

Quality of Life of Glaucoma Patients with its Socio-demographic and Clinical Associates

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Abstract— Medical Glaucoma is a major cause of blindness. It affect quality of life of patients. So the present study was carried out in ESI Hospital, Jaipur with the aim to assess quality of life of glaucoma patients as per WHOQOL-Bref. Along with assessment of quality of life of patients various socio-demographic and clinical associates of this quality of life was also found. It was observed that quality of life of glaucoma patients was lowered in all four domains i.e. Physical, Mental, Social and Environmental. Among socio-demographic variables, quality of life was not found to be associated with sex and marital status but it was found more poorer in elder age groups and low socio-economic status. Among clinical variables its quality of life of glaucoma patients was not found to be associated with papillary reaction, Anterior chamber depth (ACD), type of glaucoma and duration of glaucoma but it was found more poorer in glaucoma patients with pain, congestion and defective visual equity. Quality of life was significantly lowered in sever glaucoma. Glaucoma patients should be educated to realize the severity of the disease and importance of the adherence to daily treatment.

Key words: Glaucoma, Quality of Life, WHOQOL-Bref

1. Introduction

Glaucoma is the third largest cause of blindness worldwide. Despite advances in therapy the global burden of glaucoma remains high. In 2010 an estimated 60.5 million people suffered from glaucoma and as per estimates by 2020 this will reach 79.6 million, of whom 11.2 million will be bilaterally blind.¹

Glaucoma affect the quality of life (QoL) of patients. Using generic QOL assessments, glaucoma was found to have an adverse impact on QoL as other systemic chronic diseases like osteoporosis, diabetes, or dementia.²

Quality-of life assessment in glaucoma patients is as important as the clinical parameters as it is an indicator of whether the disease is advancing.^{3,4,5} It can aid the clinician and patient to make difficult clinical decisions, and can guide choices to individualize therapy.^{6,7} So, a comprehensive assessment of QoL has become important in clinical research of glaucoma also.

Recently the US Food and Drug Administration has endorsed that QoL assessment be included in all clinical trials evaluating disease impact and treatment assessment in glaucoma.⁸ Keeping in view the wide recognition of QoL in glaucoma patients like any other chronic disease and its impact on clinical decisions and clinician perspective, this present study was planned to assess the quality of life and to found its socio-demographic and clinical correlates in glaucoma patients.

2. Methodology

After taking approval from Institutional Ethics committee, this observational study was carried out as joint venture of Department of Psychiatry and Department of Ophthalmology in a multi-specialty

referral centre from January 2013 to June 2013. This hospital caters population belonging to defined income group from each corner of the province and neighbouring state as well.

Study sample comprised of 100 Patients with glaucoma. Patients were recruited from both outpatient department in glaucoma clinic and the ward. Equal number of healthy controls was also enrolled from attendants of patients to make a comparison group. Utmost care was taken to ensure the homogeneity of the sample population by recruiting the close relatives or friends of the patients as control group. Ethical committee approval was obtained and the nature and purpose of the study was explained to all the participants before obtaining their consent prior to their inclusion in study sample.

Patients 18 years or above of either sex with a glaucoma diagnosis more than 6 months prior to enrolment were included in the study group. Glaucoma was diagnosed based on glaucomatous disc cupping and reproducible visual field damage in one or both eyes. Patients with primary open-angle glaucoma (POAG) including normal tension glaucoma (NTG), primary angle closure glaucoma (PACG) and secondary glaucoma (SG) comprising exfoliation syndrome, pigmentary glaucoma, lens induced glaucoma uveitis, complication of vitreo- retinal surgery and traumatic eye surgery were included in this study.

Exclusion criteria to exclude the patients from this study were: (1) Present or past history of major psychiatric illness, Insomnia or substance use disorders that could affect quality of life (2) inability to speak, read and understand Hindi; (3) laser treatment within the previous one month; (4) disability in visual field testing due to causes other than glaucoma (*e.g.* cognitive impairment); (5) other severe vision-impaired eye diseases (*e.g.* cataracts (Lens Opacities Classification System III grade 2 or more and age-related macular degeneration).

All the sample subjects including glaucoma patients and controls were interrogated to have information regarding age, gender, income, family history of glaucoma, educational level, and duration of illness etc.

Quality of life of all the study population including patients and controls were assessed by WHOQOL- Bref. QOL scores for different four domains viz. Physical, Mental, Social and Environmental domains were assessed.

WHOQOL-BREF, was developed by the World Health Organization Quality of Life Group, in 15 international field centers⁹. It is a self-report questionnaire that contains 26 items. Among the 26 items, 24 of them make up the 4 domains of physical (7 items), psychological (6 items), social (3 items) and environment (8 items) health. Other 2 items measure overall quality of life and general health. In this study Hindi version¹⁰ was used. The scale has been shown to have good discriminate validity, sound content validity and good test-retest reliability at several international WHOQOL centers.

Glaucoma patients underwent comprehensive ophthalmic examination for presentation symptoms like pain, congestion, anterior chamber depth by slit lamp examination, visual acuity by refraction unit and detailed fundus examination for glaucomatous cupping. Cup disc ratio and automated static perimetry (Humphrey visual field analyzer 30-2 was used to detect peripheral visual field defects) of each patient was assessed. Gonioscopy was also done to find out status of angle, whether open or closed. Patients were categorized as mild, moderate and severe depending on the results of status of cup and fields.

Data thus collected was compiled in MS Excel 2007 worksheet in the form of master chart. To determine the significance of difference of means unpaired 't' test and one way analysis of variance

(ANOVA) was applied with the help of Statistical Software Primer (version 6). For significance *P* value 0.05 or less was considered significant.

3. Results

Total 100 patients of glaucoma consisting 75 % of OAG and 25 % ACG along with equal number of age and sex matched healthy control constituted the study sample. Mean age of patients was 55.5 years with age range 18 to 82 years.

Significant difference ($p < 0.001$) was observed between cases and controls in respect of all the four domains viz physical (48.57 v/s 65.47 mean scores with $P < 0.001$), psychological (49.70 v/s 69.23 mean scores with $P < 0.001$), social (47.41 v/s 71.42 mean scores with $P < 0.001$) and environmental (47.55 v/s 68.09 mean scores with $P < 0.001$). Glaucoma patients had significantly lower QoL in all the four domains than the control group. (Table 1)

Table No. 1

Comparison of QoL in Glaucoma patients and Controls

S. No.	Domains	Glaucoma (N=100) Mean $\pm$ SD	Control Group (N=100) Mean $\pm$ SD	Unpaired 't' test, P Value, LS
1	Physical (D ₁)	48.57 $\pm$ 65.47	65.47 $\pm$ 20.6	5.9 at 198 DF, $P < 0.001$ S
2	Psychological (D ₂)	49.70 $\pm$ 69.23	69.23 $\pm$ 19.52	7.3 at 198 DF, $P < 0.001$ S
3	Social (D ₃)	47.41 $\pm$ 71.42	71.42 $\pm$ 21.8	7.5 at 198 DF, $P < 0.001$ S
4	Environmental (D ₄)	47.55 $\pm$ 68.09	68.09 $\pm$ 18.84	7.9 at 198 DF, $P < 0.001$ S

When association of socio demographic variables with QoL was observed, it was revealed that lower income group had significantly poor QoL in all the four domains. Similarly middle age group patients reported significantly low scores in physical, psychological and environmental domains. (Table 2)

Table No. 2

Association of Socio-demographic variables with QoL in Glaucoma patients

S. No.	Socio-demographic Variables	Number of Patients	Physical (D ₁) Mean $\pm$ SD	Psychological (D ₂) Mean $\pm$ SD	Social (D ₃) Mean $\pm$ SD	Environmental (D ₄) Mean $\pm$ SD
1.	Sex					
	Males	50	50.24 $\pm$ 19.78	52.06 $\pm$ 18.52	49.84 $\pm$ 22.83	48.96 $\pm$ 22.83
	Females	50	48.46 $\pm$ 17.76	48.72 $\pm$ 16.48	58.66 $\pm$ 73.32	47.1 $\pm$ 17.35
Unpaired 't' test P value & LS			P > 0.05 N S	P > 0.05 N S	P > 0.05 N S	P > 0.05 N S
2	Age Groups					

	<30 yrs	7	64±19.97	65±19.81	65.57±25.28	58.43±19.6
	31-50 yrs	38	55.47±19.19	56.21±18.05	54.18±23.43	52.94±17.99
	50-70 yrs	50	45.3±11.97	44.18±14.1	41.54±19.7	43±16.02
	>70 yrs	5	60.6±15.45	57.4±6.98	60.4±17.51	53.6±3.28
*ANOVA test P value & LS			P=0.002 S	P<0.001 S	P>0.05 N S	P=0.015 S
3	Marital Status					
	Married	95	48.09±18.59	49.17±17.61	46.81±22.88	47.16±17.59
	Unmarried	5	57.6±31.53	59.8±21.44	58.8±30.41	55±21.34
Unpaired 't' test P value & LS			P>0.05 N S	P>0.05 N S	P>0.05 N S	P>0.05 N S
4	Income Gp					
	<5000	59	44.12±18.17	44.92±16.05	41.53±22.62	43.58±17.58
	5000-10,000	34	56.09±18.04	55.68±18.96	56.26±22.52	52.74±17.18
	10000-15000	3	79.33±25.4	71.67±14.29	73±25.24	65.67±17.16
	>15000	4	45.5±16.25	60±16.25	56±20.85	53.25±14.77
*ANOVA test P value & LS			P<0.001 S	P=0.003 S	P=0.005 S	P=0.024 S

*Post Hoc Tukey Test (P<0.05 i.e. **Significance Difference in Means of various Age Groups**)

Physical(D ₁) Means	Psychological (D ₂) Mean	Social (D ₃)Mean	Environmental (D ₄) Mean
<30 v/s 50-70 31-50 v/s 50-70 50-70 v/s > 70	<30 v/s 50-70 31-50 v/s 50-70 50-70 v/s > 70	-	<30 v/s 50-70 31-50 v/s 50-70 50-70 v/s > 70

*Post Hoc Tukey Test (P<0.05 i.e. **Significance Difference in Means of various Income Groups**)

Physical(D ₁) Means	Psychological (D ₂) Mean	Social (D ₃)Mean	Environmental (D ₄) Mean
<5000 v/s 5000-10,000 <5000 v/s 10,000-15000	<5000 v/s 5000-10,000 <5000 v/s 10,000-15000	<5000 v/s 5000-10,000	<5000 v/s 5000-10,000 <5000 v/s 10,000-15000

Likewise when association of clinical variables with QoL was observed, it was revealed that pain , congestion and diminished visual acuity in both right were significantly associated with poor QoL in all domains. Glaucoma patients also reported statistically poor scores (p<0.05) in physical and social domains with positive pupillary reaction and shallow anterior chamber depth. (**Table 3**)

Table No. 3

Association of Clinical Variables with QoL in Glaucoma patients

S. No.	Clinical Variables	No. Of Patients	Physical Mean $\pm$ SD ((D ₁	Psychological (D ₂)Mean $\pm$ SD	Social (D ₃)Mean $\pm$ SD	Environmental (D ₄) Mean $\pm$ SD
1.	Pain					
	Yes	34	42.65 $\pm$ 18.46	43.41 $\pm$ 17.11	40.14 $\pm$ 19.42	42.47 $\pm$ 15.98
	No	66	51.53 $\pm$ 19.18	52.76 $\pm$ 17.5	51.06 $\pm$ 24.3	50.06 $\pm$ 18.12
Unpaired 't' test P value & LS			P=0.029 S	P=0.012 S	P=0.028 S	P=0.040 S
2	Congestion					
	Yes	23	42.57 $\pm$ 17.52	42.39 $\pm$ 18.41	40.22 $\pm$ 21.5	41.55 $\pm$ 19.55
	No	77	52.51 $\pm$ 18.48	52.36 $\pm$ 16.92	50.94 $\pm$ 22.75	50.55 $\pm$ 16.67
Unpaired 't' test P value & LS			P=0.024 S	P=0.017 S	P=0.047 S	P=0.032 S
3	Pupillary Reaction					
	Yes	53	47.26 $\pm$ 13.32	48.39 $\pm$ 12.84	43.61 $\pm$ 20.1	46.24 $\pm$ 13.67
	No	47	56.09 $\pm$ 18.78	54.3 $\pm$ 19.59	55.57 $\pm$ 22.63	51.02 $\pm$ 19.31
Unpaired 't' test P value & LS			P=0.007 S	P>0.05 N S	P=0.006 S	P>0.05 N S
4	Anterior Chamber Depth					
	Normal	72	53.31 $\pm$ 17.96	52.57 $\pm$ 18.22	52.93 $\pm$ 22.72	50.18 $\pm$ 18.16
	Shallow	28	45.93 $\pm$ 12.22	46.5 $\pm$ 13.57	38.79 $\pm$ 19.34	43.79 $\pm$ 14.59
Unpaired 't' test P value & LS			P=0.048 S	P>0.05 NS	P=0.005 S	P>0.05 NS
5	Visual Acuity Right Eye					
	>6/60	63	54.05 $\pm$ 19.18	55.11 $\pm$ 16.37	54.25 $\pm$ 22.24	52.75 $\pm$ 16.29
	6/60 or less	37	40.54 $\pm$ 16	42.19 $\pm$ 16.95	38.19 $\pm$ 21.1	40.08 $\pm$ 17.28
Unpaired 't' test P value & LS			P<0.001 S	P<0.001 S	P<0.001 S	P<0.001 S
6	Visual Acuity left Eye					
	>6/60	72	52.49 $\pm$ 18.75	52.94 $\pm$ 17.53	51.94 $\pm$ 22.43	50.79 $\pm$ 17.09
	6/60 or less	28	43.43 $\pm$ 15.53	44.14 $\pm$ 16.36	40.18 $\pm$ 22	41.14 $\pm$ 17.6
Unpaired 't' test P value & LS			P=0.025 S	P=0.024 S	P=0.020 S	P=0.014 S

Glaucoma characteristics were also analyzed with QoL. Although type of glaucoma and duration of illness was found to be associated with QoL but psychological domain scores were significantly lower in CAG than OAG. Severity of glaucoma and lower visual field in right eye were found to associated with QoL. Severe glaucoma cases had significantly lower score in all the four domains than the mild

cases ($p < 0.01$). Likewise patients with lower visual field in right eye scored less in each domain than those with normal visual field ($p < 0.05$). Constricted visual field in right eye also scored significantly less in physical domain ($P < 0.05$). (**Table 4**)

Table No. 4

Association of Characteristics of Glaucoma with QoL in Glaucoma patients

S. No.	Characteristics Variables	No. Of Patients	Physical Mean $\pm$ SD ((D ₁	Psychological (D ₂)Mean $\pm$ SD	Social (D ₃)Mean $\pm$ SD	Environmental (D ₄) Mean $\pm$ SD
1.	Type of Glaucoma					
	OAG	75	49.37 $\pm$ 18.76	51.41 $\pm$ 17.32	48.52 $\pm$ 22.68	48.61 $\pm$ 17.64
	CAG	25	46 $\pm$ 20.98	40.92 $\pm$ 19.89	43.33 $\pm$ 23.87	41.66 $\pm$ 20.95
	Unpaired 't' test P value & LS		P>0.05 N S	P=0.013 S	P>0.05 N S	P>0.05 N S
2	Duration of Illness					
	< 6	19	52.47 $\pm$ 18.32	54.95 $\pm$ 15.93	53.37 $\pm$ 23.92	48.53 $\pm$ 18.55
	6 to 9	7	53.43 $\pm$ 21.46	48.71 $\pm$ 30.96	42.14 $\pm$ 31.21	43.86 $\pm$ 30.78
	10 to 12	7	52.57 $\pm$ 10.13	50 $\pm$ 13.94	50.86 $\pm$ 14.61	51.86 $\pm$ 13.95
	13 to 24	13	58.77 $\pm$ 19.85	56.54 $\pm$ 12.42	55.23 $\pm$ 22.19	54.92 $\pm$ 11.14
	> 24	54	48.54 $\pm$ 15.46	48.46 $\pm$ 16.75	46.56 $\pm$ 22.11	46.91 $\pm$ 16.57
	ANOVA test P value & LS		P>0.05 N S	P>0.05 N S	P>0.05 N S	P>0.05 N S
3	Severity of Glaucoma					
	Mild	34	58.74 $\pm$ 19.25	59.74 $\pm$ 17.46	57.91 $\pm$ 24.11	55.85 $\pm$ 17.35
	Moderate	42	46.9 $\pm$ 17.67	46.88 $\pm$ 16.46	46.33 $\pm$ 21.62	45.45 $\pm$ 17.42
	Severe	24	44.17 $\pm$ 7.13	41.78 $\pm$ 13.41	38.26 $\pm$ 16.29	41.7 $\pm$ 13.66
	*ANOVA test P value & LS		P=0.001 S	P<0.001 S	P=0.003 S	P=0.006 S
4	Visual Field Right Eye					
	Normal	41	56.24 $\pm$ 18.51	57.76 $\pm$ 17.23	56.76 $\pm$ 23.25	53.22 $\pm$ 17.64
	Constricted	59	47.76 $\pm$ 14.73	46.08 $\pm$ 15.6	48.64 $\pm$ 50.39	45.03 $\pm$ 16.57
	Unpaired 't' test P value & LS		P=0.012 S	P<0.001 S	P=0.038 S	P=0.020 S
5	Visual Field left Eye					
	Normal	42	55.26 $\pm$ 20.13	54.86 $\pm$ 19.18	52.79 $\pm$ 26.53	50.38 $\pm$ 19.75

	Constricted	58	48.42±13.51	48.82±13.83	47.02±18.27	47.77±14.32
Unpaired 't' test P value & LS			P=0.045 S	P>0.05 N S	P>0.05 N S	P>0.05 N S

4. Discussion:

In the present study, the overall quality of life in all four domains viz. physical, psychological, social and environmental health was observed significantly poor glaucoma patients than controls. Various studies¹¹⁻¹⁸ in the past also reported poor quality of life in glaucoma patients. Sherwood et al¹¹ found that glaucoma patient had significantly lower scores than controls as per SF-20. Similarly Goldberg I et al¹² administered Glaucoma Quality of Life-15 (GQL-15) questionnaire to assess QoL in glaucoma patients and found similar observations.

Many factors may be attributed to the relatively poor quality of life among glaucoma subjects which includes visual impairment, inconvenience, side effects and the cost of treatment etc.¹³

Among socio-demographic variables the aged between 50 to 70 year had significantly lower QoL. This decreasing QOL with increasing age was also observed by Sun et al¹⁴ in their Chinese patients with angle closure glaucoma. Perception of life and priorities determining the QoL are different in older adults than do young adults.¹⁵ Other reasons may be their limited adaptability to changing needs and poor cognitive abilities of older patients.

Poor quality of life in all four domains was found to associate with lower income in this study. This may have been the result of increased financial burden and reduced ability to work due to glaucoma in already economically compromised population. This fact is supported by Gupta V et al.¹⁶

Most of the clinical variables including pain, congestion, diminished visual acuity in eyes, shallow anterior chamber depth and positive papillary reaction were found have poor QoL. Similarly constricted visual field and sever glaucoma also had lower scores in each domain of QoL. Onakoya AO et al¹⁷ also found that the increasing severity of disease defined by increasing visual field deficit (mean deviation values) correlated significantly with worsening QoL. Glaucoma restrict patient's ability to perform activities of daily living and reduce their satisfaction with their lifestyle¹⁸ thus impairing their QoL.

Assessment of QoL in glaucoma patients could be useful in determining the management strategies customized according to the patient's need for daily living which seem to be of paramount importance in these patients and are significantly correlated with their QoL.¹⁹ Information gained from QoL studies could improve the education of newly diagnosed patients and help them to realize the severity of the disease and the importance of the adherence to daily treatment, despite the fact that symptoms are absent in early stages²⁰.

CONCLUSIONS

Quality of life of glaucoma patients was lowered in all four domains i.e. Physical, Mental, Social and Environmental. Quality of life was not found to be associated with sex and marital status but it was found more poorer in elder age groups and low socio-economic status. Among clinical variables its quality of life of glaucoma patients was not found to be associated with papillary reaction, Anterior chamber depth (ACD), type of glaucoma and duration of glaucoma but it was found more poorer in glaucoma patients with pain, congestion and defective visual equity. Quality of life was significantly lowered in sever glaucoma. Glaucoma patients should be educated to realize the severity of the disease and importance of the adherence to daily treatment.

REFERENCES

1. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol*. 2006; 90:262–7.
2. Mills T, Law SK, Walt J, et al. Quality of life in glaucoma and three other chronic diseases: a systematic literature review. *Drugs Aging*. 2009;26:933-506.
3. Nelson P, Aspinall P, Papasouliotis O, et al. Quality of life in glaucoma and its relationship with visual function. *J Glaucoma*. 2003; 12:139-50.
4. Jampel HD, Schwartz A, Pollack I, et al. Glaucoma patients' assessment of their visual function and quality of life. *J Glaucoma*. 2002;11:154-63.
5. 10. Gutierrez P, Wilson MR, Johnson C, et al. Influence of glaucomatous visual field loss on health-related quality of life. *Arch Ophthalmol*. 1997;115:777-84
6. Janz NK, Wren PA, Lichter PR, et al. Quality of life in newly diagnosed glaucoma patients: the Collaborative Initial Glaucoma Treatment Study. *Ophthalmology*. 2002;108:887-97.
7. 9. Parrish RK 2nd, Gedde SJ, Scott IU, , et al. Visual function and quality of life among patients with glaucoma. *Arch Ophthalmol*. 1997;115:1447-55.
8. Varma R, Richman EA, Ferris FL, et al. Use of patient reported outcomes in medical product development: a report from the 2009 NEI/FDA Clinical Trial Endpoints Symposium. *Invest Ophthalmol Vis Sci*. 2010;51:6095–6103.
9. Skevington SM, Lotfy M, O'Connell KA. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. *Qual Life Res*. 2004;13:299-310.
10. Saxena S, Chandramani K, Bhargava R. WHOQOL Hindi: a questionnaire for assessing quality of life in health care setting in India. *Natl Med. J. India*. 1998; 11: 160–166.
11. Sherwood MB, Garcia-Siekavizza A, et al. Glaucoma's impact on quality of life and its relation to clinical indicators. A pilot study. *Ophthalmology*. 1998;105: 561-566.
12. Goldbrg I, Clement CL, Chiang TH. Assessing quality of Life in patients with glaucoma using the Glaucoma Quality of Life-15 questionnaire. *J Glaucoma*. 2009;18:6-12
13. Iester M, Zingirian M . Quality of life in patients with early, moderate and advanced glaucoma. *Eye*. 2002; 16:44-49.
14. Sun X, Zhang S, Wang N, et al. Utility Assessment among patients of primary angle closure/glaucoma in China: a preliminary study. *Br J Ophthalmol*, 2009;93:871–874.
15. Saxena S, Carlson D, Billington R. The WHO quality of life assessment instrument (WHOQOL-Bref): the importance of its items for cross-cultural research. *Qual Life Res*. 2001;10:711–721.
16. Gupta, V., Dutta, P., Mary, O. et al. Effect of glaucoma on the quality of life of young patients. *Invest Ophthalmol Vis Sci*. 2011; 52: 8433-8437.
17. Onakoya AO, Mbadugha CA, Aribaba OT, et al. Quality of life of primary open angle glaucoma patients in laos, Nigeri: Clinical and sociodemographic correlates. *J Glaucoma*. 2012;21:287-95.
18. Turano KA, Massof RW, Quigley H . A self-assessment instrument designed for measuring independent mobility in Retinitis Pigmentosa patients: generalizability to glaucoma patients. *Invest Ophthalmol & Vis Sci*. 2002; 43: 874-2881
19. Aspinall PA, Johnson ZK, Azuara-Blanco A et al. Evaluation of quality of life and priorities of patients with glaucoma. *Invest. Ophthalmol. Vis. Sci* 2008;49:1907–1915.
20. Pfeiffer N, Krieglstein GK, Wellek S. Knowledge about glaucoma in the unselected population: a German survey. *J Glaucoma*. 2002;11:458–463.