Determinants of Quality of Life in Geographic Atrophy Secondary to Age-Related Macular Degeneration

Sandrine H. Künzel,[1] Philipp T. Möller,[1,2] Moritz Lindner,[3] Lukas Goerdt,[1] Jennifer Nadal,[4] Matthias Schmid,[4] Steffen Schmitz-Valckenberg,[1,2,5] Frank G. Holz,[1,2] Monika Fleckenstein,[1,2,5] and Maximilian Pfau[1,2,6]

[1]Department of Ophthalmology, University of Bonn, Bonn, Germany
[2]GRADE Reading Center, Bonn, Germany
[3]The Nuffield Laboratory of Ophthalmology, Sleep and Circadian Neuroscience Institute, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom
[4]Institute for Medical Biometry, Informatics and Epidemiology, University of Bonn, Bonn, Germany
[5]John A. Moran Eye Center, University of Utah, Salt Lake City, Utah, United States
[6]Department of Biomedical Data Science, Stanford University, Stanford, California, United States

Correspondence: Monika Fleckenstein, Department of Ophthalmology, University of Bonn, Ernst-Abbe-Str. 2, Bonn, Germany; mfleckenstein@web.de.

Received: January 13, 2020
Accepted: April 15, 2020
Published: May 27, 2020

Citation: Künzel SH, Möller PT, Lindner M, et al. Determinants of quality of life in geographic atrophy secondary to age-related macular degeneration. *Invest Ophthalmol Vis Sci.* 2020;61(5):63. https://doi.org/10.1167/iovs.61.5.63

Purpose. To longitudinally evaluate vision-related quality of life (VRQoL) in geographic atrophy (GA) secondary to age-related macular degeneration (AMD) and define its relation to visual function and structural biomarkers.

Methods. Patients with GA secondary to AMD were recruited in the context of the prospective, non-interventional, natural-history Directional Spread in Geographic-Atrophy study (NCT02051998). Fundus autofluorescence and infrared reflectance images were semi-automatically annotated for GA. Linear mixed-effects models were applied to investigate the association of putative determinants with the National Eye Institute Visual Function Questionnaire 25 (NEI VFQ-25) VRQoL.

Results. A total of 87 patients with a mean age ± SD of 77.07 ± 7.49 years were included in the analysis. At baseline, median (IQR) best-corrected visual acuity (BCVA) was 0.3 (0.51) for the better eye and 0.89 (0.76) for the worse eye; 46% of the patients showed binocular and 25.3% monocular non-central GA. The VRQoL composite score was impaired: 69.96 (24.03). Sixty-six patients with a median of 2 (2) follow-up visits after 1.08 (0.78) years were examined longitudinally.

In the multivariable cross-sectional analysis, predictors of the VRQoL composite score were BCVA, GA size, and low-luminance visual acuity (LLVA) for the better eye and BCVA, foveal sparing status, and LLVA for the worse eye (cross-validated $R^2 = 0.32$).

In the longitudinal analysis, a similar prediction accuracy for VRQoL was determined (cross-validated $R^2 = 0.28$). Prediction accuracy for VRQoL did not improve when follow-up time was added as an independent variable.

Conclusions. Vision-related quality of life is significantly impaired in patients with GA secondary to AMD. The cross-sectional and longitudinal association of VRQoL with visual functional and structural biomarkers supports the validity of the NEI VFQ-25 VRQoL.

Keywords: geographic atrophy, quality of life, vision-related quality of life, patient reported outcomes, age-related macular degeneration

Age-related macular degeneration (AMD) is one of the most common causes of central vision loss worldwide, especially in industrial countries.[1–3] Around 28 million people are affected by AMD, and a drastic increase to 288 million by 2040 is expected.[4] In contrast to neovascular AMD, there is no therapy currently available for patients with geographic atrophy (GA). Its high prevalence, the expected increase due to demographic trends, and the lack of treatment options make the dry late form of AMD an important study subject.[2] Therapeutic trials are currently emerging.

The non-exudative late-stage manifestation GA is hallmarked by atrophy of the retinal pigment epithelium and concurrent atrophy of the outer neuroretina.[5–8] Typically, foci of GA manifest initially in the parafovea and may spare the fovea, a phenomenon known as foveal sparing.[5,9–11] Over time, these foci tend to slowly expand in size and coalesce with eventual involvement of the fovea.[5,11] Foveal sparing may persist for a considerable time due to the significantly faster centrifugal compared with centripetal GA spread.[11] Although the best-corrected visual acuity (BCVA) may be preserved in patients with foveal sparing,[12–14] patients typically experience visual impairments such as reading difficulties, as has been recently demonstrated quantitatively.[15–17] This complex monocular relationship between

Copyright 2020 The Authors

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

Downloaded from intl.iovs.org on 04/19/2024

structure and function, as well as the binocular nature of the disease, suggests that monocular enlargement of atrophy as detected by fundus autofluorescence (FAF), an accepted endpoint by the U.S. Food and Drug Administration (FDA),[18] may not necessarily correlate strongly with patient-reported outcomes.

Both the FDA and the European Medicines Agency (EMA) strongly advocate the use of patient-reported outcomes as endpoints in clinical trials.[19–21] The 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25)[22] may constitute a feasible patient-reported outcome measure (PROM) to quantify vision-related function in patients with GA secondary to AMD.[23] Of note, strong internal consistency, reproducibility, and convergent validity with binocular reading speed were recently demonstrated for the NEI VFQ-25 by Sivaprasad et al.[23] However, in ongoing and former clinical trials aiming to slow the progression of GA secondary to AMD with intravitreal injection of therapeutic agents, treatment is typically confined to the worse eye (i.e., monocular). Precise understanding of the monocular contribution of visual function and structural biomarkers to the overall (binocular) vision-related quality of life (VRQoL) in patients is a prerequisite for designing clinical trials testing for efficacy in terms of PROMs.[24]

Accordingly, the purpose of this study was to prospectively evaluate the VRQoL as assessed by the NEI VFQ-25 in patients with GA secondary to AMD, to assess it longitudinally, and to define its relation to monocular visual function and structural biomarkers in patients with binocular GA. We hypothesized that VRQoL is primarily dependent on visual function and structural biomarkers of the better eye, both in a cross-sectional and longitudinal setting. Further, we hypothesized that the association of VRQoL is overall stronger with visual function biomarkers as compared to with structural biomarkers. Last, we hypothesized that some degree of decline in VRQoL over time may occur beyond the association with the herein evaluated structural and functional biomarkers.

Methods

Patients

Patients were recruited in the context of the non-interventional, prospective, natural history Directional Spread in Geographic Atrophy study (DSGA, NCT02051998) at the Department of Ophthalmology at the University Hospital in Bonn, Germany.[11,25] This study adhered to the tenets of the Declaration of Helsinki and was approved by the University of Bonn institutional review board (approval ID 197/12). The patients included in this study had GA in both eyes and were 55 years of age or older at the baseline visit. We excluded patients with the presence of choroidal neovascular membrane or any other ocular disease that could confound assessment of the retina in the study eye, as well as patients with any systemic disease with a limited survival prognosis or any other condition that would make adherence to the examination schedule of once every 6 months for up to 24 months difficult.

Clinical Assessment

Age, gender, medical history, best-corrected visual acuity (BCVA), low-luminance visual acuity (LLVA), reading acuity, foveal involvement, and the NEI VFQ-25 visual and socioemotional function scales were collected for this study. BCVA, LLVA (2.0 log neutral density filter), and reading acuity were assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) and Radner Reading Charts.[26,27] The NEI VFQ-25 includes visual and socioemotional function scales. The base questionnaire consists of 25 items comprising a composite score and 12 subscales addressing general health and different aspects of vision-related functioning. NEI VFQ-25 scores range from 0 to 100, with a higher score representing better visual function.[22,23] Changes of four to six points have been judged to represent a clinically meaningful change, corresponding to a $\geq$15-letter change in BCVA in patients with neovascular AMD.[28]

Imaging

Following pupil dilatation with 0.5% tropicamide and 2.5% phenylephrine, all patients underwent 30° × 30° fundus autofluorescence imaging (λ excitation, 488 nm; λ emission, 500–700 nm), 30° × 30° infrared reflectance (λ, 815 nm) imaging, and 30° × 25° spectral-domain optical coherence tomography imaging (121 B-scans, ART 25) using a Spectralis HRA-OCT 2 (Heidelberg Engineering, Heidelberg, Germany).

Image Grading

Each visit, all eyes were graded for the presence of GA. The size of GA was semi-automatically annotated using the RegionFinder software for FAF and infrared reflectance (Heidelberg Engineering), as previously described.[29,30] The grading task was performed by two readers and subsequent arbitration by a third reader if the GA size deviated by more than 0.3 mm^2 between the first and second reader.

Statistical Analyses

Statistical analyses were performed using the software environment *R* and the add-on packages *lme4*, *glmnet*, *stepwise*, and *glmmLasso*. BCVA and LLVA were assessed using the ETDRS charts, and confirmed to the base-10 logarithm of minimal angle of resolution (logMAR) scale.[27] GA size was square root transformed. The better eye and worse eye were defined by the respective values in each individual determinant. Variables were assessed for normality using the Shapiro–Wilk test. For normally distributed variables, the mean and standard deviation are presented. For non-normally distributed variables, the median and interquartile range (IQR) are presented.

Univariable linear regression was applied to analyze the associations between the individual putative determinants and the dependent variable VRQoL.

Multicollinearity (two or more explanatory variables with high bivariate correlation) was evident (Supplementary Fig. S1), which can lead to instability in model coefficients and variable selection when using conventional multivariable least-squares regression.

To address this issue, we applied least absolute shrinkage and selection operator (LASSO) regression with the VRQoL as the dependent variable for the cross-sectional multivariable analysis at baseline. LASSO regression is designed to handle multicollinearity and carries out variable selection by performing regularization and shrinking coefficient estimates toward zero. This usually enhances the prediction

Investigative Ophthalmology & Visual Science

Downloaded from intl.iovs.org on 04/19/2024

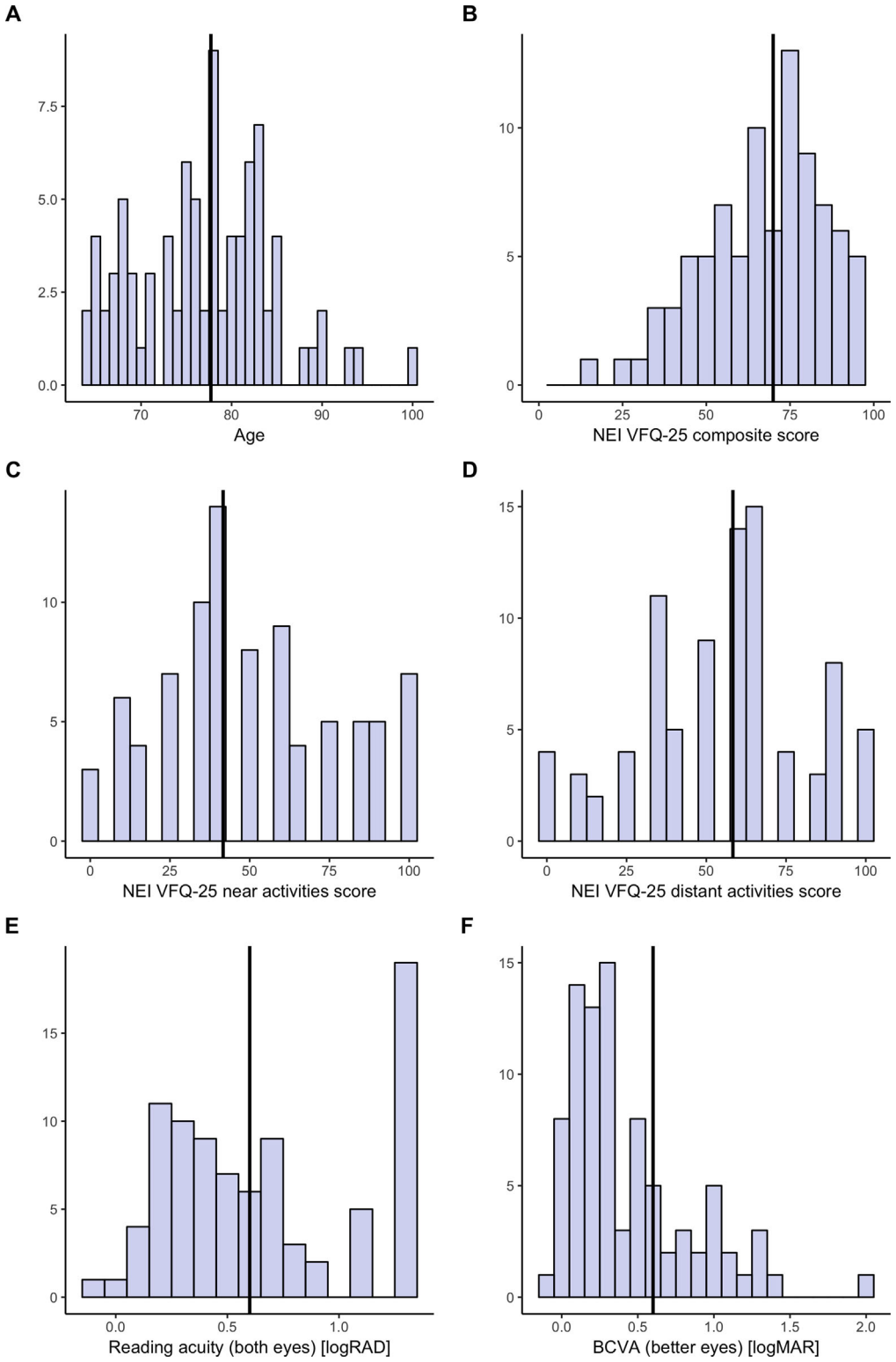

Figure 1. Data distribution. The histograms show the cross-sectional distribution of age (**A**), VRQoL composite score (**B**), near vision subscore (**C**), distant vision subscore (**D**), binocular reading acuity (**E**), and BCVA of the better eye (**F**). The *solid vertical line* denotes the median value. Please note, the Radner reading acuity (**B**) score exhibits a marked floor effect and that, due to the design of the questionnaire, some values in **C** and **D** could not be attained.

accuracy and interpretability by providing a parsimonious model (i.e., model with few predictors).[31] It is specifically designed for predictive modeling (the aim of our analysis), in contrast to conventional (unregularized) least-squares regression for explanatory modeling and statistical inference.

Investigative Ophthalmology & Visual Science

Downloaded from intl.iovs.org on 04/19/2024

Table 1. Cohort Characteristics

	Cross-Sectional Cohort	Baseline Characteristics, Longitudinal Cohort
Number of patients	87	66
Gender	40 male, 47 female	32 male, 34 female
Age (y), mean ± SD	77.07 ± 7.49	77.48 ± 7.43
Square root transformed geographic atrophy area		
Better eye (mm), mean ± SD	2.73 ± 1.31	2.94 ± 1.25
Worse eye (mm), mean ± SD	3.25 ± 1.22	3.40 ± 1.20
Progression (mm/y), median (IQR)	NA	0.21 (0.19)
Vision-related quality of life, median (IQR)		
Composite score	69.96 (24.03)	73.96 (23.80)
Distant-vision subscore	58.33 (33.33)	50.57 (30.47)
Near-vision subscore	41.67 (37.50)	41.67 (33.33)
Best-corrected visual acuity (logMAR), median (IQR)		
Better eye	0.30 (0.51)	0.30 (0.51)
Worse eye	0.89 (0.76)	0.89 (0.82)
Reading acuity (logRAD), median (IQR)		
Binocular	0.60 (0.8)	0.51 (0.59)
Better eye	0.51 (0.8)	0.51 (0.62)
Worse eye	1.30 (0.54)	1.30 (0.50)
Low-luminance visual acuity (logMAR), median (IQR)		
Better eye	0.79 (0.60)	0.80 (0.73)
Worse eye	1.10 (0.51)	1.10 (0.58)
Follow-up time (y), median (IQR)	NA	1.08 (0.78)
Follow-up visits (n), median (IQR)	NA	2 (2)

Nested cross-validation with patient-wise splits was applied to estimate the prediction accuracy of the model (outer leave-one-out cross-validation [LOOCV]) and to optimize the tuning parameter λ of the LASSO regression (nested inner LOOCV). For comparison, we present the results of a conventional (least-squares) cross-sectional multivariable regression analysis in Supplementary Table S1 and Supplementary Figure S2. Variables were selected through stepwise forward section based on Akaike information criterion.

For the longitudinal multivariable analysis, we applied LASSO regression (with nested cross-validation) for linear mixed-effects models with the VRQoL as the dependent variable in consideration of the multicollinear and longitudinal data.[32] Patients were considered as random effect. For comparison, we present the results of a conventional linear mixed-effects model analysis in Supplementary Table S2.

Results

Baseline Data

A total of 87 patients with a mean age ± SD of 77.07 ± 7.49 years at baseline (Fig. 1A; Table 1) were included in this study. The median (IQR) values for BCVA (Fig. 1F) and LLVA were 0.30 (0.51) logMAR and 0.79 (0.60) logMAR in the better eye and 0.89 (0.76) logMAR and 1.1 (0.51) logMAR in the worse eye, respectively. The mean square-root-transformed GA size was 2.73 ± 1.31 mm in the better eye and 3.25 ± 1.22 mm in the worse eye at baseline. Both, BCVA ($P < 0.05$) and GA size ($P < 0.05$) were correlated between the better and worse eye, with correlation coefficients of 0.70 and 0.93, respectively (Supplementary Fig. S1).

The patients had impaired vision-related functioning and quality-of-life scores, as evidenced by a median NEI VFQ-25 composite score of 69.96 (24.03) at baseline (Fig. 1B), with a near vision subscale score of 41.67 (37.50) (Fig. 1C) and with a distant vision subscale score of 58.33 (33.33) (Fig. 1D), representing the worst affected subscores. Patients had a median reading acuity of 0.60 (0.80) logarithm of the reading acuity determination (logRAD) binocular (Fig. 1E), with monocular 0.51 (0.80) logRAD in the better eye and 1.30 (0.54) logRAD in the worse eye, respectively. In this study, 25.3% of the patients had a monocularly and 46% a binocularly non-center-involving GA (foveal sparing or non-central GA). Spearman correlation analysis revealed strong multicollinearity among the features (Supplementary Fig. S1).

Cross-Sectional Univariable Analysis of Determinants of Vision-Related Quality-of-Life at Baseline

In the univariable analysis (Fig. 2; Table 2), binocular and monocular reading acuity, visual acuity, low luminance visual acuity, and GA size for both eyes exhibited a significant association with the VRQoL composite score (all $P < 0.0001$). The same holds for the near and distant vision subscores (all $P < 0.0001$). The presence of a preserved central visual field (foveal sparing or non-central GA) in at least one eye was significant for the near vision subscore ($P = 0.0002$) but not for the composite or distant vision scores.

The distribution of reading acuity (Figs. 1E, 2) revealed a negative skew due to frequent recordings of the worst possible reading acuity of 1.3 logRAD, indicating a marked floor effect of the Radner Reading Charts in the setting of GA.

Cross-Sectional Multivariable Analysis of Determinants of Vision-Related Quality-of-Life at Baseline

In Figure 3, we present the coefficient estimates for cross-validation (Figs. 3A, 3C, 3E), as well as the magnitude of the coefficient estimates dependent on the regularization parameter (Figs. 3B, 3D, 3F). With regard to the composite score, in

Investigative Ophthalmology & Visual Science

Downloaded from intl.iovs.org on 04/19/2024

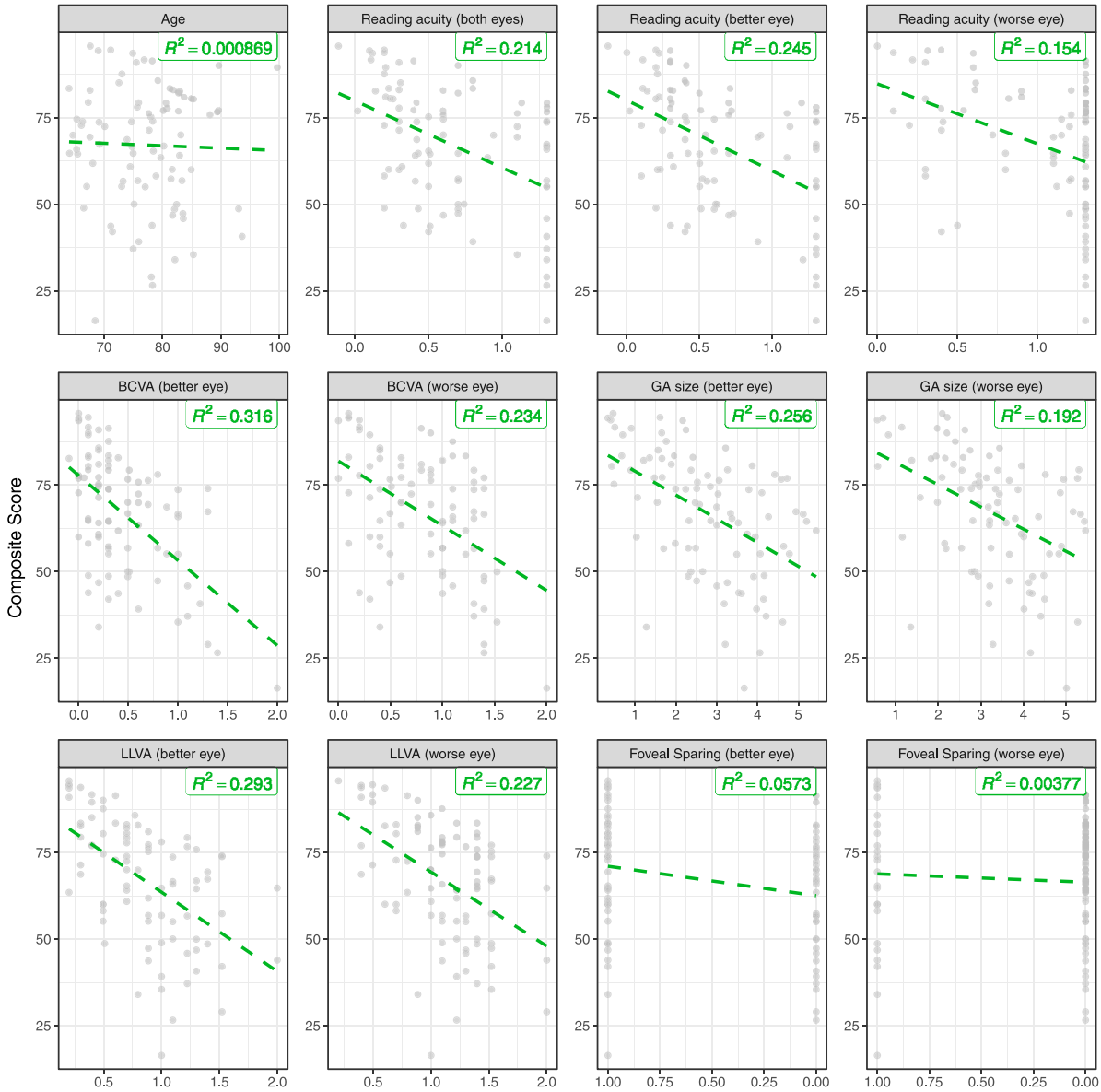

Figure 2. Cross-sectional determinates of vision-related quality of life. All plots show VRQoL composite scores on the *y*-axis and the corresponding determinants on the *x*-axis. The *dashed green lines* show the univariable linear regression lines. The shown R^2 estimates were obtained from models fit to the complete data (cross-validated R^2 estimates are provided in Table 2).

Figure 3B, moving from left to right (i.e., increasing values for the regularization parameter), age and foveal sparing of the better eye were the first variables eliminated from the model. Functional characteristics of the worse eye including BCVA, LLVA, and reading acuity were among the next variables to be eliminated. In contrast, LLVA, BCVA, and GA size of the better eye were the last variables to be eliminated. This ranking of the features is also reflected in in the coefficient estimates in the cross-validation provided in Figure 3A and Table 3.

The final cross-sectional multivariable model was obtained by fitting a linear model to the complete dataset at baseline using LASSO regression with the optimal regularization parameter determined by cross-validation. With composite score as the dependent variable, the most important predictors were BCVA of the better eye (regularized effect estimate on the composite score, –11 units/logMAR), LLVA of the better eye (–10 units/logMAR), and BCVA of the worse eye (–10 units/logMAR), yielding a cross-validated $R^2 = 0.32$ (Table 3). Similar coefficients were obtained with conventional (least-squares) multivariable analysis (Supplementary Table S1); however, cross-validation revealed more instability in model coefficients and variable selection for the least-squares multivariable analysis (Supplementary Fig. S2).

In Figure 3D, for the near vision subscore, the age as well as the LLVA of the worse eye were the first variables eliminated from the model (when increasing regularization parameter). In contrast, BCVA, LLVA, reading acuity, and GA size of the better eye and the BCVA of the worse eye were the last variables to be eliminated.

With the near vision subscore as the dependent variable, the most important determinants in the resulting cross-sectional multivariable model were BCVA of the worse eye (–15 units/logMAR), LLVA of the better eye

Investigative Ophthalmology & Visual Science

Downloaded from intl.iovs.org on 04/19/2024

Table 2. Determinants of VRQoL Composite Score (Univariable Cross-Sectional Analysis)

	Coefficient	LOOCV R^2
Reading acuity (logRAD)		
Binocular	–19.41	0.17
Better eye	–20.43	0.21
Worse eye	–17.35	0.12
Best-corrected visual acuity (logMAR)		
Better eye	–24.55	0.28
Worse eye	–18.70	0.19
Square root transformed geographic atrophy area (mm)		
Better eye	–6.87	0.22
Worse eye	–6.39	0.15
Low-luminance visual acuity (logMAR)		
Better eye	–22.90	0.26
Worse eye	–21.44	0.19
Foveal sparing		
Better eye	8.49	0.01
Worse eye	2.40	–0.05

The different biomarkers are listed with their coefficient obtained from linear least-squares regression, and coefficient of determination (R^2) determined by LOOCV of the univariable cross-sectional analysis.

(–13 units/logMAR), and reading acuity of the better eye (–11 units/logMAR), resulting in a cross-validated $R^2 = 0.58$.

In Figure 3F, for the distant vision subscore, the reading acuity of the better eye, foveal sparing of the better eye, and binocular reading acuity were the first variables eliminated from the model (when increasing the regularization parameter). In contrast, LLVA and BCVA of the better and worse eyes were the last variables to be eliminated. With the distant vision subscore as the dependent variable, the most important determinants in the resulting cross-sectional multivariable model were BCVA of the worse eye (–17 units/logMAR), foveal sparing of the worse eye (–11 units/eye), and LLVA of the worse eye (–9 units/logMAR), resulting in a cross-validated $R^2 = 0.27$.

Longitudinal Determinants of Vision-Related Quality-of-Life

The longitudinal data contained 66 patients with a median (IQR) of 2 (2) follow-up visits spanning a median of 1.08 (0.78) years. The patients in our study had an average square-root GA progression rate (mean change ± SD) of 0.21 ± 0.19 mm/year per eye. There was no significant change in VRQoL composite (–3.07 ± 9.55/year) or near (–3.44 ± 16.13/year) and distant (–3.56 ± 20.97/year) vision subscores over time (Fig. 4). BCVA (better eye, 0.07 ± 0.39; worse eye, 0.07 ± 0.27 logMAR/year), LLVA (better eye, 0.12 ± 0.38; worse eye, 0.12 ± 0.35 logMAR/year), and binocular and monocular reading acuity (binocular, 0.07 ± 0.39; better eye, 0.06 ± 0.29; worse eye, 0.04 ± 0.22 logRAD/year) also did not change significantly.

Longitudinal Multivariable Analysis of Determinants of Vision-Related Quality-of-Life

To determine whether longitudinal assessments in VRQoL are paralleled in the above-mentioned structural and functional biomarkers or whether decline in VRQoL may be observed independently of these associations, we repeated the analysis on the longitudinal data, including the follow-up time as a new covariate. The longitudinal multivariable model was obtained by fitting the linear mixed-effects model to the complete dataset using LASSO regression with the optimal regularization parameter determined in the cross-validation.

The multivariable longitudinal analysis revealed that the LLVA of both eyes, the reading acuity of both eyes, and the BCVA, GA size, and foveal sparing status of the better eye constituted important predictors of the VRQoL composite score, explaining 27.8% of the variability in VRQoL (cross-validated R^2). Importantly, age and follow-up time were eliminated by the LASSO regression as prognostic features. Again, the variable selection was similar for the LASSO regression and conventional mixed-effects model analysis (Supplementary Table S2).

Similar results were obtained for the near and distant vision subscores. For near vision, the binocular reading acuity and reading acuity of the better eye and the worse eye, the BCVA and GA size of both the better eye and the worse eye, and the LLVA and foveal sparing status of the better eye constituted important predictors of VRQoL, explaining 52.4% of the variability in the near vision subscore (cross-validated R^2). Again, age and follow-up time were eliminated by the LASSO regression as prognostic features.

For the distant vision subscore, BCVA and LLVA of both eyes, as well as binocular reading acuity, reading acuity, GA size, and foveal sparing status of the better eye, were significant predictors of VRQoL, explaining 20.2% of the variability in the near vision subscore (cross-validated R^2). Again, age and follow-up time were eliminated by the LASSO regression as prognostic features.

Discussion

In this study, we demonstrated that VRQoL and near and distant vision subscores are associated with conventional structural and functional biomarkers in patients with GA secondary to AMD. The LLVA of the better eye and the BCVA of both eyes were the most important determinants of VRQoL. Moreover, the longitudinal analysis further underscored these results. The significant effect of presence of foveal sparing in at least one eye on the near vision subscore but not on the composite score or distant vision subscore suggests that the presence of GA in the fovea does not affect

Investigative Ophthalmology & Visual Science

Downloaded from intl.iovs.org on 04/19/2024

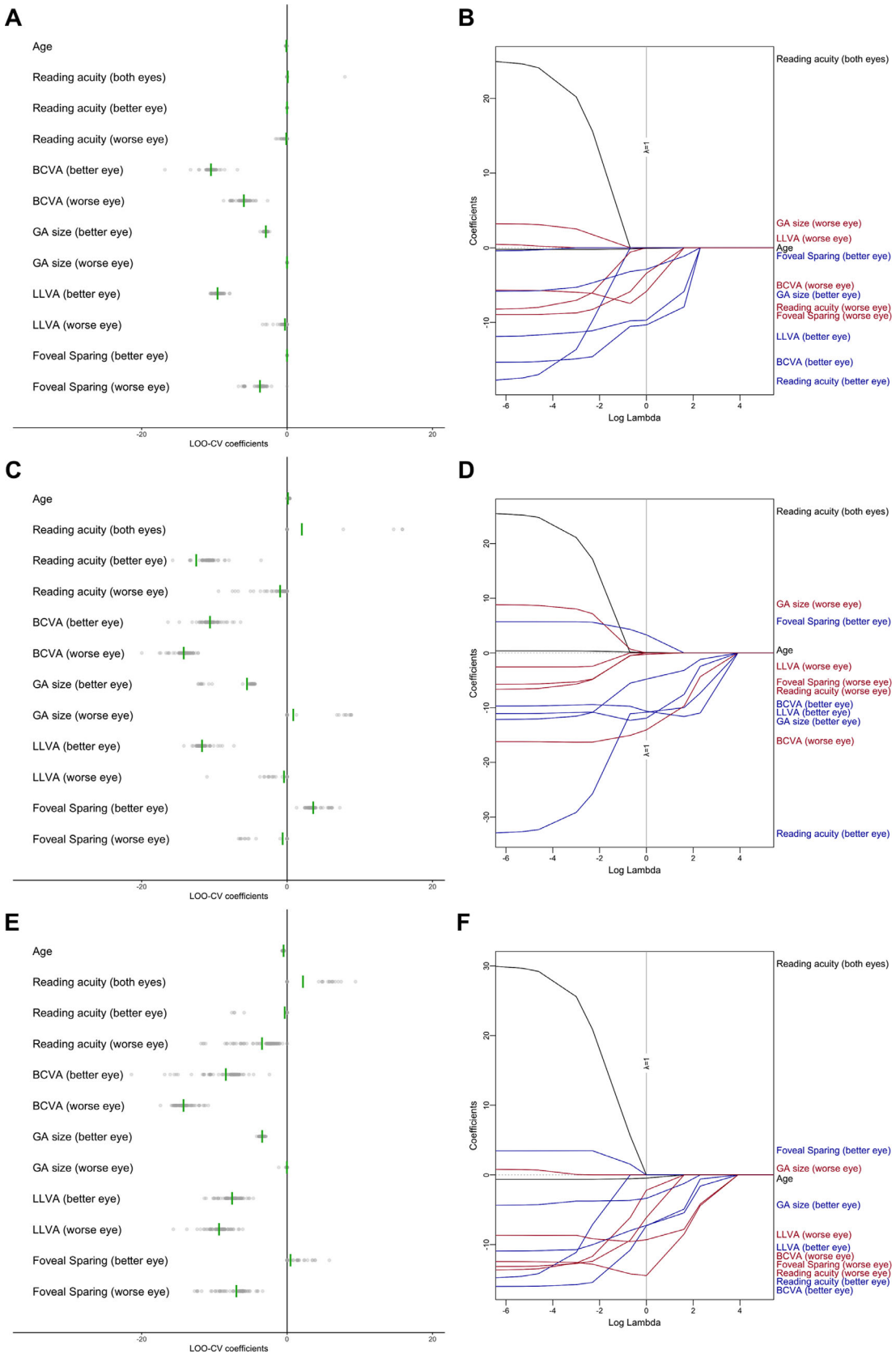

Figure 3. Cross-sectional multivariable analysis of determinants of VRQoL. Dot plots of regression coefficients derived from the training splits for each of the outer cross-validation folds are shown for the composite score (**A**), near vision subscore (**C**), and distant vision subscore (**E**). Cross-validation within these training splits (inner resampling) was used to determine the optimal tuning parameter λ of the LASSO regression model. Note that the points were plotted semitransparently to avoid overplotting. The *green vertical lines* indicate the

Investigative Ophthalmology & Visual Science

Downloaded from intl.iovs.org on 04/19/2024

mean coefficient. A zero coefficient estimate effectively implies exclusion of the respective variable from the LASSO regression model. The coefficients dependent on tuning parameter λ for the complete dataset are shown for the composite score (**B**), near vision subscore (**D**), and distant vision subscore (**F**). The *dashed gray line* indicates the optimal value of tuning parameter λ derived from the inner resampling. Biomarkers of the better eye are highlighted in *blue* and biomarkers of the worse eye in *red*.

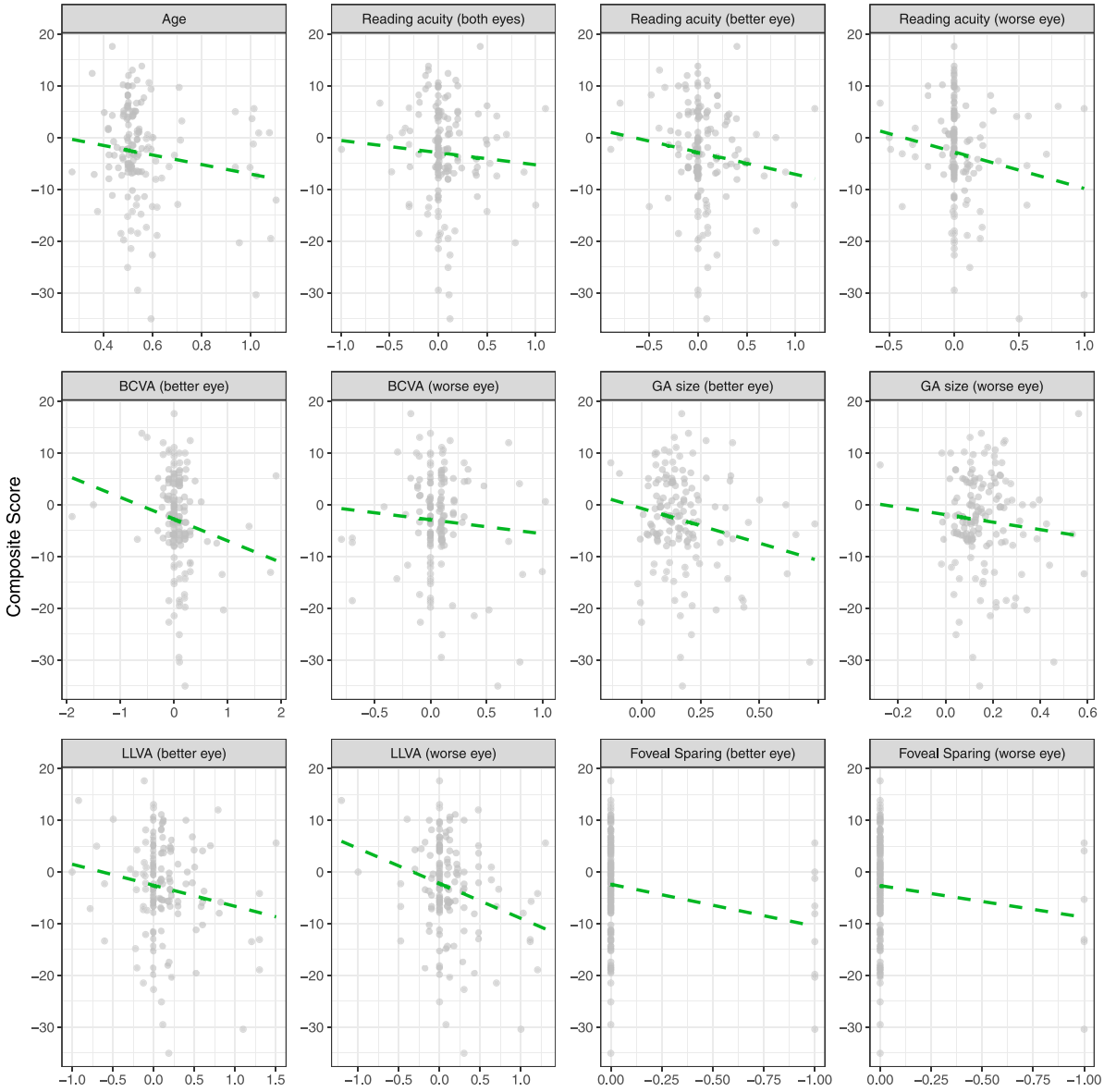

Figure 4. Longitudinal change of VRQoL. All plots show changes in VRQoL composite scores on the *y*-axis and changes in the corresponding determinants on the *x*-axis. The *dashed green lines* show the fitted linear regression lines derived from mixed-effects models with consideration of patients as a random factor. None of the features exhibited a significant change over the given follow-up time.

Table 3. Cross-Sectional Multivariable Analysis of Determinants of VRQoL

	Coefficient	95% Confidence Interval
Best-corrected visual acuity (better eye)	–10.72	–15.24 to 91.95
Best-corrected visual acuity (worse eye)	–9.63	–169.56 to –6.20
Square root transformed geographic atrophy area (better eye)	–3.50	–7.76 to –1.35
Low-luminance visual acuity (better eye)	–9.71	–312.18 to –9.37
Low-luminance visual acuity (worse eye)	–0.34	2.91 to 443.50
Foveal sparing (worse eye)	–8.13	–18.96 to –1.32

LASSO regression was applied for variable selection and shrinkage of coefficient estimates. The selected biomarkers are listed with their coefficient obtained from the LASSO and the corresponding 95% confidence interval.

Investigative Ophthalmology & Visual Science

Downloaded from intl.iovs.org on 04/19/2024

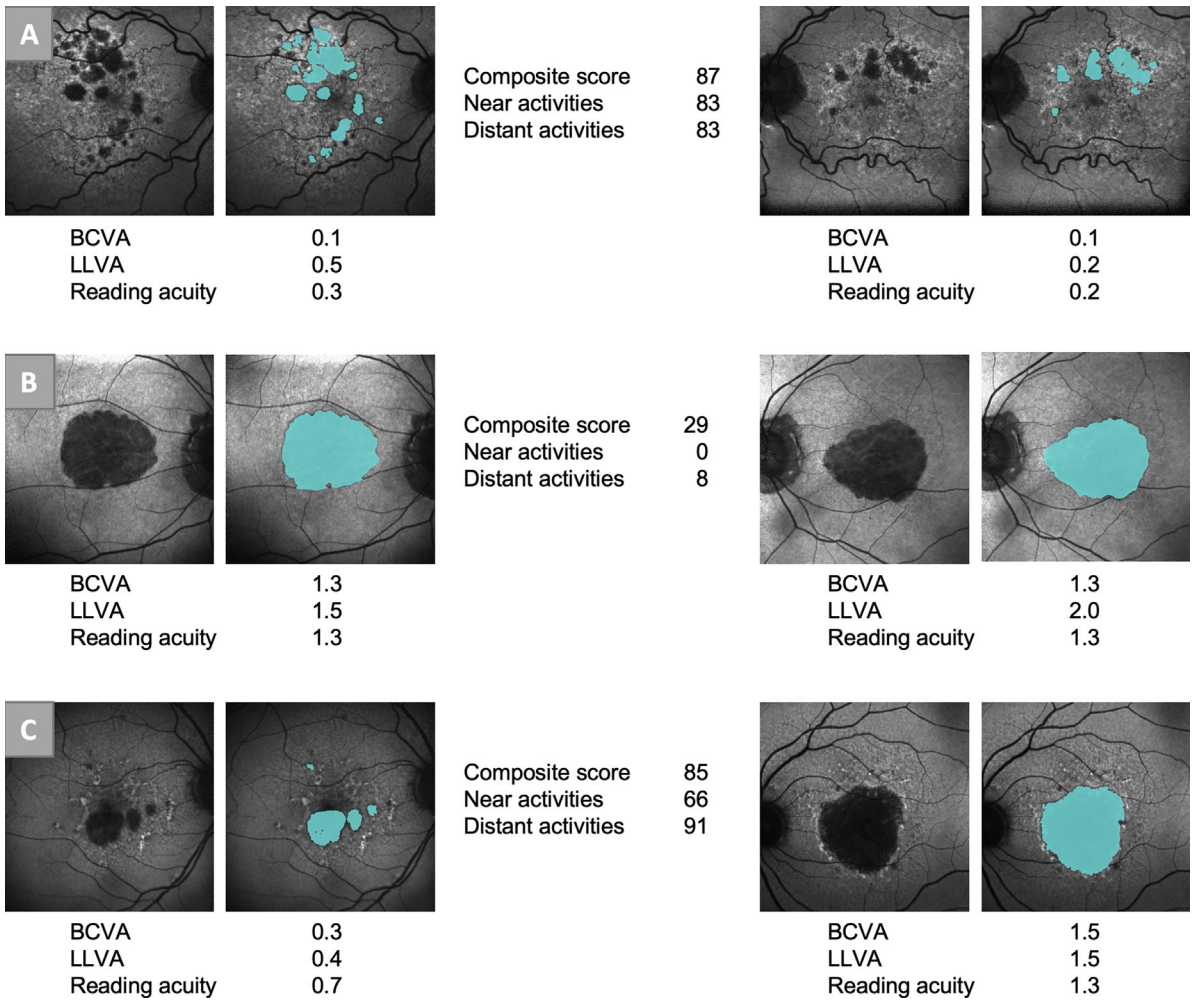

Figure 5. Example patients. The figure shows the FAF and semiautomatically graded GA (*blue areas*) of three patients. The BCVA and LLVA (logMAR) and the reading acuity (logRAD) are shown. Patient A had high VRQoL scores and good visual function in both eyes. Patient B had low VRQoL scores and poor visual function in both eyes. Patient C had high VRQoL scores but only one eye with good function.

independently domains other than near vision in terms of VRQoL. No evidence for a decline in VRQoL or subscores over time beyond the aforementioned associations was identified. (Fig. 4) These results have important implications for the application of the VRQoL for PROMs in clinical trials for GA secondary to AMD as outlined below.

In view of the call for PROMs in clinical trials by regulatory agencies, including the FDA and EMA,[19–21] PROMs such as the NEI VFQ-25 have been previously applied in GA secondary to AMD.[23] In addition to the robust psychometric properties of PROMs, their validity in a disease-specific context is a prerequisite to their application. Sivaprasad et al.[23] demonstrated strong internal consistency and reproducibility for the NEI VFQ-25 with regard to GA secondary to AMD. Moreover, they validated the binocular MNREAD Acuity Charts and patient-reported Functional Reading Independence Index.[23,33] However, to the best of our knowledge, there are no published data regarding the monocular influence on VRQoL, a highly important aspect considering that the study eyes in clinical trials regarding GA are typically the structurally and functionally worse eyes.[34]

This motivated us to develop our first hypothesis, and this study indeed confirmed that VRQoL was primarily dependent on the better eye (Fig. 5), in both cross-sectional and longitudinal settings. Interestingly, LLVA exhibited the most stable coefficient in the model across a variety of values of the LASSO regularization parameter λ, highlighting its relevance for VRQoL. Although previous studies demonstrated that LLVA is significantly reduced and also prognostic for subsequent BCVA loss in eyes with GA secondary to AMD, its precise cellular correlate is not well understood.[9,35] BCVA is primarily limited by the retinal peak cone density, but LLVA may be indicative of decreased cone dark-adaptation and postreceptoral cell dysfunction.[36,37] For the near and distant vision subscores, the results were very similar.

In terms of the second hypothesis, we observed that functional biomarkers were indeed more prognostic for VRQoL and the subscores, as compared with structural biomarkers (GA size and status of foveal sparing). In the univariable analysis, structural variables (i.e., GA area of the better eye) could only explain up to 22% of the variability in VRQoL, highlighting the fact that these variables are rather unsuitable for demonstrating drug efficiency in patient-relevant

Investigative Ophthalmology & Visual Science

Downloaded from intl.iovs.org on 04/19/2024

terms, despite the obvious suitability to measuring biological effectiveness.

Finally, we expected that some degree of decline in VRQoL over time might be observable beyond the above-mentioned associations; however, based on the longitudinal analysis, we found that neither age nor follow-up time was able to improve predictions of VRQoL when added to the multivariable LASSO models. This finding highlights the close association between the evaluated functional and structural biomarkers and VRQoL, as well as the near and distant vision subscores. Further, this suggests that the residual unexplained variability in VRQoL among patients may be representative of rather unspecific factors such as retest variability and general patient attitudes rather than disease-specific factors, which would be correlated to follow-up time.

Multiple important implications can be drawn from these results. First, the results highlight the relevance of LLVA as a functional outcome measure in GA secondary to AMD. Second, for clinical trials designed to prove efficiency in terms of patients' VRQoL rather than safety and biological efficiency, treatment should be allocated to the better eye. This is very much in contrast to previous clinical trials, in which the eyes with the worse BCVA were typically allocated to treatment.[34] To address this matter, one could use a model to indirectly infer the expected effect on VRQoL of a given treatment. For this purpose, a model would be trained only on the data of the better eyes from a natural-history study to infer VRQoL. This model could then be applied to infer the expected effect of a given treatment on VRQoL with the assumption that the treated (worse) eye would have been the better eye. Third, in clinical practice, the decision to refer patients to low-vision clinics or counseling via patient-led groups should be based primarily on the function of the better eye.

Strengths of this study include the large number of functional and structural biomarkers that were assessed in a monocular setting to evaluate the validity of the NEI VFQ-25 as a PROM. Moreover, the stringent analysis with nested resampling (inner resampling for model optimization and outer resampling for the evaluation of model performance) provided a rather unbiased estimate of the prognostic model accuracy. Limitations of the study include the limited sample size for the longitudinal cohort and limited follow-up time, as well as inherent test characteristics of some of the functional tests. Longer follow-up times may be advantageous to detect significant changes in VRQoL over time; however, current interventional trials feature similar follow-up times.[34] For the Radner reading acuity distribution, an excess of the value of 1.3 logRAD (floor of the test) was observed. Accordingly, a revised version of the test allowing for larger optotypes or a longer maximal time per line may be warranted in the setting of GA. As highlighted by Owsley et al.,[38] a target questionnaire such as the Low Luminance Questionnaire may have revealed further facets of loss of visual function in association with AMD.

In conclusion, this study underscores the validity of the NEI VFQ-25 for measuring the impact on patients' VRQoL of GA secondary to AMD. The markedly higher association of VRQoL with visual function and structural biomarkers of the better eye compared to the worse eye has important implications for the design of future clinical trials. Specifically, treatment should be allocated to the better eye in trials aiming to evaluate efficiency in terms of patient VRQoL.

Acknowledgments

The authors thank Joanna Czauderna, Verena Bonn, and Ruth Hassenrik for patient coordination and data acquisition.

Supported by a dissertation grant from the German Ophthalmological Society (SHK), by grants from the German Research Foundation (PF 950/1-1 to MP, 658/4-1 and 658/4-2 to MF, and 2846/1-1 to ML), and by grants from the BONFOR GEROK Program of the Faculty of Medicine, University of Bonn (O-137.0022 and O-137.0025 to MP). CenterVue SpA (Padova, Italy) provided research equipment (Scotopic Macular Integrity Assessment device) for this study. CenterVue had no role in the design or conduct of the experiments. MF was supported in part by an unrestricted grant from Research to Prevent Blindness to the Department of Ophthalmology & Visual Sciences, University of Utah.

Disclosure: **S.H. Künzel**, Heidelberg Engineering (F), Optos (F), Carl Zeiss Meditec (F), CenterVue (F), Novartis (F); **P.T. Möller**, Heidelberg Engineering (F), Optos (F), Carl Zeiss Meditec (F), CenterVue (F), Novartis (F); **M. Lindner**, Heidelberg Engineering (F), Optos (F), Carl Zeiss Meditec (F), CenterVue (F), Novartis (F); **L. Goerdt**, Heidelberg Engineering (F), Optos (F), Carl Zeiss Meditec (F), CenterVue (F), Novartis (F); **J. Nadal**, None; **M. Schmid**, None; **S. Schmitz-Valckenberg**, Acucela (F), Alcon/Novartis (C, F, R), Allergan (C, F, R), Bayer (F, R), Bioeq/Formycon (F, C), Carl Zeiss MedicTec (F, R), CenterVue (F), Galimedix (C), Genentech/Roche (F, R), Heidelberg Engineering (F), Katairo (F), Optos (F); **F.G. Holz**, Acucela (C, F, R), Allergan (F, R), Apellis (C, R), Bayer (C, F, R), Boehringer-Ingelheim (C), Bioeq/Formycon (F, C), CenterVue (F), Ellex (R), Roche/Genentech (C, F, R), Geuder (C), Grayburg Vision (C, R), Heidelberg Engineering (C, F, R), Kanghong (C, F), LinBioscience (C, R), NightStarX (F), Novartis (C, F, R), Optos (F), Pixium Vision (C, F, R), Oxurion (C, R), Stealth BioTherapeutics (C, R), Zeiss (F, R); **M. Fleckenstein**, Novartis (F, C), Heidelberg Engineering (F), STZ GRADE Reading Center (E), Genentech/Roche (C), Ophthalmo Update GmbH (C), pending patent US20140303013A1; **M. Pfau**, Heidelberg Engineering (F), Optos (F), Carl Zeiss Meditec (C, F), CenterVue (F), Novartis (F)

References

1. Cheung LK, Eaton A. Age-related macular degeneration. *Pharmacother J Hum Pharmacol Drug Ther*. 2013;33:838–855.
2. Holz FG, Schmitz-Valckenberg S, Fleckenstein M. Recent developments in the treatment of age-related macular degeneration. *J Clin Invest*. 2014;124:1430–1438.
3. Rasmussen A, Sander B. Long-term longitudinal study of patients treated with ranibizumab for neovascular age-related macular degeneration. *Curr Opin Ophthalmol*. 2014;25:158–163.
4. Wong WL, Su X, Li X, 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 Heal*. 2014;2:e106–e116.
5. Sarks JP, Sarks SH, Killingsworth MC. Evolution of geographic atrophy of the retinal pigment epithelium. *Eye*. 1988;2:552–577.
6. Fleckenstein M, Issa PC, Helb H-MM, et al. High-resolution spectral domain-OCT imaging in geographic atrophy associated with age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2008;49:4137–4144.
7. Zanzottera EC, Ach T, Huisingh C, Messinger JD, Freund KB, Curcio CA. Visualizing retinal pigment epithelium phenotypes in the transition to atrophy in neovascular age-related macular degeneration. *Retina*. 2016;36:S26–S39.

Downloaded from intl.iovs.org on 04/19/2024

8. Sadda SR, Guymer R, Holz FG, et al. Consensus definition for atrophy associated with age-related macular degeneration on OCT: Classification of Atrophy Report 3. *Ophthalmology*. 2018;125:537–548.
9. Sunness JS, Rubin GS, Applegate CA, et al. Visual function abnormalities and prognosis in eyes with age-related geographic atrophy of the macula and good visual acuity. *Ophthalmology*. 1997;104:1677–1691.
10. Sunness JS, Margalit E, Srikumaran D, et al. The long-term natural history of geographic atrophy from age-related macular degeneration. enlargement of atrophy and implications for interventional clinical trials. *Ophthalmology*. 2007;114:271–277.
11. Lindner M, Böker A, Mauschitz MM, et al. Directional kinetics of geographic atrophy progression in age-related macular degeneration with foveal sparing. *Ophthalmology*. 2015;122:1356–1365.
12. Lindner M, Nadal J, Mauschitz MM, et al. Combined fundus autofluorescence and near infrared reflectance as prognostic biomarkers for visual acuity in foveal-sparing geographic atrophy. *Invest Ophthalmol Vis Sci*. 2017;58:BIO61–BIO67.
13. Sayegh RG, Sacu S, Dunavolgyi R, et al. Geographic atrophy and foveal-sparing changes related to visual acuity in patients with dry age-related macular degeneration over time. *Am J Ophthalmol*. 2017;179:118–128.
14. Schmitz-Valckenberg S, Nadal J, Fimmers R, et al. Modeling visual acuity in geographic atrophy secondary to age-related macular degeneration. *Ophthalmologica*. 2016;235:215–224.
15. Lindner M, Pfau M, Czauderna J, et al. Determinants of reading performance in eyes with foveal-sparing geographic atrophy. *Ophthalmol Retin*. 2019;3:201–210.
16. Sunness JS. Reading newsprint but not headlines: pitfalls in measuring visual acuity and color vision in patients with bullseye maculopathy and other macular scotomas. *Retin Cases Brief Rep*. 2008;2:83–84.
17. Sunness JS, Rubin GS, Zuckerbrod A, Applegate CA. Foveal-sparing scotomas in advanced dry age-related macular degeneration. *J Vis Impair Blind*. 2008;102:600–610.
18. Csaky KG, Richman EA, Ferris FL. Report from the NEI/FDA ophthalmic clinical trial design and endpoints symposium. *Invest Ophthalmol Vis Sci*. 2008;49:479–489.
19 . US Food and Drug Administration. Patient-reported outcome measures: use in medical product development to support labeling claims. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims. Accessed May 8, 2020.
20 European Medicines Agency. EU Regulatory Workshop – Ophthalmology – Summary and Report. Available at: https://www.ema.europa.eu/en/documents/report/european-union-regulatory-workshop-ophthalmology-summary-report_en.pdf. Accessed May 8, 2020.
21. Csaky K, Ferris F, 3rd, Chew EY, Nair P, Cheetham JK, Duncan JL. Report from the NEI/FDA endpoints workshop on age-related macular degeneration and inherited retinal diseases. *Invest Ophthalmol Vis Sci*. 2018;58:3456–3463.
22. Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD. Development of the 25-item National Eye Institute Visual Function Questionnaire. *Arch Ophthalmol*. 2001;119:1050–1058.
23. Sivaprasad S, Tschosik E, Kapre A, et al. Reliability and construct validity of the NEI VFQ-25 in a subset of patients with geographic atrophy from the phase 2 Mahalo study. *Am J Ophthalmol*. 2018;190:1–8.
24. Cheng QE, Gao J, Kim BJ, Ying G. Design characteristics of geographic atrophy treatment trials: systematic review of registered trials in ClinicalTrials.gov. *Ophthalmol Retin*. 2018;2:518–525.
25. Pfau M, Lindner M, Goerdt L, et al. Prognostic value of shape-descriptive factors for the progression of geographic atrophy secondary to age-related macular degeneration. *Retina*. 2019;39:1527–1540.
26. Radner W. Reading charts in ophthalmology. *Graefes Arch Clin Exp Ophthalmol*. 2017;255:1465–1482.
27. Pelli DG, Bex P. Measuring contrast sensitivity. *Vision Res*. 2013;90:10–14.
28. Suñer IJ, Kokame GT, Yu E, Ward J, Dolan C, Bressler NM. Responsiveness of NEI VFQ-25 to changes in visual acuity in neovascular AMD: validation studies from two phase 3 clinical trials. *Invest Ophthalmol Vis Sci*. 2009;50:3629–3635.
29. Schmitz-Valckenberg S, Brinkmann CK, Alten F, et al. Semi-automated image processing method for identification and quantification of geographic atrophy in age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2011;52:7640–7646.
30. Pfau M, Goerdt L, Schmitz-Valckenberg S, et al. Green-light autofluorescence versus combined blue-light autofluorescence and near-infrared reflectance imaging in geographic atrophy secondary to age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2017;58:BIO121–BIO130.
31 .Hastie T, Tibshirani R, Friedman J. *The Elements of Statistical Learning: Data Mining, Inference, and Prediction*. 2nd ed. New York: Springer; 2009.
32. Groll A, Tutz G. Variable selection for generalized linear mixed models by L1-penalized estimation. *Stat Comput*. 2014;24:1–35.
33. Kimel M, Leidy NK, Tschosik E, et al. Functional Reading Independence (FRI) index: a new patient-reported outcome measure for patients with geographic atrophy. *Invest Ophthalmol Vis Sci*. 2016;57:6298–6304.
34. Holz FG, Sadda SR, Busbee B, et al. Efficacy and safety of lampalizumab for geographic atrophy due to age-related macular degeneration: Chroma and Spectri phase 3 randomized clinical trials. *JAMA Ophthalmol*. 2018;136:666–677.
35. Sunness JS, Rubin GS, Broman A, Applegate CA, Bressler NM, Hawkins BS. Low luminance visual dysfunction as a predictor of subsequent visual acuity loss from geographic atrophy in age-related macular degeneration. *Ophthalmology*. 2008;115:1480–1488, 1488.e1–2.
36. Wu Z, Ayton LN, Guymer RH, Luu CD. Low-luminance visual acuity and microperimetry in age-related macular degeneration. *Ophthalmology*. 2014;121:1612–1619.
37. Stockman A, Sharpe LT. Into the twilight zone: the complexities of mesopic vision and luminous efficiency. *Ophthalmic Physiol Opt*. 2006;26:225–239.
38. Owsley C, McGwin G. Vision-targeted health related quality of life in older adults: patient-reported visibility problems in low luminance activities are more likely to decline than daytime activities. *BMC Ophthalmol*. 2016;16:92.

Investigative Ophthalmology & Visual Science

Downloaded from intl.iovs.org on 04/19/2024