Received: 19 October 2021 | Accepted: 9 March 2022 | Published online: 2 April 2022

DOI: 10.1111/opo.12984

ORIGINAL ARTICLE

OPO THE COLLEGE OF OPTOMETRISTS

Predictors of vision-related quality of life in patients with macular oedema receiving intra-vitreal anti-VEGF treatment

Petra T. Rausch-Koster[1,2] | **Katharina N. Rennert**[1] | **Martijn W. Heymans**[3] | **Frank D. Verbraak**[1] | **Ger H. M. B. van Rens**[1] | **Ruth M. A. van Nispen**[1]

[1]Ophthalmology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam Public Health Research Institute, Amsterdam, the Netherlands

[2]Department of Ophthalmology, Bergman Clinics, Naarden, the Netherlands

[3]Department of Epidemiology and Data Science, Amsterdam UMC, Amsterdam Public Health Research Institute, Amsterdam, the Netherlands

Correspondence
Petra T. Rausch-Koster, Ophthalmology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam Public Health Research Institute, Amsterdam, the Netherlands.
Email: t.p.rauschkoster@amsterdamumc.nl

Funding information
Funding for this investigator-initiated research was provided by Bayer Healthcare, Mijdrecht (Fellowship name/number: IMP20112/VUmc PROM). The sponsor or funding organization had no role in the design or conduct of this research.

Abstract

Purpose: To determine which demographic and clinical characteristics are predictive of vision-related quality of life (VrQoL) and quality of life (QoL) in patients with macular oedema receiving intravitreal anti-vascular endothelial growth factor (VEGF) treatment.

Methods: Vision-related quality of life (VrQoL) and quality of life (QoL) were measured in 712 patients with retinal exudative disease receiving anti-VEGF treatment at baseline, 6 and 12 months. VrQoL was measured using an item-response theory based 47-question item bank (EyeQ), whereas QoL was measured using the EuroQol Five Dimensions (EQ-5D) questionnaire. The EQ-5D score was dichotomized into a perfect score of 1 and a suboptimal score of <1. Demographic and clinical patient characteristics were considered as possible predictors of (Vr)QoL. Prediction models for (Vr)QoL were created with linear mixed models and generalised estimating equations, using a forward selection procedure.

Results: A worse VrQoL was predicted by poorer LogMAR visual acuity of the better eye, female sex, single civil status, older age, longer length of anti-VEGF treatment at baseline and the presence of non-ocular and ocular comorbidities. Suboptimal EQ-5D scores were predicted by poorer LogMAR visual acuity of the better eye, female sex, single civil status, older age, the presence of non-ocular comorbidities and a lower educational background.

Conclusions: Along with visual acuity of the better eye, which is the main factor used in clinical decision making, other patient characteristics should also be considered for the risk assessment of (Vr)QoL, such as sex, age, civil status, comorbidities and length of anti-VEGF treatment.

KEYWORDS
intravitreal anti-vascular endothelial growth factor (anti-VEGF), macular oedema, Quality of Life, Vision-related Quality of Life

Petra T. Rausch-Koster and Katharina N. Rennert contributed equally as co-first authors

INTRODUCTION

Retinal exudative disease, or macular oedema, refers to conditions where fluid infiltrates the centre of the retina, which may have an inflammatory, degenerative or vascular origin.[1] Common causes of macular oedema are diabetic macular oedema, exudative age-related macular degeneration and retinal vein occlusion.[2–6] Age-related macular degeneration and diabetic retinopathy are among the most common causes of visual impairment worldwide, with a prevalence of more than 100 million each, and are estimated to increase in global burden.[7,8] Similarly, retinal vein occlusion affects an estimated 16 million globally and frequently leads to visual impairment.[9]

Macular oedema has a large impact on both quality of life (QoL) and vision-related quality of life (VrQoL) due to loss of visual acuity.[10–14] However, although the association between visual acuity and (Vr)QoL is generally accepted in medical practice, little is known about other clinical and demographic factors that may be predictive of (Vr)QoL. This is also the case for patients with macular oedema who receive intravitreal anti-vascular endothelial growth factor (anti-VEGF), a treatment that reduces the progression of visual loss.[15–20] Due to the long treatment duration, as well as the high frequency and the invasive nature of the injections, patients often experience a relatively high treatment burden.[21]

Patient Reported Outcome Measures (PROMs) are increasingly used to evaluate the burden of disease, to improve shared-decision making and support patients in discussing their concerns.[22,23] Routine assessment of PROMs may help in identifying unrecognised problems, as patients do not always spontaneously report their problems to their physicians.[24,25] However, implementing PROMs for the routine monitoring of (Vr)QoL in daily medical practice is proven to be difficult, and PROMs are not always readily available during consultations.[26–28] By investigating patient characteristics that are commonly assessed or registered in clinical practice and possibly predictive of (Vr)QoL, physicians may be able to identify patients in need of additional support of optometric, low vision or other health services more easily. Earlier referral to these services may increase the (Vr)QoL of these patients and prevent further decline. The aim of this study is therefore to determine which demographic and clinical characteristics are predictive of (Vr)QoL in patients with macular oedema receiving intravitreal anti-VEGF treatment.

Key points

- Although visual acuity is an important predictor of quality of life in patients with macular oedema receiving intravitreal injections, this study shows that other patient characteristics must also be considered.
- The presence of ocular comorbidities and a longer duration of anti-VEGF treatment is predictive of a poorer vision-related quality of life.
- It is recommended that physicians do not solely consider visual acuity for the risk assessment of a low quality of life, but also take other demographic and clinical parameters into account.

METHODOLOGY

This study is part of the Dutch EyeQ study, a prospective cohort study which aims to develop a new computer adaptive PROM to assess VrQoL in patients with retinal exudative disease. The study protocol was approved by the Medical Ethics Committee (METC) of Amsterdam University Medical Centers and conducted according to the tenets of the Declaration of Helsinki. The METC declared that the protocol did not fall under the scope of the Medical Research Involving Human Subjects Act (Dutch law).

Patients were recruited between January and September 2019 from nine different locations of Bergman Clinics eye hospital in the Netherlands, and were followed for 1 year up to November 2020. Patients were eligible to participate in this study if they met the following inclusion criteria: age 18 years or older; diagnosed with a retinal exudative disease (exudative age-related macular degeneration, diabetic macular oedema or retinal vein occlusion with cystoid macular oedema) and currently receiving treatment with intravitreal anti-VEGF injections. No restrictions for participation were made based on visual acuity or the duration of treatment with intravitreal anti-VEGF injections. Potential eligible patients were informed about this study through written study information that was sent to their home address. Patients who were willing to participate gave written informed consent.

Measurements

Outcome measures

Quality of life (QoL) and VrQoL were measured at baseline (T0), 6 months (T1) and 12 months (T2). QoL was measured using the Dutch version of the EQ-5D-3L (Euroqol – 5 Dimensions) questionnaire, which assesses five parameters (mobility, self-care, daily activities, pain/discomfort and anxiety/depression with a three-level response option). The five digit numbers, ranging from 11111 (full health) to 33333 (worst health) were converted to a single utility index score using the value set of the Netherlands to obtain scores on a formative scale from 0 (lowest QoL) to 1 (highest QoL).[29,30] The latent construct VrQoL was measured with a

47-question item bank questionnaire (EyeQ). The majority of the items included in the EyeQ were based on the Dutch translation of the 28-item Impact of Visual Impairment Profile (IVI), a validated questionnaire originally based on several existing questionnaires measuring VrQoL or visual functioning.[31] During the developmental phase of the IVI, item selection was based on several questionnaires.[32] The 28-item IVI measures the restriction of participation in daily activities in five domains of functioning (leisure, household, social, mobility and emotional). In previous research the IVI was translated in Dutch and subsequently the content validity was assessed in qualitative research.[33] Based on the findings of this study, we investigated the content of the Low Vision Quality of Life (LVQOL) questionnaire and the National Eye Institute Visual Functioning Questionnaire 25 (NEI-VFQ-25) for unique items to be added.[34,35] The majority of items added from the LVQOL contained basic aspects of vision in specific lighting conditions, whereas most items added from the NEI-VFQ-25 covered the driving and transportation domain. In addition, all five domains of the IVI are supplemented with one or more unique questions from the LVQOL and the NEI-VFQ-25, in order to create a broad range of items covering the construct we aimed to measure, which resulted in a 47-question item bank. This is preferred for future use of the EyeQ as a computer adaptive PROM. Questions were re-formulated using a four-point Likert scale with the response categories: never (1), sometimes (2), often (3), always (4) and "not applicable" (missing value) as in previous research no comprehensibility problems or other issues arose regarding these response categories.[33] The EyeQ items were analysed, after checking the item response theory (IRT) assumptions, in R (version 3.6.1., The R Project for Statistical Computing, r-project.org) using a constrained graded response model (GRM), which is most commonly used in IRT. Unidimensionality was investigated by performing a principle component analysis (PCA) for a one-factor and a two-factor model. The one-factor model explained 49% of the variance, and the two-factor model added 4% of explained variance. This well exceeds the minimum of 20% explained by the first factor and the minimum ratio of explained variance between two models (at least four). In addition, unidimensionality was examined graphically and non-graphically using a screeplot and acceleration factor, respectively.[36–38] The overall fit of the 47 items to the GRM was adequate, which was assessed with the root mean square error of approximation (0.035), the standardized root mean residual (0.071), the comparative fit index (0.995) and the Tucker-Lewis index (0.994). Final EyeQ scores were expressed on a theta (θ) logit-scale from −4 (highest VrQoL) to +4 (lowest VrQoL). A maximum of 25% missing values per patient were allowed for the calculation. The calibrated EyeQ itembank is available upon request.

Patients answered questions digitally or per request on paper or by telephone, and it was estimated that the questionnaire would take 60 min to complete. All participants received their usual care throughout the study.

Potential predictors

Clinical characteristics were manually searched in digital patient records. Baseline characteristics were collected by questionnaire at T0 and from digital patient records. Possible predictors collected by questionnaire were sex (male or female); age in years; civil status (single or not single); education (low or high); employment status (unemployed/retired or employed) and non-ocular comorbidities under treatment or monitored by a physician (presence or absence of at least one of the following: cancer, lung, cardiovascular, rheumatic, psychiatric or other not previously mentioned disease). Possible predictors searched from the digital patient records were ocular comorbidities throughout the study apart from retinal exudative disease (e.g., the presence of amblyopia, glaucoma, anterior segment disorders such as cornea dystrophies and cataract, and posterior segment disorders such as nonexudative age related macular degeneration or macular puckers); length of intravitreal anti-VEGF treatment at baseline in weeks; number of intravitreal anti-VEGF injections already received at baseline; number of treated eyes throughout the study (monocular, binocular or no treated eyes (in case the treatment stopped during the study) and visual acuity throughout the study. The selection of these variables was based on clinical reasoning and previous literature.[11–13,18,39,40]

Decimal visual acuity was converted to LogMAR visual acuity of the better eye. The patient's own refractive correction was taken if available, as this correction is most representative for the patient's day-to-day vision at the time of (Vr)QoL measurement. If their own refractive correction was not available, visual acuity either without correction (unaided) or subjective refraction was used for the calculation.

Statistical analyses

Baseline characteristics were calculated using descriptive statistics. Independent samples *t*-tests and chi-square tests were used to evaluate potential differences between patients who completed all three measurements and those who completed only one or two measurements. The number of intravitreal anti-VEGF injections and the length of treatment at baseline were log-transformed, as these variables were skewed.

Models were created separately for the EyeQ and EQ-5D. As nearly half of all patients had a score of 1 on the EQ-5D and scores were highly skewed, the scale was dichotomized into a perfect score of 1 and a suboptimal score <1. Linear mixed model analysis was conducted for the EyeQ, whereas generalised estimating equations analysis was conducted for EQ-5D score.

Prediction models were created for the EyeQ and EQ-5D scores using multivariable analyses with a forward selection procedure. The stopping rule for stepwise inclusion of predictors to the model was a significant

p-value ($p < 0.05$). Final models were validated and adjusted using a shrinkage factor derived from the heuristic shrinkage estimate from van Houwelingen and le Cessi.[41] A receiver-operating characteristics (ROC) curve was created with the predicted probabilities of an EQ-5D score of one in order to assess the discrimination of the final model. All outcomes were reported as regression coefficients (β) or odds ratios (OR) with 95% confidence intervals (95% CI) and *p*-values, where $p < 0.05$ was considered statistically significant. Data was analysed using SPSS Statistics version 26 (IBM, ibm.com).

RESULTS

Response and baseline characteristics

A total of 3783 patients were invited by letter to participate in this study, of which 746 patients met the inclusion criteria and gave their written informed consent. Patients were recruited between January 2019 and September 2019 at T0, of which 712 filled in the questionnaire and were included in the study. Of these, 608 patients (85%) filled in the questionnaire at T1 and 574 (81%) at T2. All three measurements were filled in by 544 (76%). Nineteen participants had deceased after T0 or T1, 11 no longer wanted to participate (reasons stated: age, too much burden to fill in questionnaire) and 74 participants were lost to follow-up for unknown reasons. Patients who filled in all three measurements were significantly younger (mean 76 years vs. 78 years, $p = 0.01$), had a higher education in years (mean 11.6 vs. 10.6, $p = 0.002$), improved LogMAR vision of the better eye (mean 0.14 vs. 0.22, $p = 0.001$) and a higher EQ-5D score at baseline (mean 0.87 vs 0.79, $p < 0.001$) than those who completed only one or two measurements. Along with this, there was a significant association between completion of all three measurements and nationality; 78% of Dutch patients completed all three measurements, versus 62% of non-Dutch patients ($p = 0.02$).

The majority of the patients eligible for inclusion in the study were diagnosed with exudative age-related macular degeneration (63%) or retinal vein occlusion with cystoid macular oedema (25%, Table 1). According to the International Classification of Diseases (11th revision), where normal vision is defined as visual acuity of the better eye equal to or better than 0.5 LogMAR, most patients (92%) had normal vision.[42] Along with this, the majority received intravitreal anti-VEGF injections in only one eye (82%). The mean age was 76.2 years, and most patients were either unemployed or retired (85%). Lastly, almost two thirds of patients had non-ocular comorbidities or ocular comorbidities.

Table 2 shows median and mean scores of the EyeQ and EQ-5D at T0, T1 and T2. A total of 292 (41%) reported a perfect (=1) EQ-5D score at baseline. The EQ-5D score appeared to remain stable over time, but the EyeQ score became slightly lower over time, representing a better VrQoL.

TABLE 1 Baseline characteristics ($n = 712$) *N* (%)

Sex	
Male	344 (48)
Female	368 (52)
Age (mean [SD])	76.2 (9.2)
Nationality	
Dutch	664 (93)
Other	45 (6)
Educational background in years (median [IQR])	11.0 (9.0–15.0)
Low	315 (44)
High	383 (54)
Civil status	
Single	238 (33)
Not single	474 (67)
Employment status	
Employed/voluntary work	109 (15)
Unemployed/retired	603 (85)
Non-ocular comorbidities	454 (64)
Ocular comorbidities	452 (64)
Diagnosis	
Exudative age-related macular degeneration	451 (63)
Diabetic macular oedema	57 (8)
Retinal vein occlusion with cystoid macular oedema	178 (25)
Other or unknown	26 (4)
Treated eye	
Right eye	299 (42)
Left eye	284 (40)
Both	129 (18)
LogMAR visual acuity of the better eye[a] (median [IQR])	0.10 (0.01–0.22)
Normal vision to mild vision loss: logMAR visual acuity ≤0.5	658 (92)
Low vision: logMAR visual acuity between 0.5 and 1.3	48 (7)
Blind: logMAR visual acuity >1.3	6 (1)
Length of anti-VEGF treatment in weeks (median [IQR])	138 (52–319)
Number of anti-VEGF injections (median [IQR])	20 (10–40)

Abbreviations: Anti-VEGF, anti-vascular endothelial growth factor; IQR, interquartile range; SD, standard deviation.

[a]In accordance with the ICD-11.

Predictors of EQ-5D and EyeQ score

Univariate analyses showed that sex, age, educational background, civil status, employment status, the presence of non-ocular comorbidities and LogMAR visual acuity of the better eye were significantly related to both the EQ-5D and EyeQ. In addition, the length of treatment and number of intravitreal anti-VEGF injections

TABLE 2 Logit vision-related quality of life (EyeQ, theta score) and quality of life (EQ-5D) at baseline (T0), 6 (T1) and 12 months (T2)

	T0	T1	T2
EyeQ			
Median (IQR)	0.02 (−0.67 to 0.79)	−0.06 (−0.79 to 0.66)	−0.30 (−0.87 to 0.38)
Mean (SD)	0.11 (1.1)	−0.01 (1.11)	−0.24 (0.93)
EQ-5D			
Median (IQR)	0.86 (0.81 to 1.00)	0.89 (0.81 to 1.00)	0.89 (0.81 to 1.00)
Mean (SD)	0.85 (0.18)	0.88 (0.16)	0.86 (0.19)
Score = 1 (*n* [%])	292 (41)	273 (46)	253 (45)
Score <1 (*n* [%])	413 (59)	324 (54)	312 (55)

Abbreviation: IQR, interquartile range; SD, standard deviation.

TABLE 3 Predictors of vision-related quality of life (EyeQ)

	Estimates	95% CI	*p*	Adjusted linear predictor
Intercept (α)	−1.77	−2.43 to −1.13	<0.001	−1.34
Predictors (β)[c]				
Time 6 months (compared to baseline)	−0.11	−0.15 to −0.07	<0.001	−0.11
Time 12 months (compared to baseline)	−0.34	−0.39 to −0.30	<0.001	−0.34
Age (years)	0.01	0.00 to 0.02	0.02	0.01
Sex - Female	0.32	0.18 to 0.46	<0.001	0.32
Civil status - Single	0.24	0.08 to 0.39	0.003	0.23
LogMAR visual acuity of the better eye	0.97	0.78 to 1.15	<0.001	0.95
Length of anti-VEGF treatment in weeks at baseline (log transformed)	0.06	0.01 to 0.11	0.02	0.06
Non-ocular comorbidities - Present	0.21	0.07 to 0.34	0.004	0.20
Ocular comorbidities - Present	0.13	0.03 to 0.23	0.01	0.13

Note: Adjusted linear predictor calculated using heuristic shrinkage.

Abbreviations: Anti-VEGF, anti-vascular endothelial growth factor; CI, confidence interval; *p*, *p*-value; ß, regression coefficient.

at baseline were significantly associated with the EyeQ, where an increase resulted in a higher EyeQ score, indicating a worse VrQoL (data not shown). In turn, the presence of ocular comorbidities was significantly associated with the EQ-5D.

Table 3 demonstrates the multivariable longitudinal analysis for the EyeQ. Over time, the EyeQ score declined significantly between baseline and the two follow-up measurements, indicating a better VrQoL. Scores at T0 were significantly higher than at T1 and T2 (T1 β −0.11, 95% CI −0.15 to −0.07, $p < 0.001$ and T2 β −0.34, 95% CI −0.39 to −0.30, $p < 0.001$). It was shown that a poorer LogMAR visual acuity of the better eye, female sex, having a single civil status, being older, having a longer intravitreal anti-VEGF treatment duration at baseline and having non-ocular or ocular comorbidities, predicted a higher EyeQ score (indicating a worse VrQoL).

Table 4 shows the multivariate longitudinal analysis for EQ-5D score. There was no significant change in the odds of having a perfect EQ-5D score over time. The final model showed that the odds of having a perfect EQ-5D score were lower for patients who have a poorer LogMAR visual acuity of the best eye, are female, have a single civil status, are older, reporting having non-ocular comorbidities and have a low educational level.

Internal validation

The longitudinal model of the EyeQ with only a random intercept at the patient level had a − 2 log likelihood (–2LL) value of 3914, whereas the final prediction model had a -2LL of 3550. The longitudinal model of the EQ-5D with only a random intercept at the patient level had a –2LL of 8413, whereas the final model had a –2LL of 8169. The lower –2LLs of the prediction models indicate that the models can explain more variance in the outcome measure than the models with only a random intercept. Using the –2LL, the heuristic shrinkage estimate was calculated to be 0.98 for VrQoL and 0.97 for QoL, which suggests a potentially good calibration of the models in an external dataset.[41] Table 3 shows the adjusted linear predictor for

TABLE 4 Predictors of an EQ-5D score of 1 (perfect score)

	OR	95% CI	*p*	Adjusted linear predictor
Intercept	15.04	3.40–66.54	<0.001	3.16
Predictors				
Time 6 months (compared to baseline)	1.20	0.92–1.58	0.50	0.18
Time 12 months (compared to baseline)	1.10	0.83–1.46	0.18	0.09
Age (years)	0.97	0.96–0.99	0.007	−0.03
Sex - female	0.63	0.45–0.88	0.006	−0.46
Educational background - high	1.48	1.06–2.07	0.02	0.38
Civil status - single	0.53	0.37–0.77	0.001	−0.61
Non-ocular comorbidities - present	0.35	0.25–0.48	<0.001	−1.03
LogMAR visual acuity of the better eye	0.15	0.07–0.34	0.001	−1.84

Note: Adjusted linear predictor calculated using heuristic shrinkage.
Abbreviations: OR: odds ratio; CI: confidence interval; *p*, *p*-value.

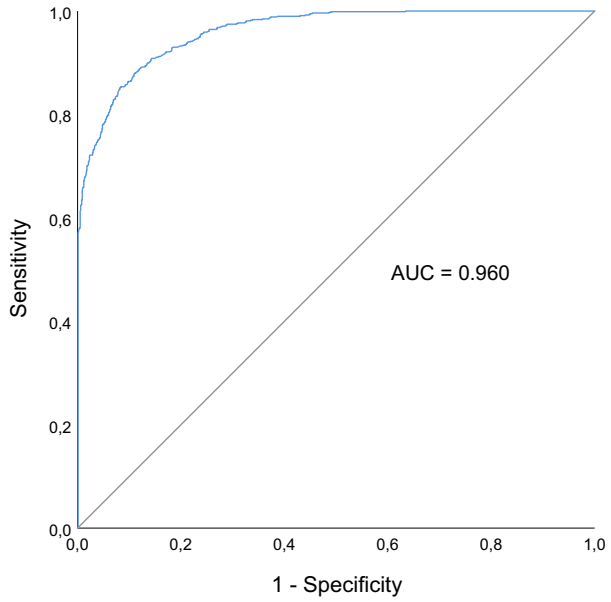

FIGURE 1 Area under the curve (AUC) = 0.96. Diagonal reference line (grey) representing chance classification (AUC = 0.50)

the EyeQ, whereas Table 4 shows the adjusted linear predictor for the EQ-5D.

Figure 1 shows the receiver-operating characteristics (ROC) curve for the accuracy of the model in predicting an EQ-5D score of 1. The area under the curve (AUC) is 0.96, which implies an outstanding discriminative ability of the model.[43] A predicted probability of 43.9% of a perfect EQ-5D score resulted in the best combination between sensitivity (88%) and specificity (88%) (Youden's *J* statistic of 1).

DISCUSSION

The aim of this study was to determine predictors of VrQoL and QoL in patients with macular oedema receiving intravitreal anti-VEGF treatment. The findings of this study suggest that poorer LogMAR visual acuity of the better eye, female sex, a single civil status, older age and the presence of non-ocular comorbidities predicted both a worse VrQoL and a suboptimal QoL. In addition, the presence of ocular comorbidities and the length of anti-VEGF treatment predicted VrQoL, whereas educational level predicted QoL.

This study confirms previous findings that visual acuity is strongly associated with both VrQoL and QoL.[10–14] It has been suggested that poorer vision leads to activity limitations, less social support, reduced self-efficacy and more depressive symptoms.[44]

This study also showed that a longer treatment duration at baseline was predictive of a worse VrQoL, but not of QoL. Although previous research suggests that intravitreal anti-VEGF treatment can have a positive influence on VrQoL, this is often dependent on improvements in visual acuity.[18] A longer treatment trajectory implies a longer disease duration, which may, in turn, be paired with a decrease in eyesight and a stronger fear of losing eyesight over time.[45,46] Along with this, the lower VrQoL may also be explained by the nature of the injections, which are often experienced as invasive and stressful.[18] Neither the length of intravitreal anti-VEGF treatment nor the number of injections was associated with QoL. This could be explained by the construct measured with the EQ-5D, which may be less sensitive to pick up changes in functioning over time as a result of treatment.

While the presence of non-ocular comorbidities was predictive of both VrQoL and QoL, the presence of ocular comorbidities was only predictive of VrQoL. In accordance with our results, Lin and Yu showed that comorbidities such as arthritis and heart disease predicted both QoL and VrQoL,[14] and other studies have also suggested a similar relationship.[47,48] Interestingly, although our population already included a selection of patients with retinal exudative disease, the presence of other ocular comorbidities (besides the exudative retinal disease for

which the patient was included here) was also predictive of VrQoL. While more research is needed to investigate this observation, other aspects important for VrQoL that may be influenced by ocular comorbidities are depth perception, night vision and other disease-specific problems, such as glare in cataracts or visual field loss in glaucoma. However, as it was not feasible to analyse ocular comorbidities separately, it is unknown which (combination of) comorbidities are responsible for this effect. Our findings were not confirmed by Lin and Yu, who did not find ocular comorbidities such as cataract or glaucoma to be predictive of VrQoL.[14]

Female sex, older age and a single civil status predicted both a worse VrQoL and lower odds of having a perfect QoL. Additionally, educational background was predictive of QoL. Similar to our results, prior studies show that women tend to score worse on (Vr)QoL than men, and that (Vr)QoL decreases with increasing age.[49–51] Previous research has also shown that single men and women experience a worse QoL than their married counterparts, which may be even more evident in older adults with visual impairment.[52,53] Lastly, in accordance with our results, associations between low educational level and poorer EQ-5D outcomes have been previously suggested, whereas no strong relationship with VrQoL has been found, or only with some specific VrQoL dimensions.[54–56]

Strengths and limitations

This study is subject to a number of strengths and limitations. A strength of this research is its large study sample and the use of item response theory analyses (IRT). Additionally, VrQoL was measured using an extensive questionnaire at three points in time in patients with different causes of macular oedema. Lastly, although the prediction model has not yet been externally validated, internal validation suggested a good calibration of the model in an external dataset. A limitation of this research is the possible reduced generalisability of the prediction model, as analyses showed that patients who completed all three measurements were significantly different from patients who did not. However, due to the use of likelihood estimation techniques that can handle missing outcome data by using all available findings, this effect is most likely minimised.[57] Another limitation is the relatively small group of patients with diabetic macular oedema (8%), which may limit the results of this study in regard to this particular group. A possible explanation for the lower response rate of patients with diabetic macular oedema (13% vs. 24% for retinal vein occlusion and 22% for age-related macular oedema) is the presence of other diabetic-related health concerns, which may carry a heavier burden than the visual impairment and thus discourage participation in the study. Lastly, it should be noted that the EQ-5D provides a rather general measure of health-related quality of life, and may not be sensitive enough to detect small changes over time.[58]

Recommendations for future research and practice

Further steps should externally assess the performance of the models in different study populations. Along with this, future studies should focus on establishing a cut-off point for the minimal important clinical change on the EyeQ. Subsequently, additional cut-off points for (change in) LogMAR visual acuity of the better eye and the length of intravitreal anti-VEGF treatment can be established. Lastly, other approaches may be able to investigate more precisely which (aspects of) ocular comorbidities are predictive of VrQoL.

Despite the fact that this study provides guidelines for the risk assessment for VrQoL and QoL without the use of a QoL instrument, routine assessment of (Vr)QoL using a PROM in clinical practice is still recommended, as this may improve other aspects of care (e.g., shared decision-making). Future research should focus on the optimal process for implementation of the EyeQ in clinical practice.

In conclusion, along with visual acuity of the better eye, which is often the main factor used in clinical decision making, other patient characteristics should be considered for the risk assessment of (Vr)QoL in patients with macular oedema receiving intravitreal anti-VEGF treatment. Female sex, older age, a single civil status and the presence of non-ocular comorbidities are additionally predictive of a lower VrQoL and QoL. In addition, the presence of ocular comorbidities and the length of anti-VEGF treatment was predictive of VrQoL, whereas educational level was predictive of QoL. Thus, it is recommended that physicians do not solely consider visual acuity for the risk assessment of low (Vr)QoL, which reflects general health and daily life functioning, but also take other demographic and clinical parameters into account. Although more research is still needed, physicians may have to offer or refer to additional support or care services to patients that fit the characteristics described in these models.

COMMERCIAL RELATIONSHIPS DISCLOSURES
Petra T. Rausch-Koster, None; **Katharina N Rennert**, None; **Martijn W Heymans**, None; **F.D. Verbraak**, None; **Ger H M B van Rens**, None; **Ruth M A van Nispen**, None.

AUTHOR CONTRIBUTIONS
Petra T. Rausch - Koster: Data curation (lead); formal analysis (equal); investigation (lead); methodology (equal); project administration (lead); supervision (equal); writing – original draft (equal); writing – review and editing (equal). **Katharina N. Rennert:** Formal analysis (equal); investigation (supporting); methodology (supporting); writing – original draft (equal); writing – review and editing (equal). **Martijn W. Heymans:** Formal analysis (supporting); writing – review and editing (equal). **Frank D. Verbraak:** Conceptualization (equal); funding acquisition (equal); methodology (equal); writing – review and editing (equal). **Ger H.M.B van Rens:** Conceptualization (equal);

funding acquisition (equal); methodology (equal); supervision (equal); writing – review and editing (equal). **Ruth M.A. van Nispen:** Conceptualization (equal); formal analysis (supporting); funding acquisition (lead); investigation (supporting); methodology (equal); supervision (equal); writing – review and editing (equal).

ORCID

Petra T. Rausch-Koster https://orcid.org/0000-0001-8558-5260
Katharina N. Rennert https://orcid.org/0000-0002-5023-3318
Martijn W. Heymans https://orcid.org/0000-0002-3889-0921
Frank D. Verbraak https://orcid.org/0000-0001-7560-1423
Ger H. M. B. van Rens https://orcid.org/0000-0003-4233-0705
Ruth M. A. van Nispen https://orcid.org/0000-0003-1227-1177

REFERENCES

1. Amer R, Nalcı H, Yalçındağ N. Exudative retinal detachment. *Surv Ophthalmol*. 2017;62:723–69.
2. Daruich A, Matet A, Moulin A, Kowalczuk L, Nicolas M, Sellam A, et al. Mechanisms of macular edema: beyond the surface. *Prog Retin Eye Res*. 2018;63:20–68.
3. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the global burden of disease study 2017. *Lancet*. 2018;392:1789–858.
4. Cohen SR, Gardner TW. Diabetic retinopathy and diabetic macular edema. *Dev Ophthalmol*. 2016;55:137–46.
5. Lim LS, Mitchell P, Seddon JM, Holz FG, Wong TY. Age-related macular degeneration. *Lancet*. 2012;379:1728–38.
6. Iijima H. Mechanisms of vision loss in eyes with macular edema associated with retinal vein occlusion. *Jpn J Ophthalmol*. 2018;62:265–73.
7. Wong WL, Su X, Li X, Cheung CMG, Klein R, Cheng CY, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health*. 2014;2:e106–16.
8. Zheng Y, He M, Congdon N. The worldwide epidemic of diabetic retinopathy. *Indian J Ophthalmol*. 2012;60:428–31.
9. Rogers S, McIntosh RL, Cheung N, Lim L, Wang JJ, Mitchell P, et al. The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia. *Ophthalmology*. 2010;117:1–14.
10. Tseng YC, Liu SHY, Lou MF, Huang GS. Quality of life in older adults with sensory impairments: a systematic review. *Qual Life Res*. 2018;27:1957–71.
11. Taylor DJ, Hobby AE, Binns AM, Crabb DP. How does age-related macular degeneration affect real-world visual ability and quality of life? A systematic review. *BMJ Open*. 2016;6:e011504. https://doi.org/10.1136/bmjopen-2016-011504
12. Pondorfer SG, Terheyden JH, Heinemann M, Wintergerst MWM, Holz FG, Finger RP. Association of vision-related quality of life with visual function in age-related macular degeneration. *Sci Rep*. 2019;9:15326. https://doi.org/10.1038/s41598-019-51769-7
13. Bertelmann T, Feltgen N, Scheffler M, Hufenbach U, Wiedon A, Wilhelm H, et al. Vision-related quality of life in patients receiving intravitreal ranibizumab injections in routine clinical practice: baseline data from the German OCEAN study. *Health Qual Life Outcomes*. 2016;14:132. https://doi.org/10.1186/s12955-016-0536-1
14. Lin JC, Yu JH. Assessment of quality of life among Taiwanese patients with visual impairment. *J Formos Med Assoc*. 2012;111:572–9.
15. Kim EJ, Lin WV, Rodriguez SM, Chen A, Loya A, Weng CY. Treatment of diabetic macular edema. *Curr Diab Rep*. 2019;19:68. https://doi.org/10.1007/s11892-019-1188-4
16. Solomon SD, Lindsley K, Vedula SS, Krzystolik MG, Hawkins BS. Anti-vascular endothelial growth factor for neovascular agerelated macular degeneration. *Cochrane Database Syst Rev*. 2019;https://doi.org/10.1002/14651858.CD005139.pub4
17. Qian T, Zhao M, Xu X. Comparison between anti-VEGF therapy and corticosteroid or laser therapy for macular oedema secondary to retinal vein occlusion: a meta-analysis. *J Clin Pharm Ther*. 2017;42:519–29.
18. Senra H, Ali Z, Balaskas K, Aslam T. Psychological impact of anti-VEGF treatments for wet macular degeneration—a review. *Graefes Arch Clin Exp Ophthalmol*. 2016;254:1873–80.
19. Garweg JG, Stefanickova J, Hoyng C, Schmelter T, Niesen T, Sowade O, et al. Vision-related quality of life in patients with diabetic macular edema treated with intravitreal aflibercept: the AQUA study. *Ophthalmol Retin*. 2019;3:567–75.
20. Finger RP, Guymer RH, Gillies MC, Keeffe JE. The impact of anti-vascular endothelial growth factor treatment on quality of life in neovascular age-related macular degeneration. *Ophthalmology*. 2014;121:1246–51.
21. Ahnood D, Souriti A, Williams GS. Assessing patient acceptance of laser pretreatment to reduce injection burden in diabetic macular edema: a large scale postal survey. *Can J Ophthalmol*. 2018;53:637–8.
22. Rodrigues IA, Sprinkhuizen SM, Barthelmes D, Blumenkranz M, Cheung G, Haller J, et al. Defining a minimum set of standardized patient-centered outcome measures for macular degeneration. *Am J Ophthalmol*. 2016;168:1–12.
23. Greenhalgh J, Gooding K, Gibbons E, Dalkin S, Wright J, Valderas J, et al. How do patient reported outcome measures (PROMs) support clinician-patient communication and patient care? A realist synthesis. *J Patisent-Rep Outcomes*. 2018;2:42. https://doi.org/10.1186/s41687-018-0061-6
24. Chen J, Ou L, Hollis SJ. A systematic review of the impact of routine collection of patient reported outcome measures on patients, providers and health organisations in an oncologic setting. *BMC Health Serv Res*. 2013;13:211. https://doi.org/10.1186/1472-6963-13-211
25. Homsi J, Walsh D, Rivera N, Rybicki LA, Nelson KA, LeGrand SB, et al. Symptom evaluation in palliative medicine: patient report vs systematic assessment. *Support Care Cancer*. 2006;14:444–53.
26. Chan EKH, Edwards TC, Haywood K, Mikles SP, Newton L. Implementing patient-reported outcome measures in clinical practice: a companion guide to the ISOQOL user's guide. *Qual Life Res*. 2019;28:621–7.
27. Boyce MB, Browne JP, Greenhalgh J. The experiences of professionals with using information from patient-reported outcome measures to improve the quality of healthcare: a systematic review of qualitative research. *BMJ Qual Saf*. 2014;23:508–18.
28. van der Wees PJ, Verkerk EW, Verbiest MEA, Zuidgeest M, Bakker C, Braspenning J, et al. Development of a framework with tools to support the selection and implementation of patient-reported outcome measures. *J Patient-Rep Outcomes*. 2019;3:75. https://doi.org/10.1186/s41687-019-0171-9
29. The EuroQol Group. EuroQol – a new facility for the measurement of health-related quality of life. *Health Policy (New York)*. 1990;16:199–206.
30. Lamers L, Stalmeier PFM, McDonnell J, Krabbe PFM, Busschbach JJ. Kwaliteit van leven meten in economische evaluaties: het Nederlands EQ-5D-tarief. *Ned Tijdschr Geneeskd*. 2005;149:1574–8.
31. Weih LM, Hassell JB, Keeffe J. Assessment of the impact of vision impairment. *Invest Ophthalmol Vis Sci*. 2002;43:927–35.
32. Lamoureux EL, Pallant JF, Pesudovs K, Hassell JB, Keeffe JE. The impact of vision impairment questionnaire: an evaluation of its measurement properties using Rasch analysis. *Invest Ophthalmol Vis Sci*. 2006;47:4732–41.

33. TP R–K, van der Ham AJ, Terwee CB, Verbraak FD, van Rens GHMB, van Nispen RMA. Translation and content validity of the Dutch impact of vision impairment questionnaire assessed by three-step test-interviewing. *J Patient-Rep Outcomes*. 2021;5:1. https://doi.org/10.1186/s41687-020-00272-z
34. Wolffsohn JS, Cochrane AL. Design of the low vision quality-of-life questionnaire (LVQOL) and measuring the outcome of low-vision rehabilitation. *Am J Ophthalmol*. 2000;130:793–802.
35. Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD. Development of the 25-list-item National eye Institute visual function questionnaire. *Arch Ophthalmol*. 2001;119:1050–8.
36. Edelen MO, Reeve BB. Applying item response theory (IRT) modeling to questionnaire development, evaluation, and refinement. *Qual Life Res*. 2007;16:5–18.
37. Courtney M, Gordon R. Determining the number of factors to retain in EFA: using the SPSS R-menu v2 0 to make more judicious estimations. *Pract Assess Res Eval*. 2013;18:1–14.
38. Reeve BB, Hays RD, Bjorner JB, Cook KF, Crane PK, Teresi JA, et al. Psychometric evaluation and calibration of health-related quality of life item banks: plans for the patient-reported outcomes measurement information system (PROMIS). *Med Care*. 2007;45:S22–31. https://doi.org/10.1097/01.MLR.0000250483.85507.04
39. Patel PJ, Steel DH, Hirneiß C, Brazier J, Aly A, Lescrauwaet B. Patient-reported prevalence of metamorphopsia and predictors of vision-related quality of life in vitreomacular traction: a prospective, multi-Centre study. *Eye*. 2019;33:435–44.
40. Vu HTV, Keeffe JE, McCarty CA, Taylor HR. Impact of unilateral and bilateral vision loss on quality of life. *Br J Ophthalmol*. 2005;89:360–3.
41. Frank E, Harrell J. Regression modeling strategies. 2nd ed. Switzerland: Springer; 2015. p. 77–87.
42. World Health Organization (WHO) International classification of diseases, 11th revision: 9D90 vision impairment including blindness [https://www.who.int/news-room/fact-sheets/detail/blindness-and-visual-impairment]. 2020. Accessed 28 Sep 2020.
43. Mandrekar JN. Receiver operating characteristic curve in diagnostic test assessment. *J Thorac Oncol*. 2010;5:1315–6.
44. Brown RL, Barrett AE. Visual impairment and quality of life among older adults: an examination of explanations for the relationship. *J Gerontol Ser B Psychol Sci Soc Sci*. 2011;66 B:364–73.
45. Elshout M, Webers CA, Van Der Reis MI, De Jong-Hesse Y, Schouten JS. Tracing the natural course of visual acuity and quality of life in neovascular age-related macular degeneration: a systematic review and quality of life study. *BMC Ophthalmol*. 2017;17:120. https://doi.org/10.1186/s12886-017-0514-3
46. McCloud C, Khadka J, Gilhotra JS, Pesudovs K. Divergence in the lived experience of people with macular degeneration. *Optom Vis Sci*. 2014;91:966–74.
47. Molzahn A, Skevington SM, Kalfoss M, Makaroff KS. The importance of facets of quality of life to older adults: an international investigation. *Qual Life Res*. 2010;19:293–8.
48. Xuan J, Kirchdoerfer LJ, Boyer JG, Norwood GJ. Effects of comorbidity on health-related quality-of-life scores: an analysis of clinical trial data. *Clin Ther*. 1999;21:383–403.
49. Zetterberg M. Age-related eye disease and gender. *Maturitas*. 2016;83:19–26.
50. Esteban JJN, Martínez MS, Navalón PG, Serrano OP, Patiño JRC, Purón MEC, et al. Visual impairment and quality of life: gender differences in the elderly in Cuenca, Spain. *Qual Life Res*. 2008;17:37–45.
51. Alcañiz M, Solé-Auró A. Feeling good in old age: factors explaining health-related quality of life. *Health Qual Life Outcomes*. 2018;16:48. https://doi.org/10.1186/s12955-018-0877-z
52. Han KT, Park EC, Kim JH, Kim SJ, Park S. Is marital status associated with quality of life? *Health Qual Life Outcomes*. 2014;12:109. https://doi.org/10.1186/s12955-014-0109-0
53. Bookwala J. Marital quality as a moderator of the effects of poor vision on quality of life among older adults. *J Gerontol Ser B Psychol Sci Soc Sci*. 2011;66 B:605–16.
54. Mielck A, Reitmeir P, Vogelmann M, Leidl R. Impact of educational level on health-related quality of life (HRQL): results from Germany based on the EuroQol 5D (EQ-5D). *Eur J Pub Health*. 2013;23:45–50.
55. Muir KW, Santiago-Turla C, Stinnett SS, Herndon LW, Allingham RR, Challa P, et al. Health literacy and vision-related quality of life. *Br J Ophthalmol*. 2008;92:779–82.
56. van Nispen RMA, Knol DL, Neve HJ, van Rens GHMB. A multilevel item response theory model was investigated for longitudinal vision-related quality-of-life data. *J Clin Epidemiol*. 2010;63:321–30.
57. Twisk J, De Boer M, De Vente W, Heymans M. Multiple imputation of missing values was not necessary before performing a longitudinal mixed-model analysis. *J Clin Epidemiol*. 2013;66:1022–8.
58. Malkin AG, Goldstein JE, Perlmutter MS, Massof RW. Responsiveness of the EQ-5D to the effects of low vision rehabilitation. *Optom Vis Sci*. 2013;90:799–805.

How to cite this article: Rausch-Koster TP, Rennert KN, Heymans MW, Verbraak FD, van Rens GH, van Nispen RM. Predictors of vision-related quality of life in patients with macular oedema receiving intravitreal anti-VEGF treatment. *Ophthalmic Physiol Opt* 2022;42:849–857. https://doi.org/10.1111/opo.12984