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ORIGINAL RESEARCH

Vision and Quality of Life in Fuchs' Endothelial Dystrophy Using a Prototype Aberrometer: A Cross-Sectional Study

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Background: Fuchs' endothelial corneal dystrophy (FECD) is a progressive disease that affects vision and quality of life (QoL). While best distance-corrected visual acuity (BDCVA) is commonly used to assess visual function, the role of optical aberrations and high-resolution imaging in explaining patient-reported outcomes remains unclear. This study aims to evaluate how clinical, optical, and QoL parameters interrelate in patients with FECD.

Methods: Prospective, cross-sectional study. Patients underwent ophthalmic evaluation including best distance-corrected BDCVA, refraction, central corneal thickness, endothelial cell density (ECD), and aberrometry using a high-resolution device. FECD severity was clinically graded (modified-Krachmer scale). Eyes were classified by lens status and presence of edema, pigment, or fibrosis. Quality of life was assessed using the NEI Visual Function Questionnaire (VFQ-25). Correlations were analyzed using univariate tests and multivariate regression.

Results: Eyes exhibiting corneal edema detected by slit-lamp examination had significantly lower BDCVA compared to those without edema (mean difference 0.2 [95% CI: 0.08–0.32], adjusted $p<0.001$). Eyes with fibrosis also had worse visual acuity compared to those without (mean difference 0.137 [95% CI: 0.02–0.26], adjusted $p=0.01$). The Fuchs' grading scale showed strong correlation with BDCVA ($r=-0.68$, $p<0.001$) and moderate correlation with advanced wavefront metrics (RMS; $r=0.3$, $p<0.001$). VFQ-25 total score had the strongest correlation with the worst eye's visual acuity ($r=0.42$, $p<0.001$). Incorporating additional variables or more complex models did not significantly enhance prediction.

Conclusion: Worse-eye BDCVA correlates with patient-reported quality of life in FECD; however, adding high-resolution optical metrics (eg, wavefront/HPFM) did not meaningfully improve explanatory or predictive performance beyond simple clinical variables. These findings highlight a current gap: advanced optical metrics are not yet sufficient to reliably predict the subjective patient experience. Any conclusions from this study should be considered highly preliminary pending confirmation by further research.

Keywords: Fuchs endothelial corneal dystrophy, optics, cornea, quality of life, visual function

Introduction

Fuchs' endothelial corneal dystrophy (FECD) is a bilateral degenerative eye disease that progressively causes the loss of endothelial cells (ECs).[1] This phenomenon induces an adaptation in which ECs change their shape and size, and the gaps become filled with extracellular matrix, forming guttae.[2,3] The prevalence ranges from 7% to 11%, depending on age, with gender also being a contributing factor.[4] Its aetiology is multifactorial, with genetic and environmental factors being associated with the onset and development of this disease. Slit-lamp biomicroscopy was initially the standard tool for diagnosing, grading, and monitoring FECD; later, more objective device-based modalities such as Scheimpflug imaging,

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anterior segment tomography, or specular microscopy were adopted as established alternatives.[5] Descemet's membrane endothelial keratoplasty (DMEK) is the most extended surgical technique to restore the patient's vision, and the combination with the cataract surgery is known as DMEK triple.[6,7]

The visual quality in FECD patients is compromised by two factors: on the one hand, optical aberrations caused by corneal changes, with high values of trefoil and spherical aberrations reported in these patients.[8,9] On the other hand, corneal turbidity results in abnormal levels of scattering.[10,11] Some studies reported backscattering as the major cause of vision impairment in these patients.[12,13] Recently, some authors have discovered that subtle signs, such as preoperative posterior stromal ripples, can affect DMEK recovery time.[14]

The visual acuity of the better eye has an association with patients' reported outcomes measurements (PROMs), followed by astigmatism.[15] There are a few questionnaires used in patients with Fuchs Dystrophy, but recently a new specific one has been developed and validated[16.] Many studies reported an improvement in PROMs after keratoplasty[17–20],this is achieved mostly when the first eye is undergone surgery.[21,22]

The high-resolution WaveFront Phase Imaging (WFPI) sensor integrated in our prototype samples the pupil at ~8.6 μm lateral resolution, revealing high-frequency phase structure that lies beyond conventional Hartmann–Shack/ Zernike descriptions.[23] In FECD, the high-pass filtered wavefront map (HPFM) shows a reproducible dark-spot pattern that mirrors the slit-lamp distribution of guttae and enables objective, quantitative metrics (eg, guttae counts, density, triangulation) that separate FECD from healthy eyes.[24] While corneal backscatter and lower-order aberrations have been studied in relation to vision, few studies have attempted a comprehensive predictive model of quality of life that combines standard clinical data with novel high-resolution wavefront metrics.

Accordingly, the primary objective of this study was to evaluate how clinical findings and high-resolution optical measurements interrelate with vision-related quality of life (NEI VFQ-25) in FECD. Secondarily, we assessed whether clinical and optical parameters, considering both standard metrics and WFPI-derived HPFM features, can explain or predict QoL outcomes using multivariable regression.

Methods

Study Design and Settings

This is a prospective, cross-sectional study. Participants were recruited consecutively between September 2022 and June 2023 at Fundación Jiménez Díaz Hospital (Madrid, Spain). This methodology adheres to the principles of the Helsinki Declaration; informed consent was obtained from all participants, and the protocol was approved by the Hospital Institutional Ethics Committee.

Diagnosis, Classification and Patient Stratification

FECD was diagnosed by three experienced ophthalmologists based on slit-lamp biomicroscopy, identifying central guttae, oedema, and endothelial changes. Disease severity was graded using the modified Krachmer scale (stages I to VI). To address clinical heterogeneity, patients were stratified by lens status (pseudophakic vs non-pseudophakic) and by the presence or absence of corneal edema, pigment, and fibrosis. This grouping allowed comparison between subtypes and supported variable selection for quality-of-life modelling outcomes and measurements.

Clinical, Optical and QoL Outcomes

Three categories of outcomes were measured in this study. Clinical variables describing FECD patients included specular microscopy, best distance corrected visual acuity (BDCVA), in decimal notation and subjective refraction (Sphere, Cylinder, and axis) performed by an experienced optometrist. Refraction was converted to power vector notation (M, J_0, J_{45}) for statistical purposes.[25] Endothelial cell density (ECD) and central corneal thickness (CCT) in microns were obtained by Specular Microscope EM-4000 (Tomey Co., Nagoya, Japan). Slit lamp variables were the presence of oedema, pigment, fibrosis, or cataract. The lens status was recorded as pseudophakic or non-pseudophakic. Furthermore, the modified-Krachmer scale was employed to stage the disease, ranging from stages I to VI.[26,27]

Regarding the second category of measurements, patients were measured with a high-resolution WFPI prototype aberrometer (T-eyede, Wooptix); five consecutive captures per eye were acquired. From the conventional wavefront, we extracted Zernike coefficients up to the 10th order and summarised the principal aberration categories(coma, astigmatism, spherical) as RMS.[28,29] In addition, we generated a High-Pass Filtering Map (HPFM) from the phase (Gaussian high-pass) and computed nine pre-specified metrics on a 3-mm pupil, including HPFM, RMS, number/density/diameter/area of guttae-like features, optical path-difference height (OPDH), phase roughness, and Delaunay-triangulation/convex-hull descriptors. The 5-mm analysis was excluded due to lower measurement availability and minimal incremental predictive value. All HPFM metrics follow previously published definitions and the same algorithmic pipeline (Figure 1 shows wavefront and HPFM examples). Although we did not perform a dedicated test–retest in this cohort, prior WFPI work shows low within-session variability, supporting measurement stability.[24]

The third approach was the quality of life (QOL) of the FECD patients, for that purpose we used the Vision Function Questionnaire 25 (VFQ-25) developed by the National Eye Institute (NEI). This form scores the patient QOL related to vision from 0 to 100. Furthermore, sub-scores could be obtained for certain specific categories such as general health score (GHs), general vision (GVs), ocular pain (OPs), near and distance activities (NAs and DAs respectively), vision social function (VSFs), vision mental health (VMHs), vision role difficulties (VRDs), vision dependency (VDs), driving (Ds), colour vision (CVs) and peripheral vision (PVs). The composite score of those mentioned sub-scales was calculated by the mean and standard deviation as recommended by the questionnaire authors.

Statistical Methods

For clinical and optical variables, we examined unadjusted differences across pseudophakia, fibrosis, oedema and pigment using the Kruskal–Wallis test and Tukey's HSD for pairwise contrasts. Multiplicity across these groups was controlled with the Benjamini–Hochberg false discovery rate (BH-FDR), and results are reported as p-adj. For VFQ-25 subscales, we compared scores across the same groups using ordinary least squares (OLS), adjusting for age and gender, reporting mean differences (β) with 95% CIs; when the same group effect was tested across the set of VFQ-25 subscales, multiplicity was controlled with BH-FDR, and results are reported as p-adj.

To study the correlation between variables, we used the Spearman correlation test. To evaluate the correlation between quantitative variables per eye and patients' quality responses, a linear regression model was constructed. For each quantitative variable, we assessed the correlation of the maximum, minimum, mean, and sum of both eyes with each subscale of the quality-of-life questionnaire. For analysis involving multiple correlations, we controlled the false discovery rate using the BH-FDR procedure. Throughout the manuscript, FDR-adjusted p-values are reported as p-adj, with two-sided testing and significance defined as p-adj <0.05. E.g. for the total score and BDCVA, we selected the eye with the minimum value (r=0.36, p-adj <0.001),

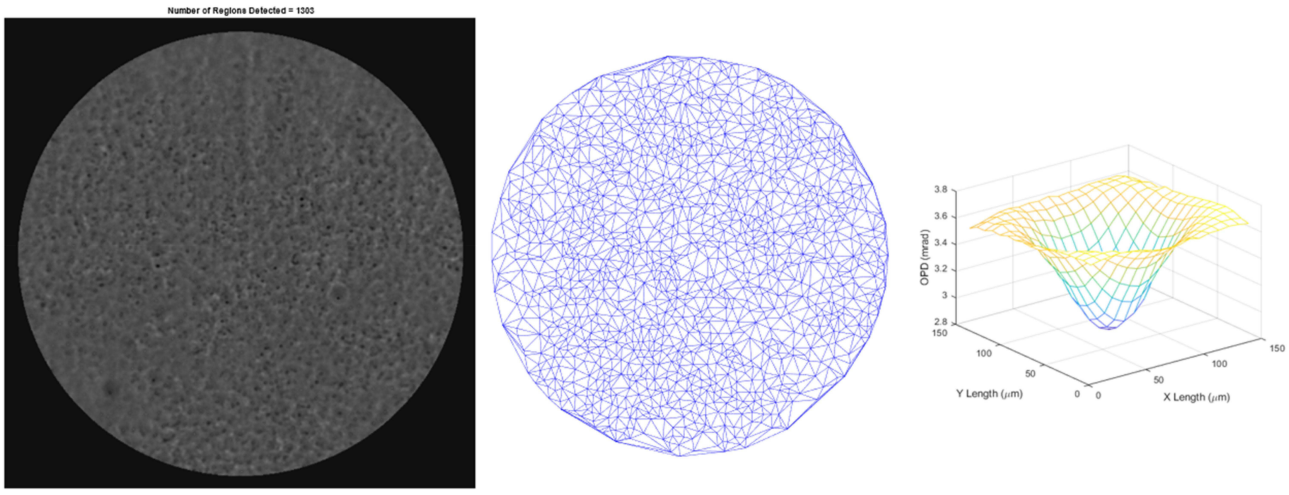

Figure 1 FECD eye: from left to right, High-Pass Filter Map, guttae distribution represented with Delaunay Triangulation, and mean guttae profile.
Abbreviation: OPD, Optical Path-Difference.

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instead of the maximum (r=0.15, p-adj =0.14), mean (r=0.31, p-adj =0.002) or the sum (r=0.31, p-adj =0.002). Then, we selected the measure with the highest correlation for each scale and added demographic data, including age and gender. To determine whether the variables obtained through HPFM played a significant role in predicting quality-of-life scores, two models were constructed: one without HPFM-derived variables, and another including metrics obtained using a 3-mm pupil. The 5-mm analysis was excluded due to low measurement completeness and redundancy. To perform database curation and analysis, we used Python programming language 3.8 and the statsmodels (v 0.14.4) and SciPy (v 1.12) libraries.

Results

A total of 100 patients (65% females, 35% males) were selected, including both eyes. **Table 1** summarises demographic and general information about the sample included in this study. Of the total patients, 40% were pseudophakic in at least one eye, and 38% were classified as Fuchs stage V. CCT was available for 75.5% of eyes and ECD for 44.5%. T-eyede (prototype aberrometer) was able to measure optical aberrations in 97% of the eyes. HPFM analysis was successfully obtained in 78.5% of the eyes using a 3-mm pupil diameter. BDCVA and NEI-VFQ 25 were successfully collected for the whole sample. Subjective refraction could not be obtained for six eyes (3%) from five patients, as their vision did not improve with any optical correction. Descriptive results including demographic variables could be seen in Table 2.

Association Between Clinical, Optical, and Quality of Life Variables

When comparing the best correlation value (minimum, maximum, mean, summatory) for each eye measurement (29 variables) and QoL scores (13 scales), 377 possibilities were considered. In 135 (35%) of those combinations, the minimum value of the variable correlates best with a QoL score (Spearman test), 86 (23%) with the mean value, 83 (22%) with the maximum value and 75 (20%) with the summation of each variable within the patient's eyes. E.g. The worst-seeing eye (BDCVA) correlates better than the other options with every sub-score of the NEI-VFQ25. A moderate correlation was found with DAs (r=0.45, p-adj<0.001), GVs (r=0.44, p-adj<0.001) and total score (r=0.42, p-adj=0.005), a complete table with these results is available at Supplementary Material 1.

The relationship between optical aberrations and quality-of-life scores was less consistent. Some optical metrics showed non-significant trends with specific subscales, but these associations did not remain significant after BH-FDR. High-resolution metrics showed limited relationships with patient-reported outcomes; however, two morphology-based HPFM measures, mean guttae size and mean guttae diameter, were positively correlated with the VMH subscale

Table 1 Baseline Characteristics of the Cohort

	N
Patients (Female/Male)	100 (65/35)
Eyes (Right/Left)	200 (100/100)
Mean Age ± Std	66.68± 15.79
Pseudophakic patients (one eye/both eyes)	7/33
Corneal edema (No/Yes)	174/26
Corneal fibrosis (No/Yes)	172/28
Corneal pigment (No/Yes)	187/13
Fuchs scale (I/II/III/IV/V/VI)	2/25/24/50/76/23
T-eyede processable eyes (No/Yes)	6/194

Notes: Values are per eye (N=200 N eyes from 100 patients). "Patients (Female/Male)" and "Pseudophakic patients (one/both eyes)" are per-patient; Age is mean ± SD. "Eyes (Right/Left)" indicates laterality. Edema/fibrosis/pigment are slit-lamp findings (No/Yes counts). Fuchs scale (I–VI) = modified Krachmer stage per eye. T-Eyede is the prototype for measuring ocular aberrations.

Table 2 Summary of Study Variables

	Metric	n	Mean ± std	Min - Max
Refraction & vision	**Power Vector M (D)**	194	0.287 ± 2	−11.625–5.62
	Power Vector J_o (D)	194	−0.159 ± 0.525	−1.625–2.38
	Power Vector J_{45} (D)	194	−0.0137 ± 0.378	−1.104–1.08
	BCVA (Dec)	200	0.764 ± 0.228	0.010–1
Corneal features (specular microscopy)	**Corneal Central Thickness (mm)**	151	540 ± 52.9	385.000–663
	Cell Density (cell/mm²)	89	1.6e+03 ± 679	449.000–2.9e+03
Optical aberrations	**RMS Astigmatism (μm)**	194	0.245 ± 0.222	0.000–1.24
	RMS Coma (μm)	194	0.102 ± 0.0994	0.000–0.783
	RMS Spherical (μm)	194	0.939 ± 1.05	0.000–5
	RMS Trefoil (μm)	194	0.0759 ± 0.0786	0.000–0.678
High Pass Filtering Maps (3mm)	**RMS (mrad)**	157	0.000104 ± 3.27e-05	0.000–0.00029
	Regions Detected (px^2)	157	353 ± 91.4	60.000–616
	Density Guttae (accounts/mm^2)	157	49.9 ± 12.9	8.488–87.1
	Diameter Guttae (μm)	157	26.4 ± 2.44	18.672–32.5
	Size Guttae ($μm^2$)	157	550 ± 101	273.823–829
	Optical Path-Difference (mrad)	157	0.169 ± 0.0473	0.042–0.291
	Roughness (mrad)	157	0.000265 ± 0.000117	0.000–0.00127
	Delaunay Triangulation (px^2)	157	538 ± 226	286.195–2.5e+03
	Delaunay Triangulation Convex Hull (px^2)	157	595 ± 217	329.119–2.23e+03
NEI VFQ-25	**Total**	200	81.9 ± 14.5	31.304–99
	General Health	200	49.6 ± 21.6	0.000–100
	General Vision	200	61 ± 16.6	20.000–100
	Ocular Pain	200	83.1 ± 19.3	25.000–100
	Near activities	200	78.2 ± 21.5	0.000–100
	Distance activities	200	78.8 ± 22.1	0.000–100
	Vision Social Functioning	200	92.6 ± 13.6	25.000–100
	Vision Mental Health	200	80.5 ± 18.3	12.500–100
	Vision Role difficulties	200	83.1 ± 25.6	0.000–100
	Vision Dependency	200	94.3 ± 14.2	16.667–100
	Driving	106	78.6 ± 23.7	0.000–100
	Color vision	200	97.8 ± 8	50.000–100
	Peripheral vision	199	87.2 ± 21.2	25.000–100

Notes: Values are mean ± SD and range (min–max); n is the number of available observations per eye (N=200) unless indicated (eg, Driving n=106). Optical aberrations and High-Pass Filtering Map (3-mm) metrics were acquired with a high-resolution prototype aberrometer. NEI VFQ-25 total, and subscales are scored 0–100 (higher = better).

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(p-adj=0.009 and p-adj=0.010 respectively). No other HPFM metrics remained significant after BH-FDR. These isolated associations did not improve explanatory or predictive performance beyond simpler clinical models. A detailed summary of all variable-subscale correlation coefficients and p-values is available in Supplementary Material 1.

Multivariate Regression Models

Three models were initially developed, but the analysis including 5-mm pupil metrics, was excluded due to low measurement completeness and no significant improvement in model performance. When no HPFM metrics were included in the model, the worst predicted QOL score was CVs with an adjusted determination coefficient (adj-R^2) of −0.02. On the other hand, the DAs score had an adj-R^2 of 0.3, the independent variables selected to predict this score were age, gender, RMS of coma, astigmatism and BDCVA and power vector J_0. The adj-R^2 results for each QoL score, both without using HPFM metrics and using metrics of different analysis diameters, are summarised in Table 3.

Considering the model that includes all variables, BDCVA appeared most frequently among the important variables in QOL scales, with a presence of 80%. Density guttae and Regions detected were among the most relevant 3-mm HPFM-derived variables in the regression models, appearing in 54% of cases. Delaunay Triangulation (DT) and DT convex hull (DTCH) also showed relevance in approximately 46% of models. More detailed information about models is available as Supplementary Material 2.

Quality of Life Differences by Clinical Subgroups

When considering the mean BDCVA of both eyes, patients who exhibited corneal oedema in at least one eye showed significantly lower values compared to those without oedema in either eye (mean difference 0.20 [0.08–0.32]; p-adj <0.001). Patients with fibrosis also had worse visual acuity than those without it (mean difference: 0.137 [0.02–0.26], p-adj = 0.01). No significant differences in BDCVA were observed between pseudophakic and non-pseudophakic eyes (mean difference: 0.06 [–0.05, 0.15], p-adj = 0.76). Regarding refractive outcomes, no significant differences in M, J_0, or

Table 3 Multivariable Linear Models Predicting NEI VFQ-25 Scores with and without High-Pass Filtering Map (3-mm) Metrics

Metrics Included	No HPFM Metrics				Adding HPFM (3mm)			
	n	Features (n)	R^2	Adj-R^2	n	Features (n)	R^2	Adj-R^2
Total	89	5	0,316	0,275	83	6	0,312	0,258
General Health	100	3	0,2	0,175	67	4	0,222	0,171
General Vision	93	6	0,354	0,309	93	6	0,354	0,309
Ocular Pain	94	3	0,1	0,07	87	4	0,127	0,084
Near activities	89	6	0,201	0,143	89	6	0,201	0,143
Distance activities	89	6	0,389	0,344	89	6	0,389	0,344
Vision Social Functioning	95	4	0,133	0,095	95	4	0,133	0,095
Vision Mental Health	94	4	0,233	0,198	67	8	0,16	0,044
Vision Role Difficulties	100	3	0,266	0,243	100	3	0,266	0,243
Vision Dependency	100	5	0,136	0,09	100	5	0,136	0,09
Driving	51	4	0,313	0,253	51	4	0,313	0,253
Color vision	100	2	0	−0,02	100	2	0	−0,02
Peripheral vision	94	5	0,16	0,112	94	5	0,16	0,112

Notes: For each outcome (Total and subscales) two specifications are shown: No HPFM metrics and Adding HPFM (3-mm). "Patients (n)" is the number of participants with complete data used in that model; "Features (n)" is the number of predictor variables included (excluding the intercept). R^2 = coefficient of determination; Adj-R^2 = R^2 adjusted for the number of predictors. Differences in n across rows reflect missing data.

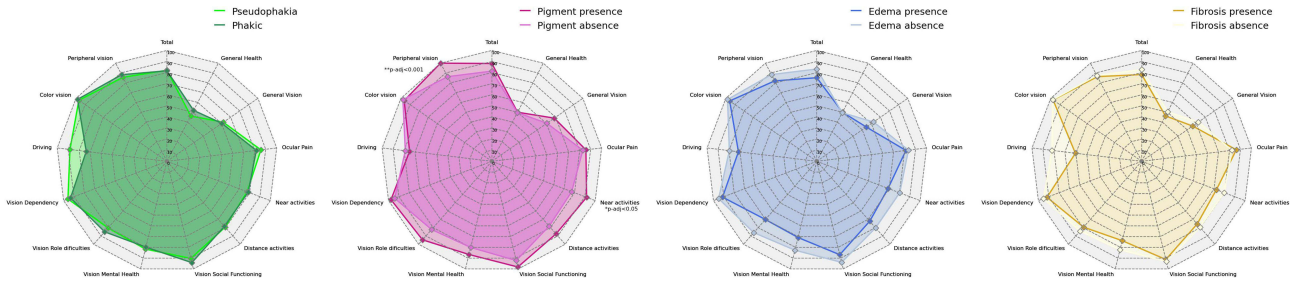

Figure 2 Radar charts of NEI VFQ-25 subscales (0–100; higher scores = better function) comparing the presence vs absence of pseudophakia, corneal pigment, corneal edema, and corneal fibrosis. Curves depict subscale means; labels are placed outside the grid. Group differences were estimated with linear models adjusted for age and gender; p-values were corrected for multiple comparisons (Benjamini–Hochberg FDR) and are reported as p-adj.

J_{45} were observed across clinical subgroups, except for astigmatism. Pseudophakic eyes had a higher mean astigmatism against the rule (mean difference J_0: 0.26 [0.03, 0.49] D, p-adj = 0.02).

No significant differences were found in any parameter between eyes with or without pigment. The mean scores for each VFQ-25 subscale, stratified by presence of pseudophakia, fibrosis, oedema, or pigment, are shown in Figure 2. After adjusting for age and gender and controlling multiplicity with BH-FDR, only corneal pigment remained associated with better VFQ-25 scores, specifically higher Near Activities (β=15.5, 95% CI 5.99–25.03, p-adj=0.009) and higher Peripheral Vision (β=14.9, 95% CI 8.85–20.96, p-adj<0.001); all other between-group contrasts were not significant after FDR control. No statistically significant differences in QOL scores were observed across Fuchs' grading stages.

Feasibility and Clinical Correlation of HPFM Metrics

Aberrometry with the T-eyede succeeded in 194/200 eyes (97%), HPFM analysis at 3 mm was feasible in 157/200 eyes (78.5%). At the eye level, several HPFM-derived metrics correlated with clinical status. RMS correlated with the clinical scale (r=0.298, p-adj<0.001) and with ECD (r=−0.314, p-adj=0.02), OPDH correlated with Fuchs clinical scale (r=0.332, p-adj<0.001), with CCT (r=–0.305, p-adj=0.018), and with ECD (r=–0.367, p-adj=0.009). Delaunay Triangulation had a negative correlation with Fuchs' clinical scale(r=−0.294, p-adj<0.001) and a positive correlation with ECD (r=0.353, p-adj=0.011). Additional associations

Table 4 Spearman Correlations Between 3-mm High-Pass Filtering Map Metrics and Clinical Measures

	Variable	Fuchs' Clinical Scale		Central Corneal Thickness		Endothelial Cell Density	
	Correlation Coefficients	r	p-adj	r	p-adj	r	p-adj
Diameter analysis	**Metric**						
High Pass Filtering Maps (3mm)	**RMS (mrad)**	0,298	<0.001	0,078	0,49	−0,314	0,02
	Regions Detected (px^2)	0,275	0,002	−0,2	0,074	−0,367	0,009
	Density Guttae (accounts/mm^2)	0,275	0,002	−0,2	0,074	−0,367	0,009
	Diameter Guttae (μm)	−0,149	0,08	0,082	0,49	0,111	0,388
	Size Guttae (μm^2)	−0,149	0,08	0,082	0,49	0,111	0,388
	Optical Path -Difference Height (mrad)	0,332	<0.001	−0,305	0,018	−0,367	0,009
	Roughness (mrad)	0,093	0,296	0,19	0,084	−0,121	0,388
	Delaunay Triangulation (px^2)	−0,294	<0.001	0,175	0,11	0,353	0,011
	Delaunay Triangulation Convex Hull (px^2)	−0,286	<0.001	0,156	0,155	0,32	0,02

Notes: Spearman's ρ (r) and two-sided p-value for associations with the Fuchs scale (Krachmer), central corneal thickness (CCT) and endothelial cell density (ECD). n (%) = number (and % of 200 eyes) with all relevant measures available for that metric. Significant results (p<0.05) are marked with †, and p<0.001 are marked with ‡.

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were observed for Regions Detected and Guttae Density with Fuchs' scale and ECD, . r=0.275, p-adj=0.002 and r=–0.367, p-adj=0.009, respectively (see Table 4). These eye-level structural associations did not improve explanatory or predictive performance for VFQ-25 beyond simpler clinical models. No statistically significant differences were observed in HPFM metrics across pseudophakic status, fibrosis, oedema, or pigment presence.

Discussion

This study evaluated the relationship between clinical and optical parameters and vision-related quality of life (QoL) in patients with FECD. Using a high-resolution aberrometer, we calculated HPFM-derived optical metrics based on a 3-mm pupil diameter. The strongest clinical association with QoL was found for the BDCVA of the worse-seeing eye, which correlated moderately with the total score and several subscales. Additionally, patients with fibrosis reported significantly worse scores in the Driving subscale, while those with oedema showed lower scores in Vision Mental Health and Vision Role Difficulties. Although some HPFM-derived metrics correlated with clinical parameters such as Fuchs stage, CCT, and ECD (as shown in Table 4), their predictive value for QoL outcomes was limited. Regression models were fitted to predict each NEI VFQ-25 subscale score, multivariate models achieved moderate performance at best (maximum adjusted $R^2 = 0.297$ for Distance Activities), and this performance did not improve meaningfully when including optical metrics.

Although specular microscopy is routinely performed in FECD, ECD was available in 89/200 eyes (44.5%). Because failed specular acquisitions are more frequent in edematous corneas, missingness is likely missing not at random (MNAR), so ECD-related correlations should be interpreted with caution. By contrast, HPFM at 3-mm pupils was successful in 157/200 eyes (78.5%), which suggests feasibility even in more advanced disease. We prioritised the 3-mm analysis because it better matches physiological pupil diameters in this population and yielded more complete data. Although this technique is promising, further studies are needed to define its role in diagnosis and follow-up.

Our results for QOL total scores and BDCVA were slightly better than the preoperative data reported by Ang et al[30] or Dunkel et al.[31] It falls within the expected, as both studies include only patients who are undergoing surgery and therefore are at a very advanced stage of the disease. Many of our cases are in FECD stages IV (25%) and V (38%) that may not imply surgical treatment. Regarding the prediction of quality of life, the only similar article to our knowledge is written by Pickel et al,[18] but they try to predict the QOL after endothelial keratoplasty. The main predictor was the diagnosis as well as densitometry, these parameters were not evaluated in our research project. In their study, BCDVA and high-order aberrations did not correlate with the postoperative total score. In our study, BDCVA is an important variable to predict 8 out of the 10 scores (except for GHs and CVs) and the RMS of Coma appears in 5 scores (total, OPs, NAs, Das and Ds).

Interestingly, Ds was reduced in patients with fibrosis but not in those with oedema. While it is well established that oedema increases scattering,[32] it may not be significant enough to be detected by the questionnaire or may have a lesser impact compared to fibrosis. Another noteworthy finding in this study is that the vision of the patient's worst eye showed the strongest correlation with QOL outcomes. This result contrasts with some previous studies that associate QOL with the vision of the better eye[33,34] but aligns with the study by Pickel et al.[18]

Although Krachmer staging reflects slit-lamp morphology, its association with worse-eye BDCVA in our cohort was modest, and VFQ-25 scores did not differ across stages. The resulting dissociation likely reflects within-stage heterogeneity, binocular averaging/adaptation, and the fact that patient-reported outcomes are not fully represented by morphological staging. These exploratory findings argue for complementary, objective grading tools and for confirmation in larger cohorts. In this study, the modified Krachmer clinical stage did not correlate with VFQ-25 scores, a disconnect that likely reflects several factors. The staging system is morphology-based and ordinal, it groups heterogeneous corneal phenotypes into broad categories, whereas patient-reported function depends on binocular integration, adaptation, glare and contrast sensitivity, and symptom fluctuation that slit-lamp grading does not capture. The VFQ-25 may show limited sensitivity in earlier disease and ceiling effects. Inter-rater variability in clinical grading, with three experts, may attenuate true associations, and our single-center tertiary recruitment together with the severity mix may limit generalizability. Taken together, these considerations support a complementary approach that combines structural staging with FECD-specific PROMs and objective optical metrics, and they motivate external validation in broader cohorts.

As a robustness check, we re-estimated the patient-level models using linear mixed-effects with a patient random intercept and the same fixed-effect set used in the multivariate regression model with ordinary least squares (OLS) (excluding ECD).

Models were fit by restricted (residual) maximum likelihood (REML), which provides approximately unbiased variance-component estimates. Mixed-model marginal R^2 values were close to OLS adjusted R^2 across VFQ-25 subscales (median difference 0.028; IQR 0.024–0.040), whereas conditional R^2 (~0.55–0.69) indicated non-negligible clustering. These checks suggest that modelling choice does not meaningfully alter the pattern of results. Full LME outputs (fixed effects, marginal/conditional R^2) are provided in Supplementary Material 2.

The decision to include patients with at least one pseudophakic eye may represent a limitation. However, minimal differences were observed between this group and those with phakic FECD patients. To be more precise, BDCVA did not show statistically significant differences (p-adj 0.76) when compared based on lens status. Since vision appears to be the variable that correlates best with quality-of-life questionnaire scores, we decided that partial correlations considering lens status would not be necessary. Another limitation is the use of the NEI-VFQ-25 questionnaire instead of a questionnaire specifically tailored for FECD, such as the V-Fuchs.[16] At the time of data collection, the V-Fuchs questionnaire had not yet been validated in Spanish. Regarding the missing data limitation, because ECD could not be obtained in ~45% of eyes, and measurement failure correlates with disease severity, ECD is Missing Not at Random (MNAR). Analyses involving ECD are therefore prone to selection bias and should be interpreted cautiously. Given the exploratory nature of this study, confirmation in larger cohorts with prospective data capture and dedicated MNAR-sensitive analyses is needed. The single-centre design limits generalizability; a multicenter study leveraging multiple calibrated prototypes will be necessary to confirm these findings across more diverse populations.

A potential line of research could involve objectively comparing the scattering caused by cataracts with that observed in patients with fibrosis. Also, further studies using high-resolution optical instruments should be carried out to improve clinical decision-making based on objective parameters.

Conclusion

In this prospective, cross-sectional cohort, the associations between clinical and optical parameters and patient-reported visual function were modest, and worse-eye BDCVA was the most consistent correlation. High-resolution optical metrics, including HPFM, did not improve explanatory or predictive performance beyond simpler clinical models, and there was no significant correlation between the modified Krachmer staging and VFQ-25 scores. Taken together, these exploratory findings and the study's design and sampling constraints suggest that available metrics capture only part of the patient's experience. Confirmation in larger, prospective, multicenter cohorts with standardized acquisition and external validation is needed, and future work should test pre-specified models, consider stratification by pseudophakia, and address missing-data mechanisms such as MNAR in ECD. Accordingly, any conclusions from this study should be considered highly preliminary pending confirmation by further research.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Hospital Fundación Jiménez Díaz under protocol number PIC109-22. Written informed consent was obtained from all participants prior to inclusion in the study.

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Disclosure

CBP and MVO are employees of Wooptix, the company developing the prototype aberrometer used in this research; however, the company was not involved in the study design, data analysis, or interpretation of results. JGMH was a co-founder of Wooptix but has no employment relationship with it now. His university remains co-owner of Wooptix, which was created as a startup from ULL. KW invented the corneal oedema prediction tool that is licensed by the University of Freiburg to Oculus Optkgeräte GmbH and she is also an inventor of V-FUCHS, which is licensed by Mayo Clinic to

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