INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com
ISSN 2230 – 8407

Research Article

# THE IMPACT OF SEVERITY, COMORBIDITIES, AND COMPLICATIONS ON QUALITY OF LIFE: A SYSTEMATIC REVIEW IN PATIENT WITH DIABETIC RETINOPATHY

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Article Received on: 26/02/19 Approved for publication: 22/03/19

**DOI: 10.7897/2230-8407.1004125**

**ABSTRACT**

People with chronic disease and its complication tend to have a decline in quality of life (QoL), as in the case of diabetic retinopathy (DR). DR severity varies, while concurrent conditions such as comorbidities and complications are common. However the evidence was concern in effect of those factors on QoL is still limited. The aim of this systematic review is to explore QoL in patients with DR by emphasizing on the impact of severity, comorbidity and complication, in order to conceive the profundity of the impact of those factors on QoL. Terms and keywords relevant to QoL and DR were systematically searched using three electronic databases (PubMed, Science Direct, Google Scholar). A total of 172 studies were initially obtained and screened. Further, after the references were reviewed, 22 studies met all the eligibility criteria were finally selected. The included studies involved 6,457 patients in DR and conducted from different countries. Diabetic patients with DR had lower QoL compared to those without DR. Due to increasing number of comorbidity, complication and DR severity, QoL among patients were decreased. Our study showed that increasing number of comorbidity, complication, and severity were associated with poor QoL. Several medical interventions could improve the QoL. This study provides new evidence of factors related to QoL for clinicians and policy makers, hence intervention was needed accordingly to prevent occurrence and worsening the progress on those factors in patient with DR.

**Keywords:** diabetic retinopathy, quality of life, comorbidity, complication, severity

## INTRODUCTION

Diabetes mellitus (DM) is a major issues of global healthcare due to its prevalence, as well as its physical and psychosocial consequences for patients.[1] As a chronic disease, the disability rates of diabetes are increasing, after cancers and cardiovascular diseases.[2] The total number of individuals with diabetes had been projected to rise from 415 million in 2015 to 642 million by 2040, mostly occurred in developing countries.[3,4] The most patients have some degree of diabetic retinopathy (DR) after 20 years of living with diabetes, therefore rising prevalence of DM would increase the number of patient with DR subsequently.[5,6]

DR constituted as one of the most incapacitating microangiopathy complications in patient with DM.[2] In early non proliferative diabetic retinopathy (NPDR) stage, mild visual impairment can occur, and it can be worsen with growing DR severity becomes to proliferative diabetic retinopathy (PDR) stage.[7] Numerous studies had shown that vision impairment is often associated with various negative health outcomes and poor quality of life (QoL).[8–10] Vision loss distress is the most devastating, as DR is one of the leading cause of blindness, that diminishes QoL.[11,12]

Severity of DR are varies across patients, ranged from mild NPDR to advance PDR.[13] It may be accompanied by complication such as diabetic macular edema (DME) that can occur at any stage and vitreous hemorrhage (VH) that can develop secondary to PDR.[7,14] Cataract sometime also presents along with DR. Meanwhile, diabetes patients tend to have comorbidities, including vascular complications, renal failures, neuropathy, heart diseases, cognitive disorders, retinopathy, and hypertension.[15] The impact of comorbidities and complications that also affect QoL could not be eliminated since they are tend to occur together. Thus, the medical intervention became a necessity to prevent or reduce the risk of developing those factors in patient with DR.[16]

There has been a lot of study on QoL in patients with DR by utilizing various kinds of QoL instruments, however no systematic review has summarized the impact of severity, comorbidity and complication to their QoL. Therefore we conducted a systematic review that aim to explore QoL in patients with DR by emphasizing on the impact of severity, comorbidity and complication in order to conceive the profundity of the impact of those factors on QoL.

## METHODS

This study is a systematic review to find out the impact of severity, comorbidities, and complications of DR to QoL based on several related study articles. There were 3 main steps to capture the articles that include identifying and selecting related research about the topic, then assessing the retrieved studies that met all eligibility criteria, and finally generating review and data

extraction for each study.

**Study Identification**

Initial searches were conducted in February 2019 using three electronic databases (PubMed, Science Direct, and Google Scholar). Key terms used in this study were following "Quality of Life" OR "Utility Values" AND "Diabetic Retinopathy" OR "Diabetic Macular Edema" OR "Diabetic Macular Oedema". We performed a systematic literature by the published studies in recent years (2004-2019), according to predetermined inclusion and exclusion criteria, as shown in Table 1.

**Table 1: Inclusion and exclusion criteria for the reviewed articles**

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| 1. Available in full text<br>2. Time frame of year from 2004-2019<br>3. Published in English language<br>4. Define any severity/comorbidity/ complication and its association with quality of life | 1. Review article, letter, and comment<br>2. Descriptive or qualitative study |

**Study Quality Assessment**

A total 172 studies were obtained and screened from three electronic databases. After excluding duplicates and non-full text articles based on Universitas Gadjah Mada database, 59 articles were selected for full text examination. Finally only 22 studies met all eligibility criteria were included for the review. The PRISMA diagram of retrieved studies is shown in Figure 1.

All the included studies underwent quality assessment analysis which was carried out using tools by Hawker et al.[17] This tool includes nine domains: abstract and title; introduction and aims; sampling; data analysis; ethics and bias; result; transferability/ generalizability; and implications and usefulness. The results from quality assessment analysis were graded, 10 articles were high quality (grade A) and 12 articles categorized as medium quality (grade B).

**Data Extraction**

Data extraction and quality assessment was undertaken by independent researchers and carried out under supervision. Disagreements were resolved through discussion. Data extracted from the studies are included, among others: author and year of publication, country of studies, study design, sample size, age average of the sample, severity, comorbidity, complication, duration of diabetes, QoL measurement tool and QoL score, and main factors associated QoL. The characteristics of 22 eligible studies for this review are shown in Table 2.

**RESULTS**

**General characteristics**

The characteristics of 22 included studies are summarized in Table 2. The retrieved studies consisted from various countries (UK, India, US, Germany, Australia, Spain, Turkey, Greece, Italy, Finland, Singapore, Japan, Taiwan, China, and Iran). The studies were published for 15 years (2004-2019). Sample size across the studies ranged from 55 to 1,064 participants. The 22 included studies involved 6,457 patients in total (3,241 females and 3,216 males). Cross-sectional design was the dominant study design in 14 studies.[7,16,18–29] The average of patient age were 62.03 years old. We found a variety of sample characteristics within studies such as grading severity of diabetic DR, comorbidity, complication, other ophthalmic disorder, and treated or untreated retinopathy in both type 1 and type 2 diabetic patients.

**Quality of life and quality of life instruments**

Quality of life (QoL) was significantly reduced in diabetic patients with DR when compared with those without DR.[19,23,24,26,28,30–32] Regarding the instrument used to measure QoL, 13 different instruments were used in the studies. Eight studies used a generic measure only, 10 studies used a specific instrument only and 4 studies applied combination instruments (≥2 instruments) among the study population. Two studies used 12-item Short Form Survey (SF-12). One of 2 studies revealed physical component score (PCS) score 40.0(11.6) and mental component score (MCS) score 47.3(11.0).[21] Five studies used 25-item National Eye Institute-Visual Function Questionnaire (NEI-VFQ-25). There were statistically significant ($p<0.001$) lower VFQ-25 composite score in DR [73.93 (SD 25.55)] compared with no DR [99.26 (SD 1.01)].[18] Two studies used Euro Quality of Life-5 Dimension-5 level (EQ-5D-5L). One of 2 studies revealed that DR/DME group had a lower EQ-5D utility score compared with participants with any DR/DME group (0.80 vs. 0.76; $p=0.04$) in univariate analysis.[7] One study used Retinopathy-Dependent Quality of Life (RetDQOL), showed that the score of quality of life was -1.73±0.92.[16] A study used Audit of Diabetes-Dependent Quality of Life (ADDQOL) showed that weighted impact scores were -0.35 (95% CI: 0.78-0.06) in no DR and −0.88 (95% CI: 1.76-0.38) in DR ($p < 0.001$).[23] A study used Vision and Quality of Life Index (VisQOL) found that among those with no DR/DME, participants with any DR/DME had QoL score 1.00(0.01) vs. 0.99 (0.00) and those with more severe DR/DME had a lower VisQoL utility value (all $p<0.001$).[26] A study used the 15D instrument of Health Related Quality of Life (15D-HRQOL), found that the PDR group had a statistically significantly lower mean score compared with those subjects with NPDR or no DR [0.931±0.086 vs. 0.965±0.044, respectively ($p=0.026$)].[30] A study used 36-Item Short Form Survey (SF-36), showed that PCS score was decreased ($p<0.001$) and MCS score was increased ($p<0.001$) after 10 years.[33] A study used 28-item Impact of Vision Impairment (IVI) using multivariable linear model, showed that any DR in unilateral better-eye classifications revealed a 9% reduction in vision related quality of life (VRQoL) compared to individuals with no DR/DME. A significant decrements in VRQoL occurred only when both eyes had either DR or DME (11%).[31] A study used Time Trade Off (TTO), revealed that utility score was 0.92±0.12 (95% confidence intervals (CI): 0.91–0.93).[28] A study used The Chinese-version Low Vision Quality of Life (CLVQOL), showed that scores of CLVQOL was improved from 76.02±24.82 preoperatively to 95.35±20.65 after 3 months (Wilcoxon signed rank test, $p<0.001$).[34] Five studies used combination questionnaire. Two studies applied different generic measures, 2 studies applied different specific measures, and 1 study applied both generic and specific measure.

**Severity of diabetic retinopathy**

Severity of DR in many studies was classified in two categories, PDR and NPDR (mild NPDR, moderate NPDR, and severe NPDR). Severity of DR affected to declining of QoL, were significantly worse off in patients with PDR than those with less severe or no DR.[16,18–20,22–24,26,30,35] More severe DR was associated with worse QOL scores on all of the NEI-VFQ-25 and SF-12 subscales ($p<0.05$).[19] In contrast, a study stated that severity grade of DR had no direct effect on the QOL but an

indirect through visual acuity impairment and DME.[21] Four studies demonstrated decreasing of QoL score as severity increased although not statistically significant.[7,25,33,36]

**Diabetic retinopathy related comorbidity**

Diabetic patients with comorbidity had worse QoL.[7,16,18,20–22,25,26,33,35,36] Additional lost in QoL was by increased number of comorbidity, including presence of at least one of comorbidity (minimum ≥1 comorbidities).[21,22,25,26,35] DR related comorbidity consists of ocular comorbidity and non-ocular comorbidity. The ocular comorbidity cited in one study was cataract.[34] The most frequently reported non-ocular comorbidities were hypertension[7,18,21,25,33,35,36], heart disease[7,21,25,35], nephropathy[18,20–22,25,26,36], neuropathy[21,22,26,33], and cerebrovascular disease.[7,20,25,35] Number of comorbidities was associated with VisQoL score ($p<0.001$). However after adjusting for all variables, number of comobidities and diabetic complication was found to be not significantly associated ($p>0.05$).[7] One study suggested that removal of cataract complication in DR by performing cataract surgery in DR patients improved VRQoL score significantly.[34] Other studies found that there was no significant association between presence of comorbidity with QoL.[28,29,31,37]

**Diabetic retinopathy related complications**

Almost studies examined DME/clinically significant macular edema (CSME) as a factor related to QoL and other complications. Nonclearing vitreous hemorrhage (VH), traction or combined traction/retinal detachment and adherent posterior hyaloid causing excessive macular traction were the most cited complication in selected studies. People with complication had lower QoL. The complications reported in the studies were (DME).[7,21,22,26,31,36,37] In a study, DME displayed a negative effect on MCS ($b=-0.29$).[21] In contrast, a study revealed that existence of DME was not significantly associated with any of the subscales ($p>005$). Patient with persistent nonclearing VH, traction or combined traction/retinal detachment and adherent posterior hyaloid causing excessive macular traction had significantly lower VFQ score than in the normal controls. Vitrectomy performed to treat those conditions, was significantly improved VFQ-25 composite score ($p< 0.005$).[27]

**Demographic, socioeconomics and clinical factors**

Association between QoL and some demographic, socioeconomics, lifestyle and clinical factors were examined in the majority of studies. Gender and age were the most frequently cited, associated with QoL. Three studies reported QoL association with sex.[16,25,29] Some studies stated that QoL in male was higher than those in female[21,29], and it is inconsistent with the result of another study.[16] Six studies examined that age was related to QoL in DR.[18,23,25,26,28,36] Older patients with DR had worse QoL, except one study reported age >65 years had higher QoL than younger.[23]

Better socioeconomics status (including income, employment, and education) of individuals was associated with better QoL. Income and employment status were reported in 4 studies.[16,26,33,35] QoL scores reduced as the income increased[16] and the unemployment status had higher general disutility attributed to DR.[22] A significant relationship was found between QoL and education in patients with DR. The studies reported that QoL was higher in patients who had better education compared to those with no education.[16,25,29,33,35] Education level was reported in 4 studies with QoL significantly associated involving 750 patients, where 675 patients reached primary to secondary education and 75 patients reached tertiary education.[16,25,29,35] The significant relationship between QoL in patients with DR and marital status has been reported in one study.[16] Two studies examined rural/urban disparities in QoL, but they were contrary results. The type of residence was significantly associated with QoL[16], but not in other study.[24] Smoking and alcohol had significant related with QoL, highlighted that smokers had lower QoL than those in non-smokers, [16,22] while alcohol drinking was significantly affected EQ-5D score.[32]

Clinical factors influenced the QoL include visual acuity, duration of diabetes, hemoglobin A1c (HbA1c) level, body mass index (BMI), higher high-density lipoprotein (HDL), therapy insulin and DR interventions. Patients with better visual acuity reported better VRQoL.[21,25,26,35] Patients with better visual acuity reported improvement VRQoL[27,34,36], following laser photocoagulation[36], after cataract surgery[34], and vitrectomy.[27] Duration of diabetes had significant association with QoL. The studies reported duration of diabetes was in 8 studies,[7,16,18,23,25,26,31,34] where duration of diabetes was on average of 14.32 years. All studies stated that longer duration of diabetes impact on better QoL.[18] People with higher HbA1c generally had lower QoL. The HbA1c levels (8.1%) reported significantly association with lower QoL in a study.[25] Two studies mentioned overweight and obesity,[7,22] found that there were negative associations between BMI and QoL. Lower level of QoL was found among people with higher BMI.[7,22] The HDL cholesterol were significantly associated with higher EQ-5D and VisQoL utility values.[7,26] Insulin affected to improved QoL in DR.[7,23,26] A total of 5 studies stated the intervention associated with QoL in patients with DR.[20,27,29,34,36] Laser intervention could improve QoL in DR.[20,36] The other interventions which could improve QoL were cataract surgery[34], dexamethasone implant[29] and vitrectomy.[27]

## DISCUSSION

This review showed wide range of factors related with QoL in patients with DR. The current study reviewed the major findings of 22 identified studies examining QoL among patients with DR. It showed that generally diabetic patients with DR experienced worsening QoL. The findings indicated that DR related severity, complications and comorbidities have a significant negative impact on QoL among the diabetic patients. However, this finding was not consistent across studies and could be partly explained by the heterogeneity of included studies.

The factors related QoL were demographic, socioeconomics, and clinical factors. Acceleration of DR development was caused by long duration of diabetes. Previous study also confirmed that longer diabetes duration strongly associated with DR.[11] Increased occurrence of DR was also related to older age of the patients and visual impairment was more prevalent in older subject.[38] Moreover, unhealthy lifestyles were worsening the health condition and might increase the severity of DR, subsequently aggravated QoL score. Greater severity of DR was associated with general and vision-specific QoL.[19] People in the most severe stage of DR may also be more likely to experience greater severity of other comorbidities and complications associated with DR. Similar result showed that presence of comorbidity and presence of DME tended to get worse VFQ score.[39]Previous study stated that patients with DR had lower scores on the dimensions of mobility, vision, eating, and usual activities compared with those without.[40] Inability in usual activities is mainly impact on working people and reduce the daily income.

**Table 2: Characteristics of the studies included in the review**

| Author, year | Sample Characteristic | | | | | | QoL Instrument and QoL Score | Main Factors associated with QoL |
|---|---|---|---|---|---|---|---|---|
| | Study design & Sample Size | age (y) | Male (%) | Severity of DR | Comorbidity & Complication (%sample) | Duration (y) | | |
| Alcubierre, 2014 | Cross-sectional 297 [DR 48; no DR 149] | 60.5 | 50.8 | Mild NPDR (40.7%); Moderate NPDR (35.9%); Severe NPDR (23.4%) | DR with Hypertension (56.6%); DR with dyslipidemia (44.1%) DME (35.9%); Not CSME (21.4%) CSME 14.5% | 11 | **ADDQoL: No DR** −0.35 **DR** −0.88 | Age, Severity of DR, Duration DM; Insulin used, DR presence |
| Alinia, 2017 | Cross-sectional 150 [DR] | 58 | 52.6 | **Without DME:** No-moderate NPDR (42.0%); Severe-very severe NPDR (33.0%); Early-High Risk PDR (25.0)% **With DME:** No-moderate NPDR (33.9%); Severe-very severe NPDR (37.1%); Early-High Risk PDR (29.0)% | Cancer (3.3 %) Heart failure (6%) Has ≥ 1 diabetic comorbidity such as diabetic gastroparesis, neuropathy, nephropathy, diabetic foot (64%) DME (41.3%) | NA | **SG** : 0.95 (0.03) **TTO** : 0.85 (0.15) **VAT** : 0.80 (0.30) | DME, Comorbidity by TTO only, Severity of DR, Income and unemployment status, Gender, Smoking status, BMI |
| Bicer, 2018 | Case-control 200 [DR 98; no DR 102] | 62.93 | 35 | No DR (51%); Mild NPDR (14.5%); Moderate-severe NPDR (14.5%); PDR (20%) | Hypertension (NA) Hypercholesterolemia (NA) Renal disease (NA) Cardiac disease (NA) DME (16.5%) | 11.36 | **NEI-VFQ-25 No DR** 70.33 (18.2) **DR** 59.72 | DME; Severity of DR |
| Cetin, 2012 | Cross-sectional 93 [DR] | 57.9 | 49.4 | Background 8.6%; NPDR 16.1%; PDR 75.3% | Hypertension (52.6%) Coronary Artery Disease (24.7%) Chronic Renal Failure (22.5%) Cerebrovascular disease (5.3%) DME (43%) | 13.3 | **NEI-VFQ-25** VFQ score 65.9 (20.1) | Age on ocular pain subscale; Visual acuity; Comorbidity; Education; Gender; Duration of DM |
| Davidov, 2009 | Cross-sectional 207 [DR] | 64 | 49.8 | Mild NPDR (21.3%); Moderate NPDR (23.2%); Severe NPDR (25.1%); PDR (30.4%) | Nephropathy (13.5%); Neuropathy (37.7%); Hypertension (80.0%); Hypercholesterol (43.0%); hyperlipidemia (15.8%); Coronary heart disease (31.5%) Coronary insufficiency (16.4); Peripheral vascular disease (9.1%); Cerebrovascular disease (7.9%); Psychiatric condition (8.5%) Other comorbidities (17.6%) DME: no CSME (2.9%); CSME (19.3%) | 20 | **SF-12** PCS score 40.0 (11.6), MCS score 47.3 (11.0) | DME; Visual acuity; comorbidity |
| Fenwick, 2012 | Cross-sectional 577 [DR 354; no DR 223] | 66 | 65.6 | No DR-No DME (38.6%); Mild NPDR-Mild DME (6.1%); Moderate NPDR-Moderate NPDR (22.0%); VTDR (Severe NPDR or PDR)-Severe DME (33.3%) | hypertension, heart attack/angina, irregular heartbeat, stroke, high cholesterol, asthma, anemia, migraine, arthritis, and osteoporosis **Without DR**: 89.2% **With DR**: 84.8% Neuropathy,Nephropathy, and Peripheral vascular disease **Without DR**: 21.5% **With DR**: 39.6%, DME | 18 | **EQ-5D No DR** 1.00 (0.01) **DR** 0.99 (0.00) (p<0.001) | With any DR/DME severity; Comorbidity; Income; Duration of DM; Insulin used; BMI; HDL level |
| Fenwick, 2012 | Cross-sectional 203 [DR 153; no DR 50] | 65 | 68.5 | No DR (24.6%); Mild NPDR and/or Mild DME (11.8%); Moderate NPDR and/or moderate DME (23.2 %); Severe and PDR and/or severe DME (40.4%) | hypertension, heart attack/angina, irregular heartbeat, stroke, high cholesterol, asthma, anemia, migraine, arthritis, and osteoporosis **Without DR**: (98%) **With DR** : (87.6%) Neuropathy, Nephropathy, and Peripheral vascular disease **Without DR**: 14% **With DR** : 43.1% , DME | 17 | **VisQoL No DR** 0.80 (0.31) **DR** 0.76 (0.34) | With any DR/DME; Age; Visual impairment; Comorbidity Severity; Duration of DM; Insulin use; HDL level |
| Gabrielian, 2010 | Cross-sectional 104 [DR] | 59 | 28.8 | Mild NPDR (26.0 %); Moderate NPDR (19.2%); Severe NPDR (3.8%); PDR (51%) | **Non-ocular:** Hypertension (77%); Hyperlipidemia (27%); Renal Failure (12%); Arthritis (24%); Cardiovascular (cardiac) (16%); Pulmonary (19%) **Ocular:** Cataract (40%); Epiretinal membrane (5%) | 17 | **NEI-VFQ 25 VPVS** | Severity; Laser intervention; Renal failure; Insulin used |
| Hannula, 2014 | Cohort 123 [All T1D; DR 115; no DR 6] | 29 | 60.2 | No DR or NPDR (67.48%); PDR (30.89%); Non assessed (1.62%) | NA | 23 | **15D-HRQoL No DR** 0.965 (0.044) **DR** 0.955 (0.046) | Severity |
| Hirai, 2013 | Cohort 520 [All T1D; DR 509; no DR 11] | 49 | 49.3 | No DR (2.2%); Mild NPDR (33.5%); Moderate NPDR (12.9%); Severe NPDR (0.5%); PDR (50.9%) | Nephropathy (48.6%); Neuropathy (58.5%); Limb amputation (6.6%); Cardiovascular disease (25.7%) | 35.1 | **SF-36** PCS 46.2 (11.1); MCS 52.9 (8.9) | Cardiovacular disease; education; Working status |
| Kamran, 2017 | Cross-sectional 316 [DR] | 59 | 40.5 | NPDR (NA) PDR (NA) | 81.5% had diabetes with organ involvement, and none of the subjects developed lymphoma, leukemia, immune deficiency syndrome and metastatic solid tumors, and others | 19.1 | **RetDQOL** 1.73(0.92) | Diabetic foot, neuropathy, other eye disease Severity of DR; sociodemographic |
| Ligda, 2019 | Cross-sectional 140 [DR 70; no DR 70] | 56 | 45.7 | No DR (50%); DR: Mild NPDR (35%); Moderate-Severe NPDR (15%) | NA | 14.1 | **WHOQOL-BREF No DR** 3.70 (0.56) **DR** 2.42 (0.79) | Severity; Presence of DR |
| Man, 2016 | Case-control 390 [DR 201;no DR 189] | 58 | 70.2 | **Unilateral DR and DME status:** No DR (48.5%); DR without DME (42.0%); DR with DME (9.5%) | **Non-ocular comorbidity:** Hypertension 55.8%; Hyperlipidemia 51.0%; Chronic Kidney Disease 18.2%; AMD 8.5% | 11.5 | **28-item IVI** Any DR : 9 % reduction in | DME; Age; Diabetes duration; Gender; Ethnicity |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | **Bilateral DR and DME status:** Any DR/any DR or DME (42.1%); DME in both eyes (9.7%) | **Ocular comorbidity:** Cataract 4.1% Unilateral DME 42.0% | | QoL score (p=0.035) | |
| Mazhar, 2011 | Cross-sectional 1064 [DR 486; no DR 578] | 59 | 43.3 | No DR (54.3%) **Unilateral:** NPDR (15.6%); PDR (2.2%) **Bilateral:** NPDR (25.2%); PDR (2.7%) | Presence of comorbidity in DR mean= 3 (Arthritis, Cancer, Hypertension, Angina, Heart attack Heart failure, Asthma,, Back problem; Deafness | NA | **SF-12 NEI-VFQ-25** | Severity |
| Okamoto , 2008 | Cross-sectional 97 [DR 51; non DM 46] | 55 | 47.4 | PDR 52.6%; No DR 47.4% | Mild refractive errors; Mild cataract; VH: 11 eyes (21.6%); Tractional retinal detachment: 17 eyes (33.3%); Excessive macular traction: 23 eyes (45.1%) | 16.9 | **NEI-VFQ-25 Non DM** 85.2 (10.2) **DR ostoperative** 68.5 (18.3) | Visual acuity; Vitrectomy intervention |
| Pan, 2018 | Quasi Experimental 913 [DR 191; no DR 722] | 65 | 44.1 | No DR 82%; Unilateral DR 6.4%; Bilateral DR 11.6% | Nephropathy Unilateral (16.1%), Bilateral (11.3%); Myopia Unilateral (43.6%), Bilateral (27%); Hypertension Unilateral (50%), Bilateral (58.8%); Hyperglycemia Unilateral (23.2%), Bilateral (31.4%); Heart Disease Unilateral (33.9%),Bilateral (26.5%) | Unilateral : 12.2 Bilateral: 11.0 | **EQ-5D No DR** 0.986 (0.045) **Unilateral DR** 0.971 (0.082); **Bilateral DR** 0.970 (0.145) (p<0.05) | Heart disease; Diabetic foot; Alcohol |
| Pereira, 2017 | Cross-sectional 123 [DR 97; no DR 26] | 55 | 55.3 | **Unilateral :** Mild NPDR (32.6%); Severe NPDR (33.1%); Severe NPDR (23.8%); PDR (10.5%) | Hypertension (67%); hypercholesterolemia (30%); Cardiac disease (5%); Stroke (5%); Nephropathy (20%); Neuropathy and foot problems (16%) DME (30%) | 11 | **NEI-VFQ-25 No DR** 99.26 (1.01) **DR** 73.93 (25.55) (p=0.0001) | Severity; Age; Serum urea, blood glucose; Duration of DM; HbA1C |
| Polack, 2014 | Case-control 249 [DR 219; no DR 30] | 58 | 55 | No DR (12%);NPDR (29.3%); STDR(severe NPDR/PDR): (45.8%); Blind due DR (12.9%) | Number of comorbidities ≥ 3 (Hypertension, Arthritis, Heart condition, Asthma, Stroke) | NA | **EQ-5D & TTO No DR**: 0.80 (0.16), **DR**: 0.60 (NA) | Visual acuity; comorbidities; Severity; Education, Income |
| Torre, 2017 | Cross-sectional 137 [DR 38; no DR 99] | 65 | 65 | No DR (72.3%); DR (27.7%) | Hypertension (41.6%); Hyperlipidemia (40.1%); Obesity (26.3%) DME (27.7%) | 10 | **SF-12: No DR** MCS 43.4, PCS 42.1 **DR:**MCS 40.4, PCS 39.4 | Education, Gender, dexamethasone implant treatment |
| Tranos, 2004 | Cohort 55 [DR] | 65 | 30.9 | NPDR: Mild (23.6%); Moderate (58.2%); Severe (18.2%) | Cholesterol (43.63%); Cardiovascular disease (15.54%); Cerebrovascular accident (9.09%) DME(100%) | 11.6 | **51-item NEI-VFQ** Before laser 77.9; After laser 82.8 | Age, Laser treatment; Visual acuity, Urea and hypertension |
| Tung, 2005 | Cross-sectional 406 [DR 119; no DR 289] | 60 | 38.4 | No DR (71.2%); NPDR (21.4%); PDR (5.2%); Blind (2.2 %) | Number of other chronic disease: 1 (31.9%); ≥2 (11.9%) | NA | • **T TO: No DR** 0.92 (0.12); **DR** 0.80 (0.11) | Age; Severity; Duration of DM ≥15 year |
| Zhu, 2017 | Quasi Experimental 126 [DR] | 65 | 49.2 | NA | Cataract 100% DME | 13.77 | **CLVQOL** post operative 95.35 (20.65) | Visual acuity; Duration of DM; Cataract surgery intervention |

ADDQoL=Audit of Diabetes Dependent Quality of Life; BMI=Body Mass Index; CLVQOL=Chinese-version Low Vision Quality of Life; CSME= clinically significant macular edema; DME=Diabetic Macular Edema; DR=Diabetic Retinopathy; DWHQOL-BREF=Greek questionnaire' version for WHOQOL; EQ-5D= Euro Quality of Life-5 dimension; HbA1c= hemoglobin A1c; HDL=High-density Lipoprotein; IVI=Impact of Visual Impairment; MCS= Mental Component Summaries; NEI-VFQ-25=National Eye Institute Visual Function Questionnaire 25; NPDR=Nonproliferative Diabetic Retinopathy; PDR=Proliferative Diabetic Retinopathy; PCS=Physical Component Summaries; QoL=Quality of Life; RetDQoL= Retinopathy-Dependent Quality of Life; SF-12=12-item Short Form Survey; SF—36=36-Item Short Form Survey; SG=Standard Gamble; TTO=Time Trade Off; VAT=Visual Analog Thermometer; VH= vitreous hemorrhage; VisQoL= Vision and Quality of Life Index; VPVS = Vision Preference Value Scale; WHOQOL-BREF=WHO Quality of Life; 15D-HRQoL=15D instrument of Health Related Quality of Life

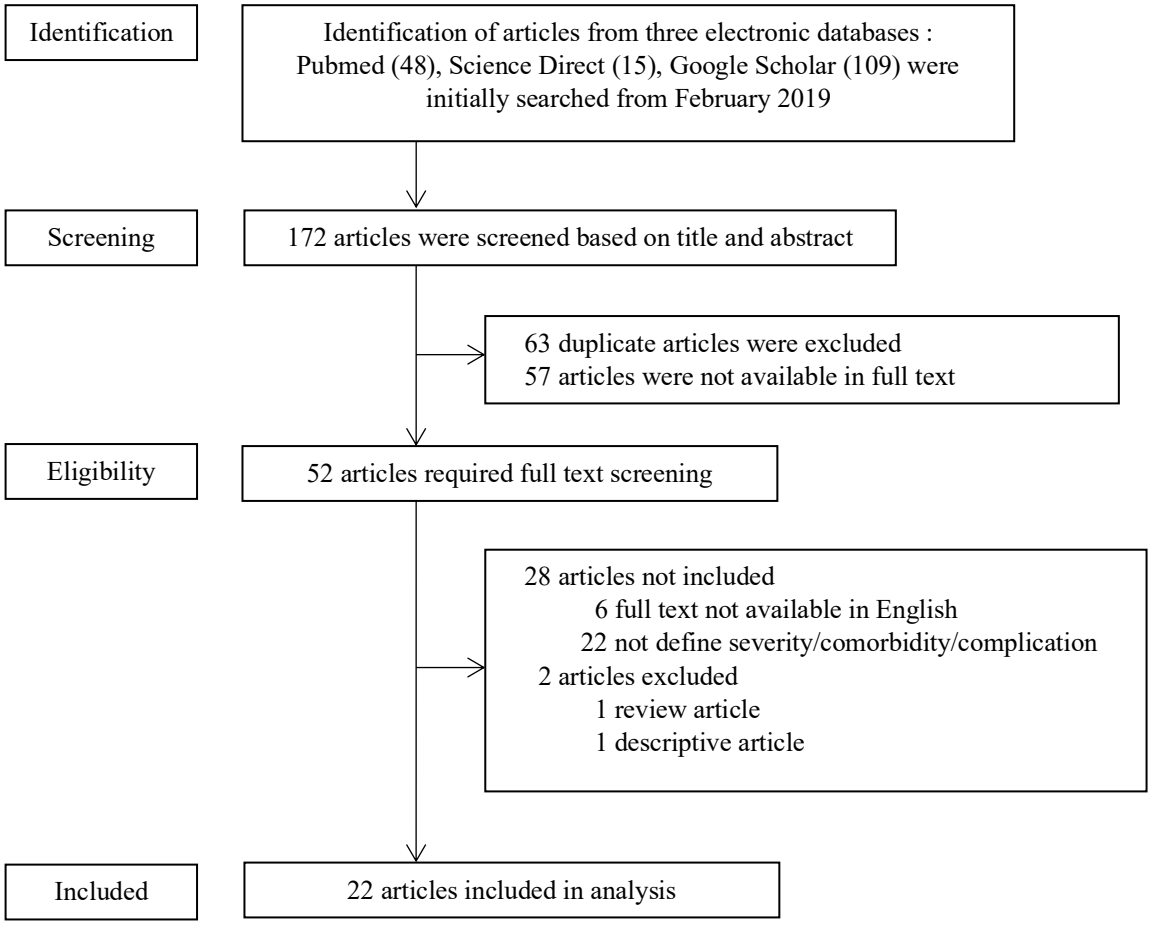


**Figure 1: PRISMA diagram of retrieved study**

In addition, the needs of treatment such as anti-VEGF and laser photocoagulation are emerging, to prevent the progression of NPDR to be PDR. The development of PDR usually begin to decline person's QOL compared to those with less severe DR. Presence of DR complication, other than DME, also significantly associated with QoL. Surgical vitrectomy is a usual treatment for DR-related complication, as VH, tractional retinal detachment and excessive macular traction. Removal of cataract in DR by performing cataract surgery in DR patients also improved VRQoL score significantly. Prior study stated that MCS score in DR treated with dexamethasone implant were significantly increased compared to ranibizumab as a reference.[29] Those interventions can be a useful adjunct to the QoL improvement in DR.

However, the reviewed studies were suffer from major methodological and reporting flaws which affected quality of their findings and limit their validity and generalizability. The reviewed studies mainly applied a nonrandom sampling method leading to possible selection bias. Moreover, sample size was not enough in the several studies. The various cultural background of patients in different countries lead the result can't be generalized in worldwide population. Patient's psychological conditions, that could not be controlled, while answering the questions that might affect the accuracy of answers. The study design in most studies inherently allows the study only associations and not causality. The studies did not know whether the factors related QoL was affected before DR onset, and if it was, what was the further decrease in QoL attributed to DR.

Furthermore, several studies didn't explain their limitations adequately and did not comment on the potential biases in their reported results. Both generic and specific instruments were used in the studies had limitations. The limitations of these instruments were used in capturing HRQoL and VRQoL in patients with DR were not fairly explained, except generic instruments like EQ5D was used to measure specific QoL, like VRQoL.[7] VFQ-25 was the most instruments used in this study. VFQ-25 as a superior measure of VRQoL in patients with DR. VFQ's greatest strengths over others instruments are in its assessment of the degree of anxiety, fear, and mental anguish associated with DR.[20] Moreover, several studies did not mention instruments validation process before putting to use in a new population and only referred to application of the instruments in a DR or other visual impairment population in other country.

The results of the current review should be interpreted with several cautions. As a wide range of instruments and the transparency of reported results were used in the reviewed studies was limited, it was not possible to apply statistical methods such as meta-analysis to test association between the covariates and QoL. Increasing the number of studies, applying the same instrument, and improving transparency of reporting results may make it possible to conduct a meta-analysis in the future.

## CONCLUSION

It can be concluded that DR severity, complication and ocular comorbidity have a significant negative impact on QoL among DR patients. Presence of non-ocular comorbidity may also affect QoL in negative direction. Earlier preventive intervention should

be considered to prevent the progression of DR severity. This review can provide clinicians and policymakers with evidences for more accurate assessment of the worth of specific healthcare interventions to prevent the occurrence and worsening of factors related with QoL in patient with DR and can be a useful adjunct to the regular eye examination.

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**Cite this article as:**

Novena Adi Yuhara *et al*. The impact of severity, comorbidities, and complications on quality of life: A systematic review in patient with diabetic retinopathy. Int. Res. J. Pharm. 2019;10(4):61-68 http://dx.doi.org/10.7897/2230-8407.1004125

Source of support: Nil, Conflict of interest: None Declared