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

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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
intra-vitreal anti-vascular endothelial growth factor (anti-VEGF), macular oedema, Quality of Life, Vision-related Quality of Life
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. Common causes of macular oedema are diabetic macular oedema, exudative age-related macular degeneration and retinal vein occlusion. 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. Similarly, retinal vein occlusion affects an estimated 16 million globally and frequently leads to visual impairment.

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. 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. 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.

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. Routine assessment of PROMs may help in identifying unrecognised problems, as patients do not always spontaneously report their problems to their physicians. 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. 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.

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.

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.

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). 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. The overall fit of the 47 items was examined graphically and non-graphically using a screeplot and a minimum ratio of explained variance between two models (at least four). In addition, unidimensionality was examined 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 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 investigated graphically and non-graphically using a screeplot and acceleration factor, respectively.

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 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.

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. 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 \((\beta)\) 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. 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 | Predictors of EQ-5D and EyeQ score |
|---|---|
| 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]) | 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]) | Normal vision to mild vision loss: logMAR visual acuity \(\leqslant 0.5\) \(658\) (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
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 $\beta$ $-0.11$, 95% CI $-0.15$ to $-0.07$, $p < 0.001$ and T2 $\beta$ $-0.34$, 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, 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 $-2LL$s 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. Table 3 shows the adjusted linear predictor for
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. It has been suggested that poorer vision leads to activity limitations, less social support, reduced self-efficacy and more depressive symptoms. 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. 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. Along with this, the lower VrQoL may also be explained by the nature of the injections, which are often experienced as invasive and stressful. 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, and other studies have also suggested a similar relationship. 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

### Table 4

| Predictor                                    | OR    | 95% CI       | p     | Adjusted linear predictor |
|----------------------------------------------|-------|--------------|-------|---------------------------|
| Intercept                                   | 15.04 | 3.40–66.54   | <0.001| 3.16                      |
| 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.
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);
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