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Vision-related quality of life in patients suffering from coexisting glaucoma and cataract

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Abstract

Purpose: To evaluate the quality of life (QoL) and vision-related QoL in patients suffering from coexisting glaucoma and cataract.
Study design: Cross-sectional analytical study.
Methods: This study included a total of 222 cases: 163 patients suffering from coexisting glaucoma and cataract as the patient group and 59 healthy individuals as the control group. Data were gathered via EuroQol five-dimensional (EQ-5D) and National Eye Institute-Visual Functioning Questionnaire 39 (NEI-VFQ 39). The results were then compared before and one month after cataract surgery in the patient and control groups.
Results: The mean and 95% confidence interval of overall vision-related QoL scores in healthy individuals and patients in the pre- and postoperative phases were 86.65 (69.3–104.0), 48.7 (9.4–88.1), and 56.1 (12.2–100.0), respectively. There were significant differences among the 3 groups regarding all NEI-VFQ 39 items ($P < 0.05$). The mean and confidence interval of EQ-5D scores in the pre- and postoperative phases were 0.42 (0.21–0.64) and 0.58 (0.39–0.78), respectively ($P = 0.017$); for healthy individuals it was 0.70 (0.59–0.80). After surgery, all QoL items significantly increased among patients ($P < 0.05$). There were also significant differences in the scores compared to healthy individuals ($P < 0.05$). One month after surgery, all vision-related QoL item scores obtained by NEI-VFQ 39 and all QoL items scores

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obtained by EQ-5D were significantly lower in the treated patients than in healthy individuals ($P < 0.05$).
Conclusions: In patients suffering from coexisting glaucoma and cataract, The overall QoL and vision-related QoL scores improved after cataract surgery. However, there was a significant difference between patients and healthy individuals, with the healthy group having a superior score than the patients, both pre and postoperatively.

Keywords: cataract, glaucoma, quality of life, visual function

Kualiti hidup berkaitan penglihatan dalam kalangan pesakit yang menderita glaukoma dan katarak serentak

Abstrak

Tujuan: Untuk menilai kualiti hidup (QoL) dan QoL berkaitan penglihatan dalam kalangan pesakit yang mengalami glaukoma dan katarak secara serentak.
Reka bentuk kajian: Kajian analisis keratan rentas
Kaedah: Kajian ini merangkumi sejumlah 222 kes: 163 pesakit yang menghidap glaukoma dan katarak yang wujud bersama sebagai kumpulan pesakit dan 59 individu yang sihat sebagai kumpulan kawalan. Data dikumpul menggunakan EuroQol lima dimensi (EQ-5D) dan National Eye Institute-Visual Functioning Questionnaire 39 (NEI-VFQ 39). Keputusan kemudiannya dibandingkan sebelum dan sebulan selepas pembedahan katarak dalam kumpulan pesakit dan kawalan.
Keputusan: Purata dan 95% selang keyakinan keseluruhan skor QoL berkaitan penglihatan dalam individu yang sihat dan pesakit dalam fasa pra dan pasca operasi ialah 86.65 (69.3–104.0), 48.7 (9.4–88.1), dan 56.1 (12.2–100.0), masing-masing. Terdapat perbezaan yang ketara di antara 3 kumpulan berkenaan semua item NEI-VFQ 39 ($P < 0.05$). Min dan selang keyakinan skor EQ-5D dalam fasa pra dan pasca operasi ialah 0.42 (0.21–0.64) dan 0.58 (0.39–0.78), masing-masing ($P = 0.017$); untuk individu yang sihat adalah 0.70 (0.59–0.80). Selepas pembedahan, semua item QoL meningkat dengan ketara di kalangan pesakit ($P < 0.05$). Terdapat juga perbezaan yang ketara dalam skor berbanding individu yang sihat ($P < 0.05$). Sebulan selepas pembedahan, semua skor item QoL berkaitan penglihatan yang diperolehi oleh NEI-VFQ 39 dan semua skor item QoL yang diperoleh oleh EQ-5D adalah jauh lebih rendah bagi pesakit yang dirawat berbanding individu yang sihat ($P < 0.05$).
Kesimpulan: Bagi pesakit yang menghidap glaukoma dan katarak yang wujud

bersama, QoL keseluruhan dan skor QoL berkaitan penglihatan bertambah baik selepas pembedahan katarak. Walau bagaimanapun, terdapat perbezaan yang ketara antara pesakit dan individu yang sihat, dengan kumpulan individu yang sihat mempunyai skor yang lebih tinggi daripada kumpulan pesakit, sebelum dan selepas pembedahan.

Kata kunci: katarak, glaukoma, kualiti hidup, fungsi penglihatan

Introduction

According to the World Health Organisation (WHO), health is the absence of infirmity or disease and complete mental, physical, and social well-being.[1] Visual impairment, which is further categorised into low vision (best-corrected vision < 20/60) or blindness (best-corrected vision < 20/400), is one of the most common causes of disabilities.[2] Multidisciplinary management and early detection can minimise the effect of visual impairment on these patients' quality of life (QOL).

Eye practitioners mainly focus on clinical indicators, such as visual acuity impairment and visual field defects, to describe visual disabilities. However, the most important thing for patients is the treatment outcomes on functional status, which can affect emotional wellbeing and ultimately the vision-related quality of life (VRQoL).[3-7] VRQoL is defined as a person's satisfaction with their visual ability in their daily life. It reflects the social, emotional, and physical impact of visual impairment and economic wellbeing.[8,9]

The National Eye Institute Visual Function Questionnaire (NEI-VFQ) is one of the most commonly used patient-reported outcome measures to assess VRQoL. NEI VFQ is a reliable questionnaire used to determine the influence of vision on VRQoL. It is used in many countries worldwide to evaluate individuals' QoL.[7,10-13] This questionnaire can be used in both interview and self-reported formats. The validity and reliability of this questionnaire have been examined and approved by a research team in our country.[14]

Visual impairments increase the disease burden in countries and reduce the quality of life in individuals.[15-17] Previous studies have shown that many ocular diseases can affect QoL.[18-22] Cataract and glaucoma are two of the leading causes of visual impairment, which remain a major public health problem worldwide and have a significant impact on the QoL of patients, mainly due to reduced visual function and corresponding physical activity restriction.[21,23-26]

Although some studies have shown the effect of cataract surgery on visual function and QoL, these studies have been performed in different communities with different backgrounds.[13,27] Despite that, QoL is defined as an individual's perception of their position in the context of the culture and value systems in which they live, in relation to their goals, expectations, standards, and

concerns.[28] On the other hand, the coexistence of glaucoma and cataract in patients can signify the effect of disease on QoL, and the literature provides limited information about VRQoL in patients suffering from coexisting glaucoma and cataract.[29-32] In addition, most previously published papers on patients with coexisting glaucoma and cataract had a small sample size[30] did not involve original research.[29] Also, most studies were performed only on patients with cataracts or glaucoma.[11,13,19-21,25,26,30,33,34] Therefore, due to the lack of research results in the field of QoL and visual function in a group of patients suffering from coexisting glaucoma and cataracts compared to healthy individuals, we conducted a study to examine the QoL of these patients.

Methods

Study design

This cross-sectional-analytical study was performed in Khatam Al-Anbia Hospital in Mashhad, Iran, from 2017 to 2018. After explaining the study's objectives to the patients, consent forms were obtained, and the patients were asked to complete the questionnaire. The study was performed using the tenets of the Declaration of Helsinki and approved by the ethics committee of Mashhad University of Medical Sciences (IR.MUMS.REC.1397.240).

Inclusion and exclusion criteria

All patients underwent a comprehensive ophthalmic examination, including best-corrected visual acuity (BCVA) assessment, slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy using a Volk G-6 lens, and dilated fundus examination with a 78 D lens. Visual field testing was performed using 24-2 SITA Standard on the Humphrey Field Analyser (Carl Zeiss Meditec, Jena, Germany), and intraocular pressure (IOP) was recorded.

Patients were eligible for inclusion if they were 40 years of age or older, had a confirmed diagnosis of primary angle-closure glaucoma (PACG) based on gonioscopic evidence of at least 180° of angle closure (either appositional or synechial), elevated IOP (> 21 mmHg or controlled with medication), and characteristic glaucomatous optic neuropathy as evidenced by visual field defects or optic disc changes. In addition, participants were required to have a visually significant cataract, defined either by a BCVA of 20/30 or worse, or by subjective visual complaints interfering with daily activities, as judged by the examining physician. Cataract severity was graded using the Lens Opacities Classification System III (LOCS III), and only patients with nuclear or cortical cataracts of grade 2 or higher were included. In cases where both eyes met the inclusion criteria, the eye with more advanced disease or greater visual impairment was selected for analysis.

Exclusion criteria included a history of intraocular surgery, ocular trauma, secondary glaucoma (*e.g.*, neovascular, uveitic, pseudoexfoliative), corneal or iris abnormalities, angle neovascularisation, or any systemic or neurological condition that could affect visual function or QoL. Patients with acute angle-closure attacks, those on chronic miotic therapy, and monocular individuals were also excluded. To minimise confounding, individuals with significant systemic comorbidities such as uncontrolled diabetes or neurological disorders were not enrolled.

For the control group, visually healthy individuals were selected from companions of patients attending routine ophthalmic examinations. These individuals had no history of ocular disease, systemic illness affecting vision, or refractive error.[35]

Participants and group characteristics

Based on the data represented in Hatt's article[36] with a confidence interval of 95% and a test power of 80%, 163 adult patients participated in this study as a sample group. The first group included 163 patients who were diagnosed with glaucoma and cataracts. An expert glaucoma surgeon made the diagnosis. The second group included visually healthy individuals with no ocular, mental or musculoskeletal diseases, nor refractive error. This group was selected from the companions of patients recently undergoing ophthalmological examinations. The sampling was done randomly.

Questionnaires and data collection

These questionnaires have been translated into Persian, and their validity and reliability have been confirmed.[14,36] However, the reliability of the questionnaires (EQ-5D and NEI-VFQ 39) was evaluated using Cronbach's alpha test at a confidence level of 0.95 in SPSS software.

The questionnaire was the Persian version of NEI-VFQ (EuroQoL five-dimensional [EQ-5D] and 39-item Visual Functioning Questionnaire structure [NEI-VFQ 39]). The EQ-5D questionnaire measures the ability of individuals to perform tasks in five dimensions of mobility, personal care, normal activities (such as working, studying, doing household chores, having family or leisure activities), pain (discomfort), and anxiety (depression). This concise but comprehensive questionnaire takes one to five minutes to answer, depending on the situation. Then, each health condition is evaluated on a scale of 0 to 1. The NEI-VFQ 39 QoL is one of the most common questionnaires to measure the QoL and measures performance of various aspects of life, including general health, visual health, mental health, eye pain, distance and near vision activities, social performance, peripheral vision, color vision limitation of doing an activity, driving, and dependency. According to the questionnaire instructions, each question's answer is converted into a score between 0 and 100, in which 0 indicates the worst and 100 the best score.[37]

The interview format of the questionnaire was used to determine the QoL score. In addition to completing the questionnaire, demographic information affecting the QoL of patients (including age, sex, and education) was also obtained. Finally, compared to healthy individuals, the QoL score of patients suffering from glaucoma with cataract during the pre- and postoperative phases was evaluated.

Statistical analysis

The statistical package SPSS-24 (IBM Corp, Armonk, New York, USA) software was used for data analysis. The Kolmogorov-Smirnov test was used to evaluate the normality of the data, which is a prerequisite for the analysis of variance. For showing the QoL data, the mean with confidence interval, and for investigating and evaluating the difference in the QoL during pre- and postoperative phases, one-way analysis of variance was used at a confidence level of 0.95. A p-value less than 0.05 was considered a significant level. Cronbach's alpha test was used to examine the validity of the questionnaire used according to its main variables.

In addition to descriptive analyses and one-way ANOVA to compare mean QoL scores across the study groups, a multiple linear regression analysis was conducted to evaluate the independent impact of surgery after adjusting for demographic covariates. In this model, the composite score from the NEI-VFQ-39 and the overall score from the EQ-5D served as dependent variables. The independent variables included study group (preoperative, postoperative, and healthy controls), age, education level (categorised into five levels: illiterate, primary, secondary, diploma, and university), and occupation (categorised as employed, self-employed, and other). This analytical approach allowed simultaneous assessment of the surgical effect and the influence of demographic modifiers, enhancing the robustness and interpretability of the findings.

Results

Table 1 shows the difference in demographic characteristics between the two study groups. Table 2 presents the characteristics of descriptive statistics related to QoL items of 163 patients during the pre- and postoperative phases compared to 59 healthy individuals. The mean and confidence interval of overall NEI-VFQ 39 scores in the pre- and postoperative phases in patients and healthy individuals were 48.7 (9.4–88.1), 56.1 (12.2–100.0), and 86.65 (69.3–104.0), respectively ($P < 0.05$). The mean and confidence interval of EQ-5D score for patients during the pre- and postoperative phase were 0.42 (0.21-0.64) and 0.58 (0.39–0.78), respectively ($P = 0.017$), while for healthy individuals it was 0.70 (0.59–0.80). Table 2 shows the overall QoL score, vision-related QoL, and its components of patients during the preoperative and postoperative phases and healthy individuals. In pre- and postoperative, the lowest scores among patients were observed in general vision

Table 1. Demographic characteristics in patients and control groups.

Demographic variables		Control group number (%)	Patient group number (%)	*P*-value
Gender	Male	37 (63%)	99 (61%)	0.002
	Female	22 (37%)	64 (39%)	
Education	Illiterate	4 (7%)	15 (9%)	0.3
	Primary school	6 (10%)	21 (13%)	
	Secondary school	10 (17%)	23 (14%)	
	Diploma	24 (41%)	65 (40%)	
	University graduated	15 (25%)	39 (24%)	
Occupation	Employee	20 (34%)	62 (38%)	0.02
	Self employed	22 (37%)	48 (29%)	
	Others	17 (29%)	53 (33%)	
Visual outcomes	CDVA	0.05 ± 0.05	0.23 ± 0.14	0.04
	UDVA	0.05 ± 0.1	0.25 ± 1.5	0.03
	Spherical equivalent	-0.25 ± 0.75	-2.02 ± 0.5	0.001

CDVA: Corrected distance visual acuity; UDVA: Uncorrected distance visual acuity

(43.9 and 55.4, respectively), and the highest scores were found in color vision items (83.19 and 88.21, respectively). Cronbach's alpha test results for EQ-5D and NEI-VFQ were 0.79 and 0.77, respectively. These results indicate that Cronbach's alpha is higher than 0.7 in both questionnaires, indicating reliability (Fig. 1).

Based on the Scheffe post hoc test results, which are presented in Table 3, three comparisons have been made. The first comparison examined the QoL items among patients suffering from glaucoma with cataracts (during the preoperative phase) and healthy individuals. The second comparison examined the vision-related QoL items during the pre- and postoperative phases of patients with glaucoma with cataracts. Finally, in the third comparison, vision-related QoL items among patients suffering from glaucoma with cataracts during the postoperative phase compared to healthy individuals were examined. As can be noticed, the results of the variance analysis showed that the difference between the QoL items of these three groups was significant. As seen in Table 3, all vision-related QoL items among the three compared groups (preoperative phase, postoperative phase, and healthy individuals) were significantly different in all items. The results showed that all vision-related QoL items in the preoperative group were substantially lower than both the postoperative group and healthy individuals ($P < 0.05$). However, the second comparison between the QoL items scores among the postoperative phase was significantly lower than those of healthy individuals ($P < 0.05$).

Table 2. Comparison of vision-related QoL obtained by NEI-VFQ 39 and EQ-5D questionnaires between patients suffering from glaucoma with cataracts and healthy individuals

Questionnaire	Variables (number of questions)	Mean (± SD)		
		Patient group		Healthy control group
		Preoperative	Postoperative	
NEI-VFQ 39	General health (2)	59 (4.83)	70 (1.4)	84.62 (2.6)
	General vision (2)	43.9 (5.24)	55.4 (3.2)	87.53 (2.25)
	Ocular pain (2)	79.36 (3.92)	95.87 (2.6)	96.79 (1.26)
	Near activities (6)	51.45 (7.2)	63.21 (1.2)	95.9 (1.26)
	Distance activities (6)	59.83 (6.29)	74.76 (3.5)	98 (0.79)
	Vision-specific social functioning (3)	66.11 (5.76)	80.11 (0.9)	100(00)
	Vision-specific mental health (5)	51.63 (6.9)	61.87 (0.69)	95.84 (1.26)
	Vision-specific role difficulties (4)	59.65 (7.91)	73.2 (4.3)	94.9 (1.44)
	Vision-specific dependency (4)	62.72 (8.16)	78.5 (4.7)	98.89 (0.34)
	Driving (3)	50.97 (8.36)	61.8 (2.9)	91 (1.8)
	Colour vision (1)	83.19 (4.49)	88.2 (1.5)	97 (1.57)
	Peripheral vision (1)	62.09 (6.54)	75.12 (4.9)	99 (0.83)
	Composite score (39)	62.96	73.41 (3.2)	95 (0.72)
EQ-5D	Quality of life	0.42 (0.21–0.64)	0.58 (0.39–0.78)	0.70 (0.59–0.80)

NEI-VFQ 39: National Eye Institute-Visual Functioning Questionnaire; EQ-5D: EuroQol five-dimensional

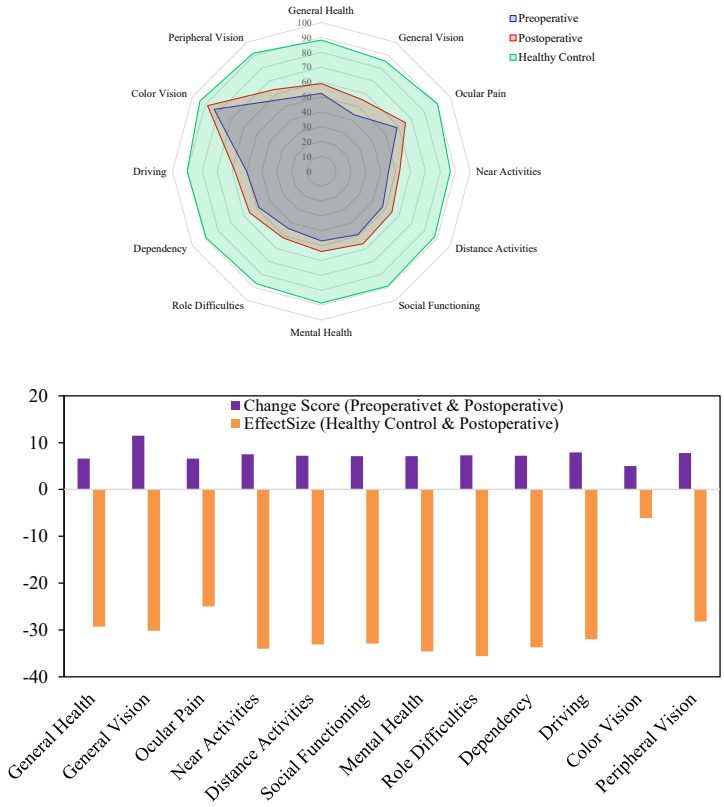

Fig. 1. (Top) Radar chart comparing NEI-VFQ 39 subscale scores across preoperative, postoperative, and healthy control groups. *(Bottom)* Bar graph showing change scores and effect sizes across the same subscales.

Multiple linear regression analyses were performed to assess the effect of surgery on the outcomes of both QoL instruments. Regarding the NEI-VFQ-39, the results showed that after adjusting for age, education, and occupation, patients in the postoperative phase scored an average of 7.3 points higher than in the preoperative phase ($P < 0.001$). Moreover, healthy individuals scored 37.8 points higher than the preoperative group ($P < 0.001$). Among the covariates, age was inversely associated with visual QoL ($\beta = -0.21$, $P = 0.028$), and individuals with university-level education had significantly higher scores than illiterate participants ($\beta = +6.1$, $P = 0.004$). Occupation was not statistically associated with outcome scores.

Table 3. The statistical difference (P-value) between patients suffering from glaucoma and cataracts (before and one month after surgery) and control groups

Questionnaire	Preoperative vs healthy control	Preoperative vs postoperative	Postoperative vs healthy control
National Eye Institute Visual Functioning Questionnaire			
General vision	0.002	0.033	0.02
Ocular pain	0.041	0.012	0.001
Near activities	0.001	0.001	0.015
Distance activities	0.005	0.001	0.03
Vision-specific social functioning	0.03	0.007	0.017
Vision-specific mental health	0.001	0.028	0.008
Vision-specific role difficulties	0.011	0.01	0.001
Vision-specific dependency	0.047	0.007	0.004
Driving	0.049	0.001	0.019
Color vision	0.004	0.036	0.021
Peripheral vision	0.03	0.028	0.048
Composite score	0.039	0.044	0.04
EuroQol five-dimensional			
Quality of life	0.001	0.02	0.037

Values are *p*-values.

The regression model for the EQ-5D showed similar patterns. Patients in the postoperative group had a 0.14-point increase in overall QoL scores compared to the preoperative group ($P < 0.001$). In contrast, healthy controls scored 0.28 points higher than the preoperative group ($P < 0.001$). Age again showed a negative association ($\beta = -0.006$, $P = 0.034$), and university education was associated with a 0.042-point increase compared to the illiterate category ($P = 0.012$). These findings confirm that cataract surgery's positive effect on visual and general QoL remains statistically significant even after adjusting for key demographic factors.

Discussion

This study evaluated the QoL and visual performance of patients suffering from glaucoma with cataract during the pre- and postoperative phases. According to the results of this research, although the overall QoL score and vision-related QoL score in glaucoma patients with cataract improved after cataract surgery, there was a significant difference between the results for patients in the postoperative patients and those of healthy individuals. Based on the results of this study, the total score of QoL VFQ 39 patients during the pre- and postoperative phase was 48.7 and 56.1, respectively; in healthy individuals it was 86.65. There was a significant difference between mean QoL VFQ-39 scores during the pre- and postoperative phases. Similar to our results, other studies have shown a significant improvement in the QoL VFQ scores observed after eye surgery. However, most have been conducted in different eye surgeries with different races and social factors.[29,38,39] The mean EQ-5D scores of patients during the pre- and postoperative phases were 0.42 and 0.58, respectively, which shows a significant difference between them. In this study, the QoL score was lower than in previous studies.[39-42] The main reason for this difference is the effect of economic, social, and racial factors on QoL scores. Also, this study's sample size was larger than that of the other mentioned studies.

Numerous studies have provided evidence of the advantages of phacoemulsification in treating. Phacoemulsification surgery yields a similar reduction in IOP compared to phacotrabeculectomy, but with a lower incidence of complications. However, individuals who undergo phacotrabeculectomy may experience slightly lower IOP levels and require fewer medications to lower IOP, which can be particularly beneficial for patients with advanced PACG or challenges in adhering to medication regimens.[43]

The lower QoL observed in patients with combined glaucoma and cataract may be attributed to the compounded impact of both conditions on visual function. Glaucoma causes irreversible damage to the optic nerve and visual field loss, while cataract impairs visual acuity and contrast sensitivity. Together, these conditions can significantly reduce functional vision and increase psychological distress, leading to lower QoL scores compared to patients with a single condition. Our findings align with previous studies that report reduced QoL in patients with coexisting ocular diseases.[29,38,39] These results underscore the importance of tailored clinical decision-making. For patients with both glaucoma and cataract, combined surgical approaches, such as phacotrabeculectomy, may offer better IOP control and reduce the need for medications, potentially improving long-term QoL outcomes. These QoL improvements following cataract surgery have important implications for clinical decision-making, especially in patients with coexisting glaucoma. While visual acuity and IOP remain key clinical metrics, integrating patient-reported outcomes such as vision-related QoL can help guide the choice between cataract extraction alone and combined cataract-glaucoma procedures.

For patients with moderate to advanced glaucoma or poor medication adherence, combined surgeries like phacotrabeculectomy may enhance IOP control and lead to more meaningful gains in functional vision and overall well-being. Incorporating QoL assessment tools into preoperative consultations may support more personalized surgical planning and improve long-term satisfaction with care. A previous study has shown that vision-related QoL increased following cataract surgery. In addition, increasing glaucoma severity had a negative impact on vision-related QoL.[29] However, other researchers have not evaluated the QoL and visual performance of patients suffering from glaucoma with cataract.

This study evaluated the QoL in 12 main subgroups with a total score. The results indicate a significant difference between patients and healthy individuals during the postoperative phase in all subgroups. Some studies aligned with this study's results and confirmed the correlation between QoL and visual performance in different eye diseases.[44]

In another study, education was significantly correlated to overall QoL and vision-related QoL. Due to the better awareness of patients with higher education about the need for surgery, QoL in these patients was higher than that of lower educated ones, which was in line with a previous study.[38] In examining QoL factors, including the psychosocial perspective, the cognitive environment among patients based on their education status can indicate that better-educated patients had better QoL than less educated ones. The correlation of age with these variables was inverse, which means that as age increases, the score of QoL decreases.[45]

This study has several limitations. First, its cross-sectional design restricts assessing long-term outcomes and causal relationships. Second, the absence of longitudinal follow-up limits insights into the sustainability of postoperative improvements in QoL. Third, potential selection bias may have influenced the findings, as participants were recruited from a single clinical setting. Additionally, cultural and socioeconomic factors may have affected self-reported QoL scores, introducing variability that is difficult to control. While this study focused on descriptive and comparative analyses, we acknowledge that multivariable statistical approaches, such as regression analysis, could have provided deeper insights by adjusting for confounding variables. Future research using this dataset may explore predictive modelling to assess the independent impact of demographic and clinical factors on QoL outcomes.

Conclusion

Several factors contribute to the observed differences, including the criteria for participant inclusion, disease severity and type, the participants' average age, random sampling, and individual and social factors. Overall, it can be inferred that both glaucoma and cataracts impact physical well-being and have psychosocial

implications. The combination of vision impairment and increased stress negatively affects the interpersonal relationships of patients. To summarise, while cataract surgery significantly improves the QoL and vision-related aspects for patients with glaucoma and cataracts, these measures remain lower than those of healthy individuals after the surgery.

Declarations

Ethics approval and consent to participate
The Helsinki Declaration and the Ethics Committee in Medical Ethics Committee approved the research protocol at Mashhad University of Medical Sciences (IR.MUMS.REC.1397.044).

Competing interests
None to declare.

Funding
None to declare.

Availability of data and materials
The datasets generated and analysed during the current study are not publicly available since all relevant data are included in the manuscript. However, they are available from the corresponding author upon reasonable request.

Author contributions
AA and FK were responsible for the study's conception and design. MF acquired the data. AM, AA, and FK analysed and interpreted the data. AM and FK wrote the draft. AA, MF, and revised the manuscript critically. All authors have read and approved the final manuscript.

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