379918	A	0.0031	0.0015
32	rs3825942	15	74219582	A	−0.0026	0.0016
33	rs41283694	10	60156574	A	0.0029	0.0016
34	rs41543317	17	44087500	A	−8.00E−04	0.0015
35	rs4414666	2	66537344	T	0	0.0015
36	rs4577906	7	82955177	C	0.0035	0.0015
37	rs4652964	1	38078300	A	0.0012	0.0015
38	rs4653159	1	36579215	A	0.0022	0.0015
39	rs4819641	22	18353630	C	0.0014	0.0015
40	rs55882252	2	153361700	T	0	0.0015
41	rs56233426	3	186128816	A	−0.0028	0.0015
42	rs58073046	11	120248493	A	−0.0011	0.0015
43	rs581796	11	86355565	T	0.003	0.0015
44	rs6117318	20	6507717	A	−9.00E−04	0.0015

(Continued)

TABLE 1 (Continued)

Number	SNP	CHR	BP	A1	Beta	SE
45	rs62283809	3	171820211	T	−0.0015	0.0017
46	rs6475604	9	22052734	T	8.00E−04	0.0015
47	rs6490697	13	22679011	T	−0.0017	0.0016
48	rs6602453	10	10840849	A	−1.00E−04	0.0015
49	rs676015	6	2064648	T	−7.00E−04	0.0015
50	rs6845653	4	7899379	T	0.0032	0.0015
51	rs7137828	12	111932800	T	−0.0064	0.0015
52	rs72482850	1	101117684	A	4.00E−04	0.0015
53	rs7275118	20	18010447	T	−5.00E−04	0.0015
54	rs7284245	22	29613441	T	−4.00E−04	0.0016
55	rs7946009	11	128387422	T	−0.0037	0.0015
56	rs7972874	12	28203245	A	−3.00E−04	0.0015
57	rs935328	15	57538801	A	−0.0022	0.0015
58	rs9494457	6	136474794	A	−4.00E−04	0.0015
59	rs9819278	3	85144350	A	−0.0052	0.0015
60	rs9913911	17	10031183	A	1.00E−04	0.0015

SNP, SNP number; CHR, chromosome number; BP: location, A1: effector allele.

employed four regression models: MR-Egger regression, weighted median estimator (WME), inverse-variance weighted (IVW) random-effects model, and simple model. The IVW method directly calculates causal effect estimates using summary data, without the need for individual-level data. MR-Egger regression fits a linear function by assessing the correlation between each SNP and anxiety (Y) and between each SNP and Glaucoma (X). Sensitivity analysis utilized the leave-one-out method. All analyses were conducted using the TwoSampleMR package (version 0.5.11) in R Studio software (version 4.3.3), with a significance level of $\alpha = 0.05$.

3 Results

3.1 SNP information screening results

A total of 14,219,919 SNP information was obtained for Glaucoma. After filtering based on a criterion of P-value $< 5 \times 10^{-8}$, 4,358 SNPs remained. The file "exposure_GLA.csv" was exported and placed in the TwoSampleMR folder. After renaming the sequence names, SNPs were selected to ensure independence by setting a linkage disequilibrium coefficient (r^2) of 0.001 and a linkage disequilibrium region width of 10,000 kb, excluding the influence of genetic pleiotropy. This resulted in the removal of 4,297 SNPs, leaving 61 SNP data. At this time, the SNP database of anxiety was imported, and the number of SNPs obtained was 18,485,882. Then, the anxiety data and Glaucoma data which just screened were merged, and 60 SNPs were finally obtained (Table 1). Heterogeneity test was carried out on these 60 SNP data, and three sets of outlier data were found, namely data No. 17, 45, and 49. No significant changes were found when they were removed. According to MR Egger regression model, $p = 0.56$, IVW regression model, $p = 0.56$, both of which are greater than 0.05, suggesting that glaucoma does not cause anxiety disorder.

TABLE 2 Regression model results of the four methods.

Four methods MR regression model results				
Method	β	se	OR (95% CI)	*P*
MR-Egger	0.003	0.006	1.004(0.991∼1.016)	0.563
WME	0.000	0.003	1.000(0.995∼1.005)	1.000
IVW	0.002	0.003	0.998 (0.993∼1.004)	0.556
Simple mode	0.002	0.006	1.002 (0.992∼1.013)	0.725

WME, weighted median estimator; IVW, inverse-variance weighted.

3.2 Causal relationship verification

The regression results of the four methods are shown in Table 2. And all the calculation result of the regression models are greater than 0.05. So this Mendelian randomization study tells us that glaucoma patients do not have a higher incidence of anxiety. The scatter plot is shown in Figure 2.

3.3 Sensitivity analysis

The sensitivity analysis was performed using the leave-one-out method, and the results showed that regardless of which SNP was removed, the conclusions have not changed. This suggests that removing any individual SNP would not have a significant impact on the results, indicating the robustness of the MR findings in this

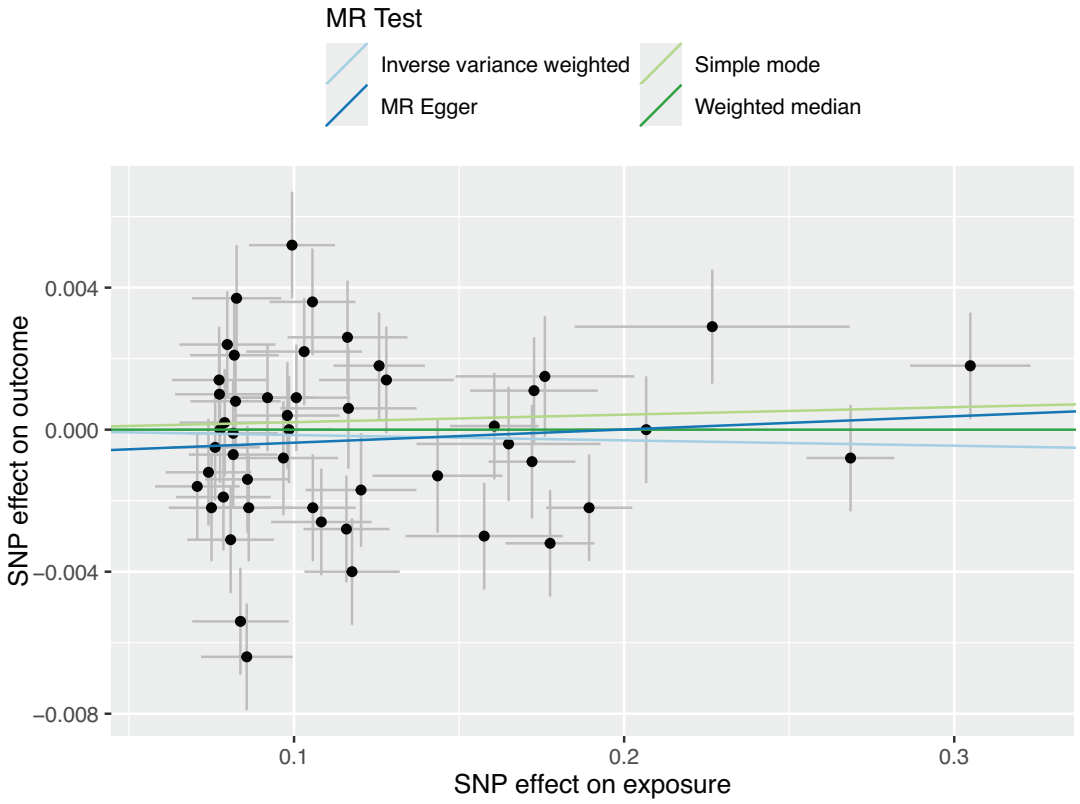

FIGURE 2
Four Scatter plots of regression models are shown in the figure. Apart from the MR Egger regression line, all other regression lines pass through the origin, and the intercept of the MR Egger regression line with the *y*-axis has an absolute value of less than 0.001. This indicates that there is virtually no apparent confounding in this study.

study. The funnel plot and detailed sensitivity analysis results can be found in Figures 3, 4, respectively.

4 Discussion

Glaucoma is characterized by optic neuropathy with a hallmark of progressive loss of retinal ganglion cells (14). Currently, there are no effective treatments for the degeneration of these cells, and the primary goal of glaucoma management is to reduce the intraocular pressure (15) and prevent progression (16). Particularly since intraocular pressure is the only treatable risk factor (17) in clinical practice, both doctors and patients give it special attention, making it a chronic condition that requires lifelong care (18). However, chronic illnesses are often associated with psychological disorders such as anxiety (19, 20). Agorastos et al. (21) found that among glaucoma patients, the prevalence of anxiety in those with visual field defects was 44.8%, compared to 24.3% in those without visual field defects (21). However, DY Shin et al. found that patients with anxiety showed faster rates of Retinal Nerve Fiber Layer (RNFL) decline, as measured by Optical Coherence Tomography (OCT) (10).

There is a substantial body of research indicating high prevalence rates of anxiety among glaucoma patients (22, 23). These studies suggest that the heightened incidence of anxiety may stem from the diagnosis of glaucoma itself, driven by concerns over potential blindness, the financial burdens of treatment, and impaired daily activities (24, 25). Anxiety, as stress responses, are thought to originate in the amygdala (26), eliciting neurotransmitter release and stimulating the autonomic nervous system (ANS), which impacts multiple organs (27). The ANS's response to emotional stress may play a significant role in the development or progression of glaucoma (28, 29). Furthermore, excessive retinal oxidative stress in glaucoma, leading to widespread loss of melanopsin-expressing retinal ganglion cells, plays a critical role in non-visual phototransduction, affecting circadian rhythm changes and melatonin production indirectly (30, 31). Additionally, some glaucoma medications may alter patients' mood (32).

Despite the abundance of studies indicating a link between glaucoma and increased rates of anxiety, contrasting research from various global scholars suggests that glaucoma patients do not exhibit a heightened probability of suffering from these mental health conditions (33–35). All these clinical investigations have yet to definitively establish the causal relationship between glaucoma and anxiety.

Traditional epidemiological studies are hindered by confounding factors and reverse causality, complicating the determination of the true causal relationship between glaucoma and mental health issues. In this context, MR offers a unique approach, utilizing genetic variants as instrumental variables to

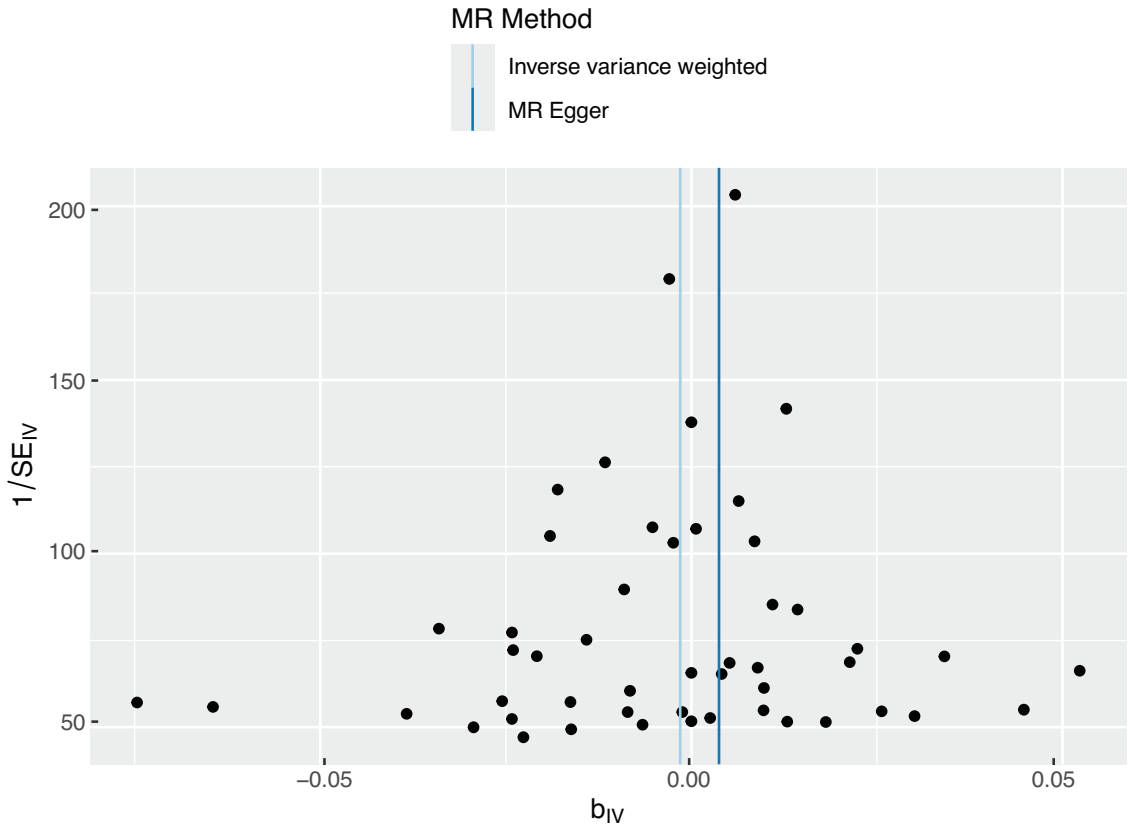

FIGURE 3
Funnel plot distribution of 44 SNP information. The funnel plot displays good symmetry, suggesting that the SNP variations included in this study are consistent regarding the effect size and direction on the exposure factor, thus indicating low heterogeneity. This supports the reliability of the study results.

estimate the causal effect of one factor on another, circumventing the limitations inherent in the aforementioned study designs (36).

Therefore, we decided to further explore the relationship between glaucoma and anxiety disorders using MR studies. Our findings across various models, including MR Egger regression, Inverse Variance Weighted (IVW) regression, and Weighted Median regression models, indicate that glaucoma does not cause anxiety disorders, with *p*-values of 0.56 for both MR Egger and IVW models, exceeding the threshold of 0.05. Even after excluding three outliers, the conclusion remained unchanged, and sensitivity analyses confirmed the stability of this conclusion. Pleiotropy analysis yielded a *p*-value of 0.38, suggesting that the trial results are reliable and not overly influenced by confounding factors. Additionally, the intercept of the MR-Egger regression line with the *y*-axis being less than 0.001 in Figure 2 also indicates a low likelihood of confounding factors. These MR study results suggest that there is no direct causal link between glaucoma and anxiety, and there are no significant confounding factors at the genetic level. It should be noted that even among Asians, studies have shown significant variability in the prevalence of anxiety among patients with glaucoma. Specifically, the prevalence of anxiety in Japanese glaucoma patients is 13.0% (8), while in Chinese patients, it is 22.9% (37). Notably, the prevalence in Singaporean glaucoma patients reaches as high as 64% (38). Scholars have found that these studies differ in terms of research design, sample size, and demographic characteristics (24). These findings contribute to a better understanding of the relationship between glaucoma and anxiety.

The availability of GWAS data for East Asian and African populations is limited. Although we found an East Asian Glaucoma SNP database through the IEU OpenGWAS project website (PubMed ID: GCST005388), a reliable database related to anxiety in the East Asian population was not found. To ensure the accuracy of our experimental results, we ultimately opted to use a European database. This decision also facilitates future comparisons with research conducted by other scholars. Finally, while this study explored the genetic association between glaucoma and anxiety within a European population database, it holds implications for the prevention and treatment of anxiety caused by glaucoma in other populations and nations. However, we must acknowledge that the lack of analysis of other ethnic groups represents a significant limitation of our research.

It is important to note that this study does not completely exclude the relationship between elevated intraocular pressure and anxiety. This indeed presents an interesting direction for research, which could further elucidate the interpretation of our results. We hope that our team can present findings in this area shortly.

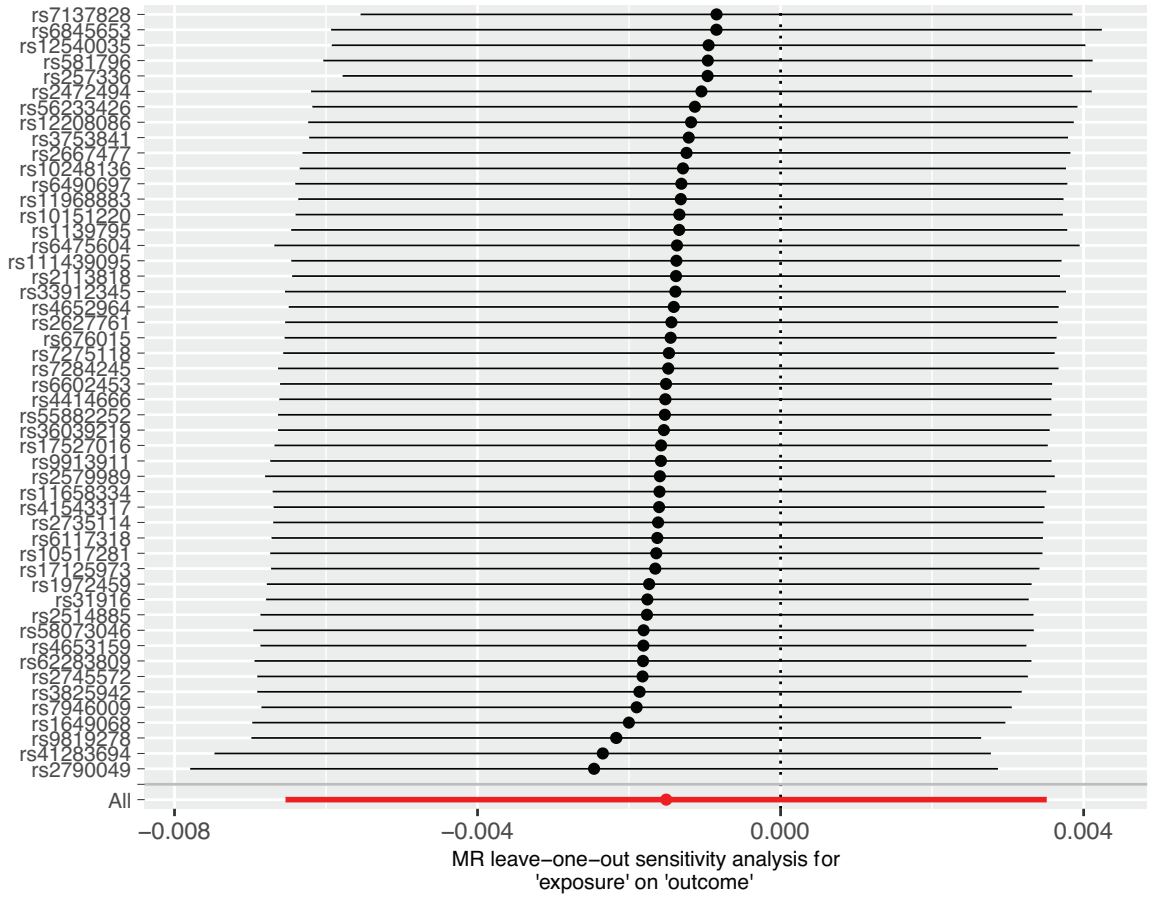

FIGURE 4
Sensitivity analysis results of the 44 SNP information. All markers observed span the coordinate zero, and excluding any single marker does not alter the conclusions. This demonstrates the robustness of the study findings.

5 Conclusion

Through rigorous Mendelian Randomization analysis, our findings indicate that glaucoma is not a causative factor for anxiety, with minimal influence from confounding factors in this study. These findings enhance our understanding of the relationship between glaucoma and anxiety.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

BL: Data curation, Formal analysis, Methodology, Software, Writing – original draft, Writing – review and editing. MX: Data curation, Formal analysis, Methodology, Writing – original draft. L-lC: Data curation, Formal analysis, Funding acquisition, Writing – original draft. D-kL: Funding acquisition, Supervision, Writing – review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This study was supported by the Xiamen Municipal Bureau of Science and Technology (3502Z202374104).

Acknowledgments

We thank Jing Tang for their help in data collection in this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Stamatiou M, Kazantzis D, Theodossiadis P, Chatziralli I. Depression in glaucoma patients: A review of the literature. *Semin Ophthalmol.* (2022) 37:29–35. doi: 10.1080/08820538.2021.1903945

2. Thylefors B, Negrel A. The global impact of glaucoma. *Bull World Health Organ.* (1994) 72:323.

3. Tham Y, Li X, Wong T, Quigley H, Aung T, Cheng C. Global prevalence of glaucoma and projections of glaucoma burden through 2040: A systematic review and meta-analysis. *Ophthalmology.* (2014) 121:2081–90. doi: 10.1016/j.ophtha.2014.05.013

4. Tiller J. Depression and anxiety. *Med J Aust.* (2013) 199:S28–31. doi: 10.5694/mjao12.10628

5. Ruscio A, Hallion L, Lim C, Aguilar-Gaxiola S, Al-Hamzawi A, Alonso J, et al. Cross-sectional comparison of the epidemiology of DSM-5 generalized anxiety disorder across the globe. *JAMA Psychiatry.* (2017) 74:465–75. doi: 10.1001/jamapsychiatry.2017.0056

6. Hoffman D, Dukes E, Wittchen H. Human and economic burden of generalized anxiety disorder. *Depress Anxiety.* (2008) 25:72–90. doi: 10.1002/da.20257

7. Cumurcu T, Cumurcu B, Celikel F, Etikan I. Depression and anxiety in patients with pseudoexfoliative glaucoma. *Gen Hosp Psychiatry.* (2006) 28:509–15. doi: 10.1016/j.genhosppsych.2006.09.004

8. Mabuchi F, Yoshimura K, Kashiwagi K, Shioe K, Yamagata Z, Kanba S, et al. High prevalence of anxiety and depression in patients with primary open-angle glaucoma. *J Glaucoma.* (2008) 17:552–7. doi: 10.1097/IJG.0b013e31816299d4

9. Skalicky S, Goldberg I. Depression and quality of life in patients with glaucoma: A cross-sectional analysis using the geriatric depression scale-15, assessment of function related to vision, and the glaucoma quality of life-15. *J Glaucoma.* (2008) 17:546–51. doi: 10.1097/IJG.0b013e318163bdd1

10. Shin D, Jung K, Park H, Park C. The effect of anxiety and depression on progression of glaucoma. *Sci Rep.* (2021) 11:1769. doi: 10.1038/s41598-021-81512-0

11. Boggs J, Beck A, Ritzwoller D, Battaglia C, Anderson H, Lindrooth R. A quasi-experimental analysis of lethal means assessment and risk for subsequent suicide attempts and deaths. *J Gen Intern Med.* (2020) 35:1709–14. doi: 10.1007/s11606-020-05641-4

12. Sanderson E, Glymour M, Holmes M, Kang H, Morrison J, Munafò M, et al. Mendelian randomization. *Nat Rev Methods Prim.* (2022) 2:6. doi: 10.1038/s43586-021-00092-5

13. Hemani G, Zheng J, Elsworth B, Wade K, Haberland V, Baird D, et al. The MR-Base platform supports systematic causal inference across the human phenome. *Elife.* (2018) 7:e34408. doi: 10.7554/eLife.34408

14. Weinreb R, Aung T, Medeiros F. The pathophysiology and treatment of glaucoma: A review. *JAMA.* (2014) 311:1901–11. doi: 10.1001/jama.2014.3192

15. Heijl A, Leske M, Bengtsson B, Hyman L, Bengtsson B, Hussein M, et al. Reduction of intraocular pressure and glaucoma progression: Results from the early manifest glaucoma trial. *Arch Ophthalmol.* (2002) 120:1268–79. doi: 10.1001/archopht.120.10.1268

16. Khatib T, Martin K. Protecting retinal ganglion cells. *Eye.* (2017) 31:218–24. doi: 10.1038/eye.2016.299

17. De Bernardo M, Casaburi C, De Pascale I, Capasso L, Cione F, Rosa N. Comparison between dynamic contour tonometry and Goldmann applanation tonometry correcting equations. *Sci Rep.* (2022) 12:20190. doi: 10.1038/s41598-022-24318-y

18. Jindal V. Glaucoma: An extension of various chronic neurodegenerative disorders. *Mol Neurobiol.* (2013) 48:186–9. doi: 10.1007/s12035-013-8416-8

19. Clarke D, Currie K. Depression, anxiety and their relationship with chronic diseases: A review of the epidemiology, risk and treatment evidence. *Med J Aust.* (2009) 190:S54–60. doi: 10.5694/j.1326-5377.2009.tb02471.x

20. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: Results from the world health surveys. *Lancet.* (2007) 370:851–8. doi: 10.1016/S0140-6736(07)61415-9

21. Agorastos A, Skevas C, Matthaei M, Otte C, Klemm M, Richard G, et al. Depression, anxiety, and disturbed sleep in glaucoma. *J Neuropsychiatry Clin Neurosci.* (2013) 25:205–13. doi: 10.1176/appi.neuropsych.12020030

22. Zhang X, Olson D, Le P, Lin F, Fleischman D, Davis R. The association between glaucoma, anxiety, and depression in a large population. *Am J Ophthalmol.* (2017) 183:37–41. doi: 10.1016/j.ajo.2017.07.021

23. Wang S, Singh K, Lin S. Prevalence and predictors of depression among participants with glaucoma in a nationally representative population sample. *Am J Ophthalmol.* (2012) 154:436–444.e432. doi: 10.1016/j.ajo.2012.03.039

24. Rezapour J, Nickels S, Schuster A, Michal M, Münzel T, Wild P, et al. Prevalence of depression and anxiety among participants with glaucoma in a population-based cohort study: The Gutenberg health study. *BMC Ophthalmol.* (2018) 18:157. doi: 10.1186/s12886-018-0831-1

25. Gelder M, Gath D, Mayou R. *Oxford textbook of psychiatry*. Oxford: Oxford university press (1989).

26. Martin E, Ressler K, Binder E, Nemeroff C. The neurobiology of anxiety disorders: Brain imaging, genetics, and psychoneuroendocrinology. *Psychiatr Clin.* (2009) 32:549–75. doi: 10.1016/j.psc.2009.05.004

27. Hoehn-Saric R, McLeod D, Funderburk F, Kowalski P. Somatic symptoms and physiologic responses in generalized anxiety disorderand panic disorder: An ambulatory monitor study. *Arch Gen Psychiatry.* (2004) 61:913–21. doi: 10.1001/archpsyc.61.9.913

28. Shin D, Jeon S, Park H, Park C. Posterior scleral deformation and autonomic dysfunction in normal tension glaucoma. *Sci Rep.* (2020) 10:8203. doi: 10.1038/s41598-020-65037-6

29. Park H, Jung S, Park S, Park C. Detecting autonomic dysfunction in patients with glaucoma using dynamic pupillometry. *Medicine.* (2019) 98:e14658. doi: 10.1097/MD.0000000000014658

30. Jean-Louis G, Zizi F, Lazzaro D, Wolintz A. Circadian rhythm dysfunction in glaucoma: A hypothesis. *J Circadian Rhyth.* (2008) 6:1. doi: 10.1186/1740-3391-6-1

31. Drouyer E, Dkhissi-Benyahya O, Chiquet C, WoldeMussie E, Ruiz G, Wheeler L, et al. Glaucoma alters the circadian timing system. *PLoS One.* (2008) 3:e3931. doi: 10.1371/journal.pone.0003931

32. Weidenthal D. Charles Bonnet syndrome precipitated by brimonidine tartrate eye drops. *J Pediatr.* (2001) 138:441–3.

33. Eramudugolla R, Wood J, Anstey K. Co-morbidity of depression and anxiety in common age-related eye diseases: A population-based study of 662 adults. *Front Aging Neurosci.* (2013) 5:56. doi: 10.3389/fnagi.2013.00056

34. Jonas J, Wei W, Xu L, Rietschel M, Streit F, Wang Y. Self-rated depression and eye diseases: The Beijing eye study. *PLoS One.* (2018) 13:e0202132. doi: 10.1371/journal.pone.0202132

35. Weiss G, Goldich Y, Bartov E, Burgansky-Eliash Z. Compliance with eye care in glaucoma patients with comorbid depression. *IMAJ Israel Med Assoc J.* (2011) 13:730.

36. Richmond R, Smith G. Mendelian randomization: Concepts and scope. *Cold Spring Harb Perspect Med.* (2022) 12:a040501. doi: 10.1101/cshperspect.a040501

37. Zhou C, Qian S, Wu P, Qiu C. Anxiety and depression in Chinese patients with glaucoma: Sociodemographic, clinical, and self-reported correlates. *J Psychosom Res.* (2013) 75:75–82. doi: 10.1016/j.jpsychores.2013.03.005

38. Lim N, Fan C, Yong M, Wong E, Yip L. Assessment of depression, anxiety, and quality of life in Singaporean patients with glaucoma. *J Glaucoma.* (2016) 25:605–12. doi: 10.1097/IJG.0000000000000393

Frontiers in Medicine

Translating medical research and innovation into improved patient care

A multidisciplinary journal which advances our medical knowledge. It supports the translation of scientific advances into new therapies and diagnostic tools that will improve patient care.

Discover the latest Research Topics

See more →

Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact