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REVIEW

Quality of Life in Glaucoma: A Review of the Literature

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ABSTRACT

The ultimate goal of glaucoma management is the preservation of patients' visual function and quality of life (QoL). The disease itself as well as the medical or surgical treatment can have an enormous impact on a patient's QoL. Even the mere diagnosis of a chronic, irreversible, potentially blinding disorder can adversely affect the patient's sense of well-being and QoL by eliciting significant anxiety. Patients with primary open-angle glaucoma rarely present with visual symptoms, at least early in the course of the disease. A better understanding of patient-reported QoL can improve patient–physician interaction and enhance treatment adherence by customizing treatment options based on individual patient profile, thus optimizing long-term prognosis. These aspects are summarized and critically appraised in this article.

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INTRODUCTION

The World Health Organization (WHO) defines health as "A state of complete physical, mental, and social well-being not merely the absence of a disease…". It follows that the measurement of health and the effects of health care must include not only an indication of changes in the frequency and severity of diseases but also an estimation of well-being. This can be

assessed by measuring improvement in the quality of life (QoL) related to health care [1].

QoL is defined as individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns. It is a wide-ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationships to salient features of their environment. QoL is thus the sum of a range of objectively measurable life conditions experienced by an individual. These may include physical health, personal circumstances (wealth, living conditions, etc.), social relationships, functional activities and pursuits, and wider societal and economic influences. The subjective response to such conditions is the domain of personal satisfaction with life. The QoL of an individual or subgroup can be established by comparing their position to that of the total population [2].

Visual impairment due to ophthalmological diseases has a negative impact on physical and mental health and is a global concern. In the USA, visual disability ranks among the top ten disabilities [3]. Visually impaired people are at higher risk than the healthy population for accidents, social withdrawal, and depression [4–7]. With population aging, the number of people with visual impairment and blindness is rapidly growing, as many eye diseases are more prevalent among the elderly. Cataract, glaucoma, age-related macular degeneration, and diabetic retinopathy are the most common causes of visual impairment [8]. In 2011, 2.71 million people in the USA had primary open-angle glaucoma (POAG), but this number is expected to reach 7.32 million by 2050 [9].

Several studies have examined the relationships between different eye diseases and QoL [10–14]. Despite substantial differences in methodological approach, these all concluded that visual impairment significantly affects QoL. This review examines the body of published literature on QoL in patients with POAG.

METHODS

The MEDLINE database was used for the literature search of this review. Although every effort was made to use references as recent as possible, articles irrespective of the year of publication were used if deemed appropriate. The keywords searched included glaucoma, ocular hypertension, quality of life, health-related quality of life, vision-related quality of life, mental health status, visual field damage, quality of life questionnaire, medical therapy, and surgical therapy. Combinations of these terms with appropriate Boolean operators were also used. After relevant articles were retrieved using these keywords, a search was conducted through the literature cited in these articles and additional papers were identified. Abstracts of papers in languages other than English were surveyed, too. Medical Subject Headings (MeSH) searches were also performed. Case reports and abstracts from meeting presentations were not used.

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

ASSESSING QUALITY OF LIFE: STANDARD APPROACH

WHO developed two instruments to measure QoL, the WHOQOL-100 and the WHOQOL-BREF. Both these questionnaires

were drafted on the basis of statements from patients and health professionals in a wide variety of cultures and diseases, in 15 collaborating centers around the world. Field centers were selected to cover differences in levels of industrialization, available health services, and other markers relevant to the measurement of QoL (e.g., role of the family, perception of time, perception of self, dominant religion) [15]. This structure means the results of WHOQOL questionnaires are comparable among populations in different socioeconomic settings [16]. WHOQOL-100 and WHOQOL-BREF have been translated into more than 20 languages (Table 1).

The 36-Item Short Form Health Survey (SF-36) is a short general health questionnaire derived from a more complex survey covering 40 health facets in the Medical Outcomes Study (MOS) [17]. The eight health concepts in the SF-36 questionnaire were selected as representing the most frequently measured facets in health surveys, and those most affected by disease and treatment. SF-36 has three levels: (1) items; (2) eight scales, aggregating 2–10 items each; (3) two summary scores, aggregating the scales. All but one of the 36 items are used to score the eight scales. Three scales (physical functioning, role-physical, and bodily pain) are linked to the physical component of QoL and contribute most to the scoring of the physical component summary measure. Mental health, emotional-role, and social functioning scales correlate with the patient's psychological status and contribute to the scoring of the mental component summary measure.

SF-36 can separate symptomatic and asymptomatic patients, distinguish stages and severity of a disease, and classify treatment effects [18–22]. The international adaptation was done by forward and backward translation, review by representative focus groups, and formal evaluation of the adapted forms. In 1996 a second version of SF-36 was introduced to correct deficiencies found in the original version.

EuroQOL-5D (EQ5D) is a generic multidimensional questionnaire composed of

Table 1 Validated questionnaires for the assessment of quality of life in the general population and glaucoma patients

Questionnaire	Brief description	No. items	Domains	Validated
WHOQOL-100	World Health Organization questionnaire	100	General health, positive feeling, social support, financial resources/physical, psychological and social relationships	Yes (in 20 languages)
WHO-BREF	Short version of WHOQOL-100	26	General health, positive feeling, social support, financial resources/physical, psychological and social relationships	Yes (in 20 languages)
SF-36	Short general health questionnaire	36	Physical component, mental health, emotional- role and social functioning	Yes (in ten languages)
Equation 5D	Multidimensional: descriptive system and visual scale	5	Mobility, self-care, usual activities, pain/discomfort, anxiety/depression	Yes (more than 100 languages)

WHOQOL-100 World Health Organization Quality of Life-100, *WHO-BREF* World Health Organization-BREF, *SF-36* Short Form-36, *EQ5D* EuroQOL-5D

two parts: the EQ5D descriptive system and the EQ visual scale (EQ-VAS). Five dimensions are inspected: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Each dimension has three levels: no problems, some problems, severe problems. Each answer is converted to a one-digit number and the digits for each dimension are combined in a five-digit number, describing the patient's health state. This five-digit number is then elaborated using a unified scoring algorithm based on time trade-off data from several European studies [23–25]. The EQ-VAS cards measure self-reported general health status, using a vertical thermometer-analogue scale, where the endpoints are labeled "best imaginable health state" and "worst imaginable health state" (Fig. 1). Equation 5D has been used in more than 3000 publications investigating QoL in a very wide range of diseases. Its widespread use is due to its design, suitable for self-completion (e.g., in postal surveys), but also useful in clinics and face-to-face interviews.

QUALITY OF LIFE IN OCULAR HYPERTENSION AND GLAUCOMA

A revised version of the WHOQOL-BREF questionnaire was used to assess the social impact of eye diseases in a developing population in Andhra Pradesh, southern India [13]. The authors calculated a total score for each of the questions and expressed this as a percentage of the total possible score, from 0 to 100, with higher scores indicating better results. Patients with glaucoma had lower mean scores than patients without visual impairment (62.6 vs. 84.1 for glaucoma and healthy subjects, respectively) and patients with other eye diseases (78.1, 74.4, and 72.7 for refractive errors, cataract and retinal diseases, respectively). The results from this study must obviously be interpreted taking account of the social context of Andhra Pradesh and the difficulties of accessing medical care. Among patients with glaucoma 52% were bilaterally blind and 88% were blind in at least one eye.

SF-36 was used to assess QoL in patients enrolled in the Ocular Hypertension Treatment Study (OHTS) [26]. This was a multicenter, randomized, prospective clinical trial to determine the efficacy of topical ocular hypotensive medications in delaying or preventing the onset of glaucoma in patients with ocular hypertension (OHT). QoL was tested overall and separately in African Americans and in patients of other ethnicities, including Caucasian, Asiatic, and Hispanic. This distinction was made to adjust for racial differences in socioeconomical substrate and in the natural history of the disease, which seems more aggressive in Africans than others. At baseline the SF-36 profile of African Americans did not differ from that of patients of other ethnicities, after adjustment for demographic factors and systemic comorbidities. Only the physical function score was lower in African Americans than others ($p = 0.03$). The SF-36 profile of the entire sample was better than age- and sex-matched population-based norms ($p < 0.001$). These results probably reflect a bias in the OHTS enrollment of patients, as it is well known that volunteers for some studies may not resemble the general population. OHTS volunteers probably had a higher educational level and socioeconomic status [26]. Baseline demographic conditions were similar in African Americans and subjects of other ethnicities, justifying similar QoL scores.

Wilson et al. submitted the SF-36 questionnaire to three groups: 121 patients with POAG, 42 patients with suspected glaucoma, and 135 patients with no diagnosis of ocular disease except cataract [27]. POAG

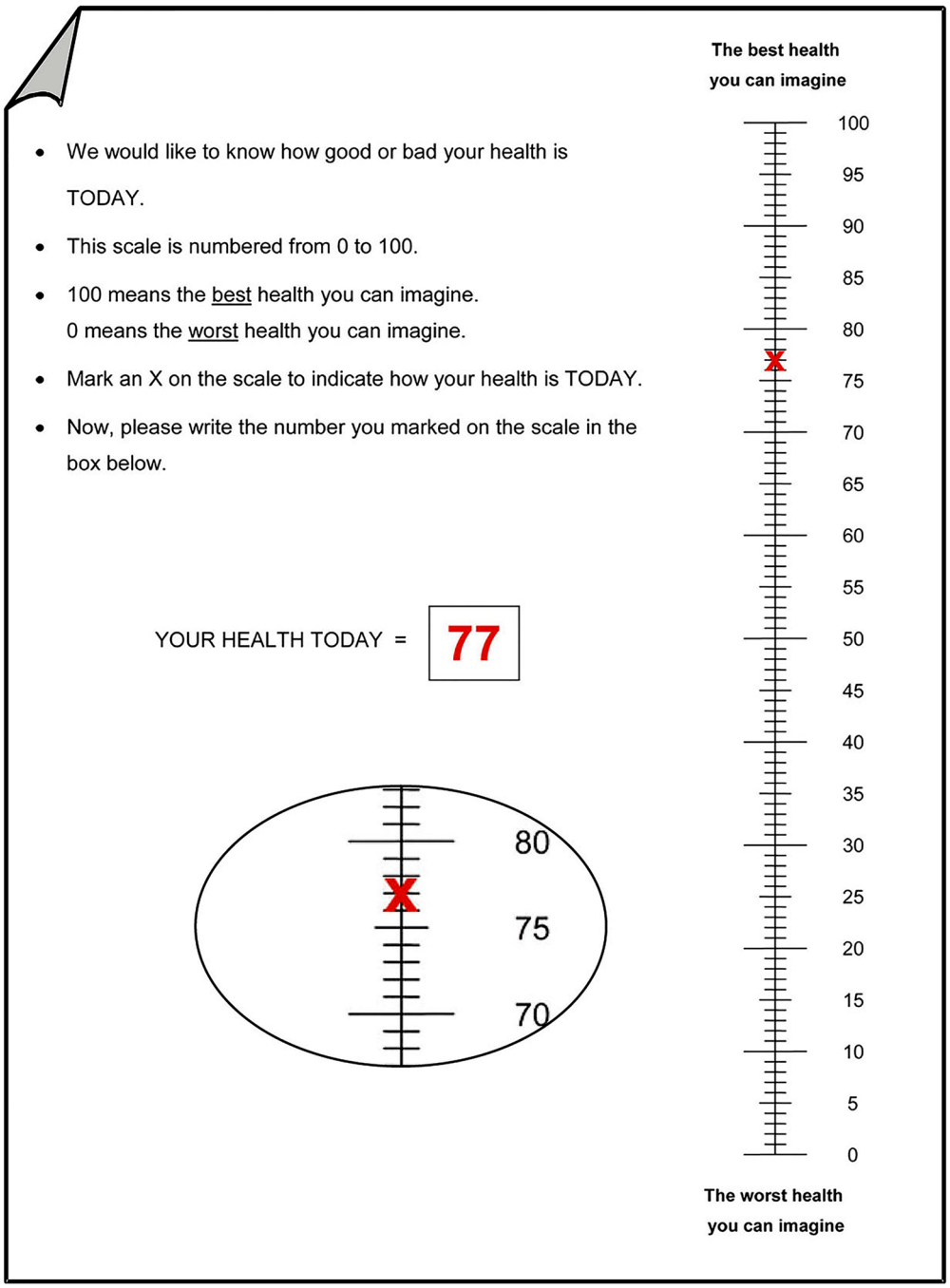

Fig. 1 An example of a completed EQ-VAS thermometer-analogue scale

patients had lower scores than those with suspected glaucoma in all domains ($p = 0.038$) except "general health" ($p = 0.065$). As expected, controls had higher mean scores than patients with POAG and suspected glaucoma on all SF-36 domains ($p < 0.001$) except the "general mental" domain, where no difference was found ($p = 0.148$). In this study, POAG was a strong predictor of lower SF-36 scores in all domains. According to these results, it seems that the mere

knowledge of having glaucoma (even without visual field (VF) damage) can have a negative effect on QoL [28, 29].

QoL was also assessed by Parrish et al. in 147 glaucoma patients, consecutively enrolled from a glaucoma clinic [30]. Scores for the eight domains of the SF-36 questionnaire were comparable with age-adjusted normative data and no significant difference was found. The SF-36 scores were not greatly affected by visual acuity impairment or VF impairment or overall visual impairment. However, it should be noted that patients enrolled in this study suffered from early glaucoma, as more than 75% had less than 50% loss of binocular VF (Esterman VF test). The SF-36 may fail to detect changes in QoL in patients at initial stages of the disease, disclosing deficiencies only when VF defects are more advanced.

Glaucoma is an ocular condition that does not normally cause systemic symptoms, having no strong impact on a patient's perception about general health and categories that examine this. In a Brazilian study, glaucoma patients scored less than controls in all the SF-36 domains, with significant differences in all but three categories (general health, vitality, and role-emotional) [31]. However in that study, body pain gave the lowest mean score, indicating very severe and extremely limiting pain in glaucoma patients (respectively 7.0 and 72.6 in glaucoma and healthy patients, $p < 0.001$). The authors explain these results by cultural bias, as the local population probably used pain as a generic complaint to gain sympathy from doctors and compassion from the family.

From a systematic review of studies that used the SF-36 survey to evaluate QoL in glaucoma patients, vitality was the most affected domain (scores 37–71), and social functioning (scores 54–92) and role limitations-emotional (score range 57–91) were the least affected [32]. General scores in the physical domains (i.e., physical functioning, role limitations-physical, bodily pain, and general health) were lower than those in the psychosocial domains (social functioning, mental health, vitality, and role limitations-emotional). It is not clear why psychosocial domains are less affected than others in glaucoma patients. One could expect the glaucoma diagnosis and its consequences on visual function to affect a patient emotionally. However, it is possible that the initial distress of glaucoma diagnosis is accepted with time by the patient, especially when no new symptom appears.

Kobelt et al. analyzed QoL in 199 patients with POAG and OHT, divided into five groups according to their disease severity [33]. Results were expressed in terms of utility score: utilities are preferences that patients or the general population have for certain health states, and the expressed scale is anchored between 1 (full health) and 0 (death). The mean EQ5D utility score in glaucoma patients was 0.8, which is close to the average for the Swedish population, where the study was run. No difference was found in utility scores for the first four severity stages of the disease, but the scores for stage 5 patients in at least one eye were significantly worse ($p < 0.05$, Fig. 2). Total visual acuity, visual acuity in the better eye, and comorbidity significantly affected utility scores ($p < 0.05$). Interestingly, QoL seems to be

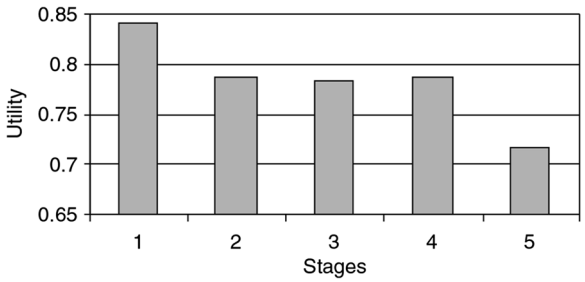

Fig. 2 Utility classified in five stages based on mean deviation in the worst eye (adapted from Kobelt et al. [33])

worsened by glaucoma only in the more advanced stages and especially when both eyes are affected.

Similarly, Aspinall et al. found no problems across almost all the scales of the EQ5D questionnaire in a cohort of 84 glaucoma patients with no other comorbidities [34]. However, scores were low in the pain scale. These results can be explained by the fact that 11% of the enrolled patients had angle-closure glaucoma, a typically painful condition. There was also the stinging sensation of eye drops (89% of patients were using topical medications) or the pain caused by dysesthesic conjunctival blebs in some patients following trabeculectomy (43% had previous surgery for glaucoma). As expected, the EQ5D summed index score was influenced by years since diagnosis ($p < 0.05$), VF loss ($p < 0.01$), and visual acuity ($p < 0.01$).

PATIENT-REPORTED OUTCOMES IN GLAUCOMA

The US Food and Drug Administration (FDA) recently recommended the use of patient-reported outcomes (PROs) as an umbrella term covering a broad range of health data reported by the patient [35, 36]. Some objective measurements used in clinical trials to describe a disease or its severity may fall short in capturing the impact of the disease on patients' daily life. For example, visual acuity and VF damage are useful to classify glaucoma stage, but they do not describe the effect on patient daily activities, such as driving, walking, or reading. The patient's point of view is important to completely understand how glaucoma and its treatment affect QoL, as some experience can only be interpreted first hand.

According to a systematic review, available PROs in glaucoma literature can be classified into three major categories [35]: PROs addressing functional status related to vision, PROs addressing overall QoL, and PROs assessing other factors related to disease and treatment (i.e., symptoms, side effects, adherence, satisfaction, self-efficacy) (Table 2).

The first category of PROs (i.e., those addressing functional status related to vision) refers to a set of questionnaires that investigate a patient's ability to undertake daily activities, fulfill life roles, and perform actions designed to maintain health and well-being [37]. All the questionnaires describe activities that need visual function and the patient is asked to rate these activities as difficult or problematic. In this category, a questionnaire was developed to measure patients' abilities to find their way, walk, and travel safely and independently (Independent Mobility Questionnaire, IMQ) [38]. Independent mobility perceived by glaucoma patients was associated with mean deviation (MD) in the better eye ($p < 0.01$) and visual acuity in the better eye, the fellow eye, and in both eyes ($p = 0.05$) [39]. In the same category of PROs, the Glaucoma Symptom Identifier (GSI) was designed to assess multiple possible glaucoma symptoms and their impact on QoL in clinical practice [40].

PROs assessing overall QoL include questionnaires that investigate the impact of eye diseases on QoL, as perceived by the patient. As QoL is a multidimensional concept, PROs in this category analyze different domains to comprise all facets of living (from physical to psychological ones).

The National Eye Institute Vision Function Questionnaires (NEI-VFQ-25 and -51 items) were developed to measure vision-targeted functioning and influence of vision problems on health-related QoL (HR-QoL) across several eye conditions [41, 42]. The creation and selection of items involved different groups of

Table 2 Patient-reported outcome questionnaires

Questionnaire	Brief description	No. items	Domains	Validated
COMTOL	Developed for use in clinical trials to compare ophthalmic medications	37	Influence of glaucoma therapy on QoL considering frequency and severity of common side effects	Yes (in patients treated with timolol and pilocarpine)
IMQ	Patient's ability to undertake daily activities, fulfill life roles, and perform actions	35	Patients' abilities to walk, travel safely and independently	Yes
GSI	Multiple possible glaucoma symptoms and their impact on QoL in clinical practice	32	Assess multiple possible glaucoma symptoms and their impact on QoL	Yes
Glau-QoL	Patients' input in view of items generation	36	Series of glaucoma-specific tests and QoL	No
NEI-VFQ	Instrument to assess vision-dependent function and QoL	51	Vision-targeted functioning and influence of vision problems on health-related QoL	Yes
TSS-IOP	Questionnaire to evaluate patient's satisfaction with various aspects of topical medications	42	Patient's satisfaction with various aspects of topical medication	No

COMTOL Comparison of Ophthalmic Medications for Tolerability, *IMQ* Independent Mobility Questionnaire, *GSI* Glaucoma Symptom Identifier, *Glau-Qol* Glaucoma Quality of Life, *NEI-VFQ* National Eye Institute Vision Function Questionnaire, *TSS-IOP* Treatment Satisfaction Survey-Intraocular Pressure

patients with glaucoma, macular degeneration, cataract, and other eye diseases. One-third of the patients involved in item selection had POAG, with a wide range of severity. The NEI-VFQ, both in the 51-item and the shorter 25-item version, have been widely used and shown to be internally consistent [43, 44], reproducible [43], and responsive in glaucoma patients [44]. NEI-VFQs were used in randomized clinical trials, such as the Early Manifest Glaucoma Trial (EMGT) [45] and The Tube versus Trabeculectomy Study [46].

Beside general vision-specific instruments, PROs assessing overall QoL include several glaucoma-specific tests, such as the Glaucoma Quality of Life (Glau-QoL) questionnaire [47], the Glaucoma Health Perception Index [48, 49], and the Glaucoma Utility Index [50]. Almost all these questionnaires include patients' input for item generation. They have good developmental characteristics, with strong evidence of validity [47].

The third category of PROs includes questionnaires developed to assess either topical treatment or disease-related factors that can influence QoL. The Treatment Satisfaction Survey-Intraocular Pressure (TSS-IOP) is designed to evaluate patient satisfaction with various aspects of topical medications employed in glaucoma. The methods used to select and organize items were adequate [51]. Although TSS-IOP is the instrument of choice for

comparing different classes of topical medication, validation is still lacking [51, 52]. Another instrument to evaluate the influence of glaucoma therapy on QoL, The Comparison of Ophthalmic Medications for Tolerability (COMTOL) questionnaire, uses common side effects reported by patients in clinical trials [53]. It was only validated in patients treated with timolol and pilocarpine, so difficulties may arise in applying it for patients who use other therapies. Beside side effects due to topical medication, which are extensively investigated both by TSS-IOP and COMTOL, TSS-IOP focuses more on patient satisfaction related to the effectiveness of eye drops, while COMTOL addresses daily activity limitations (e.g., driving) due to topical therapy.

QUALITY OF LIFE IN GLAUCOMA PATIENTS: LOSS OF VISUAL FUNCTION

Early detection of glaucoma is one of the objectives stressed by glaucoma societies to preserve visual function and patients' QoL [54, 55]. Patients with early glaucoma often remain undiagnosed until it progresses to advanced stages, when central vision is affected. Several studies have reported visual acuity loss as one of the causes associated with lower HR-QoL in POAG patients [33, 56, 57].

In the EMGT, the Swedish version of the NEI-VFQ-25 was self-administered to patients 3 and 6 years after randomization [44]. At the 3-year administration, the mean composite score (88.8) and mean subscale scores (98.0–58.3) were generally high and there were no differences between the treatment and observation groups. Although the patients showed good results in terms of QoL, NEI-VFQ scores were correlated with low visual acuity in the better eye, worse perimetric MD, and nuclear lens opacities; no correlation was found with age, sex, IOP, cardiovascular disease, or systemic hypertension. Larger drops in composite scores between the 3- and 6-year NEI-VFQ were associated with greater loss in visual acuity ($p < 0.05$), but treatment (assigned at randomization or later in the study) had no effect on QoL. These results suggest that absence or delay of treatment does not influence vision-targeted QoL in early glaucoma patients up to 6 years from initial diagnosis.

A recent report from EMGT, after 20 years of follow-up, showed that many patients with VF loss of less than 50% (e.g., VF index 50% or MD −18 dB) in the better eye rated their vision-related QoL at a level similar to that reported by patients with no VF loss in the better eye [58]. These results support the arbitrary, but widely used, limit of a better-eye VF loss of less than 50% as an important threshold for severe functional impairment.

The Collaborative Initial Glaucoma Treatment Study (CIGTS) randomized 607 newly diagnosed patients with POAG to treatment either with medications or trabeculectomy (with or without 5-fluorouracil) [59]. The authors elaborated a CIGTS-dedicated instrument consisting of a combination of generic and disease-specific PROs to compare patients' QoL between treatment groups [48]. It included 246 items, administered to the patient by phone in about 45 min. Correlation coefficients between disease-specific QoL measures and VF scores were weak even if statistically significant. At initial diagnosis, difficulty with bright lights and difficulty with light and dark adaptation were the most frequently reported symptoms related to visual function, while visual distortion was the most bothersome. Patients were divided into three VF subgroups, derived

from the worse eye CIGTS VF score, representing mild, moderate, and severe VF loss. All the means from the disease-specific questionnaires were ranked according to the level of the disease.

VF MD in the best eye was used in another study to classify POAG patients into three stages (early, moderate, and advanced) [60]. OHT patients and healthy controls were enrolled as well. General QoL and visual function QoL were evaluated in each stage of the disease. No differences were found in QoL perception between healthy patients and OHT/early POAG patients, showing that neither medications nor the knowledge of having the disease affected QoL. In contrast, a difference was found between OHT/early and moderate/severe glaucoma patients, with progressive reduction in QoL perception throughout the stages of the disease.

Three questions were strongly associated with the gravity of the binocular VF defect in glaucoma patients [61, 62]: (1) do you bump into things sometimes? (2) Do you trip on things or have difficulty with stairs? (3) Do you have difficulty in finding things you have dropped? These abilities appeared to be linearly and progressively affected in the progression of the disease, influencing QoL more in advanced stages [61], particularly in patients with MD less than −12 dB [62].

The Los Angeles Latino Eye Study (LALES) was a population-based prevalence study of eye diseases in Latinos living in Los Angeles, California, aged 40 years and more [63]. A total of 213 patients with POAG from a population of 7789 participants were included in an analysis to determine the impact of glaucomatous VF loss on QoL [64]. HR-QoL was assessed by the Medical Outcomes Study 12-item Short-Form Health Survey (SF12) and the NEI-VFQ-25 questionnaire. A monotonic correlation trend was observed between VF loss and most NEI-VFQ-25 subscale scores, showing that glaucoma patients with severe VF loss had lower QoL scores than patients with no or initial VF loss. Correlation coefficients from the better-seeing eye were significant for 6 of the 12 NEI-VFQ subscales and the NEI-VFQ composite score. Glaucoma patients had greatest difficulties driving, especially in more advanced stages of the disease. A unique feature of this study was the ability to measure self-reported QoL before the participants were diagnosed with glaucoma and therefore before they were aware of the disease. At enrollment 75% of patients affected with glaucoma were unaware of it. Interestingly, however, the association between QoL scores and VF loss persisted even after controlling for knowledge of glaucoma or when analysis was restricted to LALES patients unaware of the disease.

An objective estimation of vision-specific ability to perform activities of daily living and its correlation to clinical tests (i.e., visual acuity, visual field test, contrast sensibility, and stereopsis) was attempted in a group of glaucoma patients by Richman et al. [65]. These authors employed the ADREV (Assessment of Disability Related to Vision) test to objectively score patients' ability to perform daily-life actions, such as reading in reduced illumination or recognizing facial expressions. Interestingly, results of clinical tests had higher correlations with ADREV than with NEI-VFQ-25 scores. These data highlight a potential limit of PROs, i.e., the dependency on subjective sphere and the high variation of responses also in patients with the same severity of disease.

QUALITY OF LIFE: MONOCULAR VS. BINOCULAR VISUAL FIELD LOSS

In advanced glaucoma the areas of monocular VF defects may coincide in the two eyes, resulting in binocular VF loss. Central VF and visual acuity are generally spared until the disease is more advanced. Patients with binocular VF loss have serious difficulties in activities of daily life such as reading, mobility, or driving [66–69]. However, QoL can also be affected by VF loss in one eye independently. The location of VF in one eye may play an important role in patients' QoL perception.

A cross-sectional study investigated the relationship between VF loss and QoL in 537 OHT and POAG patients from seven hospitals in the Netherlands [70], using MD from the 30-2 threshold program of the Humphrey Field Analyzer to quantify monocular and binocular VF loss. QoL was investigated with a questionnaire containing health-generic (EQ5D and Health Utilities Index mark 3), vision-specific (NEI-VFQ-25), and glaucoma-specific (Glaucoma Quality-of-Life questionnaire, GQL-15) instruments. The relationship between QoL scores and MD was significant for the generic and disease-specific QoL instruments. However, while the relationship between VF loss and disease-specific questionnaires was linear (QoL declined with VF progression), the relationship between VF loss and health-generic instruments was not. Indeed, utility scores seemed significantly affected by VF loss when MD in the better eye was below −25 dB. The impact on QoL of VF loss in the better eye was stronger than in the worse eye. Binocular VF appeared to be mainly determined by VF in the better eye. The impact on QoL of VF loss in the better eye grew in line with the VF defect in the worse eye.

Another study investigated the vision-specific QoL in glaucoma patients on the basis of the location of VF defects [71]. A significant correlation was detected between vision-specific QoL scores and clustered VF MD in both the better and the worse eye, although correlation coefficients were generally higher for the better eye. The correlation coefficients for the lower paracentral and lower peripheral VF of the better eye were the highest for several subscales, such as general vision, near vision, distance vision, social function, mental health, role limitation, and driving.

Another investigation analyzed the association between glaucoma-induced VF defects in the superior and inferior hemifields and vision-related QoL [72]. Patients were evaluated with the 24-2 SITA Standard program of the Humphrey Visual field Analyzer, and an integrated VF was calculated using the best sensitivity method [73]. Vision-related QoL was evaluated using the NEI-VFQ-25. The MD of the superior hemifield was correlated only with near activities score ($p < 0.01$), while the MD of the inferior hemifield was positively correlated with general vision, vision-specific role difficulties, and peripheral vision. This may explain why patients with glaucoma and worse binocular inferior VF have slower walking speed, higher rates of falls, and more falls with injury among elderly individuals [74, 75].

Data from the Diagnostic Innovations Glaucoma Study (DIGS) were used to evaluate the correlation between longitudinal changes in QoL and rates of progressive VF loss [76]. A significant correlation was found between changes in the NEI-VFQ-25 scores during follow-up and changes in binocular VF sensitivity. Eyes with more severe disease at baseline were more likely to have lower

NEI-VFQ-25 scores during follow-up. For patients with the same extent of binocular sensitivity loss over time, those with shorter follow-up had larger changes in NEI-VFQ-25 scores ($p = 0.005$).

MENTAL HEALTH STATUS AND QUALITY OF LIFE IN GLAUCOMA

Many studies have investigated the relationship between glaucoma, anxiety, and depression [77–86]. Although there is no actual evidence on this topic, a higher prevalence of psychological disorders in glaucoma patients can be reasonably assumed. As a result of its asymptomatic, chronic nature and potential outcome of blindness, glaucoma often imposes a psychological burden [79, 87]. Limitation of life spaces due to a variety of factors, such as driving limitations [88, 89], fear of falling [90, 91], and worse balance [82], also contribute to the relationship between glaucoma and depression.

The prevalence of anxiety and depression in patients with POAG was evaluated in a case–control study [80] using the Hospital Anxiety and Depression Scale (HADS) questionnaire. The prevalence of patients with anxiety (13.0%) and depression (10.9%) was significantly higher than in the control group (7.0% and 5.2% respectively, $p < 0.05$). When glaucoma was evaluated as a potential risk factor for anxiety and depression, a negative correlation was found between age and the HADS-Anxiety subscore, after adjusting for demographic and clinical variables ($p < 0.01$) [81]. Interestingly, younger glaucoma patients tended to be more anxious compared to older ones, as demonstrated in studies on other chronic diseases [92, 93]. As expected, older age and decreasing MD, determined by computerized perimetry in the better eye, were associated with depression.

Jampel et al. investigated depression and mood indicators in newly diagnosed POAG patients, as a part of CIGTS [79]. At baseline patients were interviewed by telephone and answered three questionnaires about their vision in daily-life activities (Visual Activity Questionnaire, VAQ), their perception of health (Health Perception Index, HPI), and their depression status (eight questions from the Center for Epidemiological Studies Depression Scale, CES-D). Objective measures of poorer visual function (i.e., visual acuity and CIGTS VF) were not correlated with symptoms of depression and poor mood, while patients' perception of their vision (total VAQ score) was significantly correlated to each item of the HPI and CES-D ($p \leq 0.001$). In other words, QoL was more affected by the way the patients perceived their vision than the objective measurement of it. In addition, depression itself may have led to poorer responses to VAQ questions, acting as a confounding factor in the analysis.

CIGTS QoL questionnaires included an assessment of fear of blindness (FOB). As these questionnaires were administered by trained telephone interviewers every 6 months, changes in FOB were assessed continuously during the 5-year follow-up [87]. At baseline, after being told about glaucoma diagnosis but before randomization, 34% of patients reported either a moderate amount or a lot of worry about blindness (Fig. 3). This decreased to 17% by 6 months and to 11% over a 5-year period. Almost half the patients remained at least a little worried 5 years after the diagnosis of glaucoma. In multivariate analysis, younger age, white ethnicity, low-grade education, and lower income were significantly associated with increased FOB ($p = 0.006$). The decrease in FOB over time was probably due to the reassurance

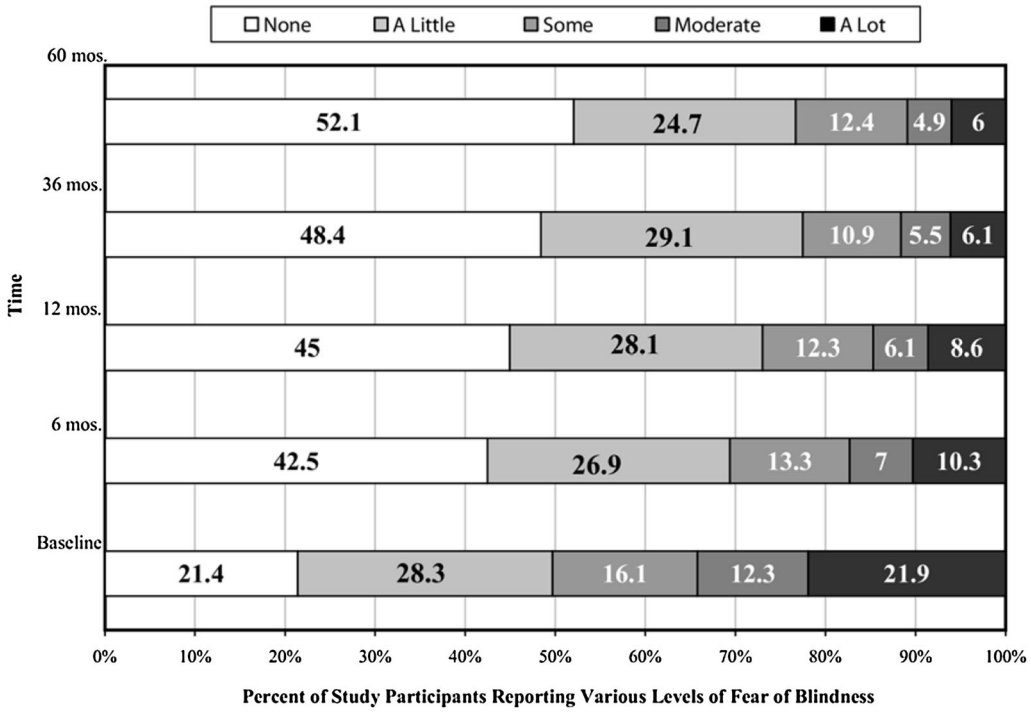

Fig. 3 Rates of fear of blindness over time in the Collaborative Initial Glaucoma Treatment Study (adapted from Janz et al. [48])

associated with receiving treatment, regular clinical follow-up, adaptation to the diagnosis, or a combination thereof.

QUALITY OF LIFE: GLAUCOMA THERAPIES

Glaucoma treatment may influence patients' QoL in several ways. Topical and systemic side effects, difficulties in administering medications, and complexity of medication regimens are all factors that can reduce patients' satisfaction with their therapy [94]. Patients satisfied with therapy are more likely to adhere to it [95], to take an active role in their own care [96], and to continue using medical care services [97].

Tsai et al., using patient interviews, created a taxonomy of reasons for poor adherence in a group of patients with glaucoma [98]. Situational/environmental tasks explained 80% of poor compliance with therapy. The need to take drops always at the same time and the inability to carry medication bottles when away from home may be decisive factors. Routines are part of life, and changes in routine often mean a change in QoL, especially for older patients. Similarly, side effects of eye drops, such as hyperemia, burning, stinging, foreign body sensation, and blurred vision, can influence social and environmental aspects of life besides making the patient dissatisfied with therapy.

Jampel et al. administered a willingness to pay questionnaire to a group of 230 patients with glaucoma or suspected glaucoma, asking them how much they would be willing to pay for certain characteristics in eye drops [99]. Patients were willing to pay more for eye drops that did not cause blurred vision (85%), drowsiness (83%), stinging or tearing (72%), or

cause sexual inhibition (59%); 59% were willing to pay more for eye drops that required once-only dosing, instead of three times a day regimens. On the other hand, only 26% of patients would have paid more to obtain branded drops instead of generic ones. Eye drop side effects and their social/environmental implications appeared to be key factors in influencing glaucoma patient QoL.

Similar results were obtained in another study, which used a Treatment Satisfaction Survey-Intraocular Pressure questionnaire (TSS-IOP) [52]. This is a PRO designed to assess patient satisfaction with various attributes of topical ocular medications. Patient satisfaction was correlated with perceived effectiveness of the medicine, ocular irritation, conjunctival hyperemia, ease and convenience of use ($p < 0.001$). Compliance was correlated with perceived effectiveness of the medicine ($p < 0.001$), ease of use ($p < 0.05$), and convenience ($p < 0.001$). When physicians were asked to rate patient compliance, no significant correlation was found with any dimension of patient satisfaction ($p < 0.05$), showing that physicians poorly predict patients' own rankings of compliance.

The association between factors linked with topical medication use and health-related QoL was evaluated by Balkrishnan et al. in a cross-sectional study on 358 glaucoma patients [100]. Patients were interviewed by mail with a 48-item questionnaire, comprising the VFQ-25, the SF12, and six questions about the use of antiglaucoma eye drops. The daily use of more than five medications and difficulty in using the eye drops were negatively associated with health-related QoL scores. In multivariate analysis, difficulty with eye drop use remained the only medication-related factor significantly predictive of lower VFQ-25 and SF-12 scores. Other studies indicated that problems with eye drop use and complex regimens may play a role in poor compliance [101, 102]. Claxton et al. performed a systematic review of the medical literature, highlighting that fewer doses per day significantly correlated with better compliance [103]. A study of add-on therapy also suggested that patients prescribed a second ocular hypotensive medication refilled their first prescribed medication less regularly [104]. Difficulties with medication use in older patients affected with glaucoma may have several causes [105]. Medication bottles are often an obstacle to treatment because of difficulties with topical application. Moreover, many older adults with glaucoma have considerable comorbidity, such as arthritis, which impairs their ability to depress the applicators of eye drops.

QUALITY OF LIFE: OCULAR SURFACE DISEASE

Ocular surface disease (OSD) is characterized by an inadequate quantity of tears, an unstable tear film secondary to poor quality of tears, ocular surface breakdown, and/or symptoms such as irritation, burning, foreign body sensation, dryness, photophobia, fatigue, and fluctuating visual acuity [106]. OSD has an estimated prevalence of 15% among individuals older than 65 years [107] and this rises to 59% in patients with glaucoma [106]. The higher prevalence among glaucoma patients is probably due to the fact that OSD and glaucoma both have an age-dependent prevalence; furthermore, the antiglaucoma eye drops and the preservative agents (especially benzalkonium chloride, BAK) may cause inflammation [108, 109], as well as other anterior segment ocular diseases (allergy, blepharitis, dry eye) [110].

Skalicky et al. evaluated the impact of OSD on QoL in 101 glaucoma patients and 23 controls [111]. All completed a glaucoma-specific QoL questionnaire (GQL-15) and an Ocular Surface Disease Index questionnaire (OSDI). OSDI is a 12-item questionnaire designed to provide a rapid assessment of OSD related to chronic dry eye, its severity, and its impact on the patient's ability to function [112]. OSDI scores correlated well with glaucoma severity in patients younger than 60 years and in the 70–79 years subgroup. Exposure to more than three BAK-preserved drops daily was independently predictive of OSD in multivariate analysis ($p = 0.018$), underlining the causal role of preservatives in OSD.

Another study examined the relationship between OSD and QoL in glaucoma and OHT patients treated with BAK-preserved eye drops [113]. Patients were asked to complete the NEI-VFQ25 and Glaucoma Symptom Scale (GSS) questionnaires. This latter includes 10 ocular complaints, some of nonvisual nature (burning/smarting/stinging, tearing, dryness, itching, soreness/tiredness, feeling of something in the eye: GSS Symptom score) and some visual (blurry/dim vision, hard to see in daylight, hard to see in the dark, halos around lights: GSS Function score), common among patients treated for glaucoma. OSD was diagnosed in 97 patients (41.6%), with no difference by sex ($p = 0.55$) or age ($p = 0.2$), and it was significantly related to the number of years of topical treatment ($p < 0.001$). Patients with OSD had significantly worse mean total NEI-VFQ and GSS scores ($p = 0.04$ and $p < 0.001$, respectively). Punctate keratitis was present in 70 (30%) patients and related to age ($p = 0.01$) and the number of topical doses per day ($p < 0.001$). Patients with keratitis had worse GSS scores as well ($p < 0.001$).

The use of BAK-preserved medications has been associated with the development of OSD [114, 115]. Few studies have examined the effects of preservative-free medications on QoL. Some looked at OSD signs (BUT, fluorescein staining, hyperemia) after changing from a preserved antiglaucoma drug to a preservative-free formulation [116–120]. However, as anterior segment signs are barely correlated with the severity of OSD [121, 122], no real conclusions can be drawn on this topic.

QUALITY OF LIFE IN MEDICALLY VS. SURGICALLY TREATED GLAUCOMA PATIENTS

The CIGTS [123] was the only study identified by a Cochrane systematic review that examined QoL in medically or surgically treated glaucoma patients [124]. For this reason no firm conclusions can be drawn on this topic.

After the first 5 years of CIGTS follow-up, the QoL impact reported by the two treatment groups was not different, except that patients who underwent surgery treatment complained more frequently of local eye symptoms (something in the eye, eye pain, red eye, excessive tearing, etc.) [123]. This was not unexpected, given the presence of a filtering conjunctival bleb in the surgical group. The effect of surgery on eye symptoms was initially larger, but the magnitude of this effect decreased over time. A trend towards a reduction of symptom frequency and symptom bothersomeness was noted during the follow-up in both the surgical and medical groups. This could be related to a combination of coping, psychological adjustment and accommodation to the glaucoma diagnosis, or to the actual decrease or cessation of the particular problem.

Guedes et al. examined QoL in 225 Brazilian glaucoma patients, divided into three groups according to their management: medical (82 patients), surgical (47 patients), and medical plus surgical (96 patients) treatment [125]. QoL was assessed by using the validated Portuguese-language version of the NEI-VFQ-25. When analysis was controlled for confounding variables, surgery was a predictor of poor QoL only in patients with early disease and did not influence QoL in more advanced cases. No difference was noted among various glaucoma surgeries ($p = 0.19$).

GLAUCOMA AND DISABILITY: WHICH TASKS OF DAILY LIFE ARE AFFECTED?

Loss of visual function in glaucoma patients can affect walking, venturing out from home, reading, seeing at night, adjusting to different levels of illumination, judging distances, and seeing objects coming from the side [126, 127]. When glaucoma patients were asked to choose which activities were most important among hypothetical scenarios in which they had different levels of difficulty with different tasks, the greatest importance was given to tasks involving central and near vision (i.e., reading), with high scores also for mobility outside the home (i.e., driving and walking outside) [34, 50]. Problems like glare, bumping into objects, and household chores were considered minor [34].

Difficulties with central and near vision tasks in general, and with reading specifically, are the most frequent complaint among people with eye disease. Near vision tasks such as reading are also the most valued visual function in those with glaucoma. While reading is clearly dependent on visual acuity, complaints of difficulty reading are commonplace and were noted in over 40% of the glaucoma patients [69].

In the Salisbury Eye Evaluation Study (SES), subjects with bilateral glaucoma were almost five times more likely to report severe difficulty with near activities than those without glaucoma [128]. This confirms several clinic-based studies that report more vision-related difficulty with near vision tasks in the presence of glaucoma-related VF loss [69]. Data from SES, however, indicated significant discordance between measured reading speed and self-reported reading difficulty, particularly in people who read poorly. This disparity between measured reading speed and self-assessment highlights the need to use both questionnaire and direct testing methods to assess reading [129].

Outdoor mobility is a priority for glaucoma patients [34, 50], and driving is the primary means of transport among the elderly in the USA [130]. An analysis of patients enrolled in CIGTS showed that over 50% of driving patients reported at least "some" difficulties in tasks involving glare, while 22% reported at least "some" difficulties with tasks requiring peripheral vision. Drivers with moderate bilateral VF loss were more likely to report at least some difficulties with all the driving tasks investigated, compared to patients with mild or no bilateral VF defects.

The role of binocular VF in driving tasks was also investigated in other studies [64, 128, 131]. The SEE study found a strong correlation between binocular VF and night driving tasks, also after adjusting for contrast sensitivity [128]. The Los Angeles Latino Eye Study reported that bilateral moderate to severe VF loss had a great impact on driving tasks, while moderate to severe unilateral VF defects had less influence on driving capabilities [131]. The influence of the better and worse eye on driving in patients

with glaucoma is not completely clear. Perceived difficulty in driving tasks seems to increase with worsening VF damage in the better eye [30, 69, 131].

Several studies have shown that glaucoma patients tend to modify their driving habits, as a result of perceiving difficulty with their vision [88, 132–135]. Discontinuation of driving was significantly more frequent in patients with glaucoma in both eyes, but not in one eye, compared with healthy subjects [88]. Moreover, when compared with people without glaucoma, patients with glaucoma in both eyes more frequently reported vision-related discontinuation of driving at night, vision-related decreased driving frequency, and vision-related cessation of driving in unfamiliar areas.

CONCLUSION

Physicians are used to claiming the success of glaucoma management with parameters like IOP, visual fields, and damage progression. However, from the perspective of the patients, other concerns may be far more important [136]. The most frequent problems related to decreased vision were reading, walking on stairs, and recognizing people. Difficulties with these activities were more often reported by older patients than younger ones. This is not surprising and is probably more closely related to age itself than to glaucomatous damage.

Assessment of QoL with a questionnaire has several limitations. QoL assessment is subjective: patients with similar disability may rate their QoL differently. An inherent limitation of QoL assessment is that self-reported visual ability evaluated by any questionnaire can be impaired, at least to some extent, by other visual and systemic morbidity or psychosocial constraints. Conceivably, even when perimetric indices such as MD are comparable, different determinants such as spatial distribution and depth of VF scotomas or speed of perimetric deterioration may affect patients with dissimilar lifestyles and expectations [76].

Early detection of glaucoma is a vital objective in clinical management so that visual function and QoL are preserved [54, 55]. Patients with early glaucoma often remain undiagnosed until progression to advanced stages. The present review underlines the importance of timely glaucoma diagnosis in preserving vision-related QoL. However, falsely diagnosing patients as having glaucoma can significantly reduce their QoL and well-being.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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