Early Photoreceptor Alterations After Retinal Detachment Repair

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Purpose. The importance of outer retinal microstructure, specifically the external limiting membrane (ELM) and ellipsoid zone (EZ), was recently highlighted for visual recovery after rhegmatogenous retinal detachment (RRD). Quantitative assessment of the EZ/ELM reflectivity, termed the relative EZ reflectivity (rEZR), is a novel SD-OCT imaging biomarker for photoreceptor integrity. This study evaluates the rEZR's functional relevance after anatomically successful RRD repair, as well as its association with the surgical techniques.

Methods. Patients with primary RRD, treated at the Department of Ophthalmology, University of Bonn/Germany between April 2021 and April 2023 and presenting to the six-week postoperative review with complete retinal reattachment, were identified. The rEZR (arbitrary units [AU]) was determined in the postoperative imaging data. Linear-mixed effect models, corrected for patient's age and preoperative macula-on/macula-off RRD situation, were applied to assess the association of the rEZR with the postoperative best-corrected visual acuity (BCVA) and with the previously applied surgical techniques.

Results. A total of 187 patients with a median [interquartile range (IQR)] age of 70.0 [9.7] years (32.1% female) were included. Out of those, 91.4% ($n = 171$) underwent vitrectomy and 8.6% scleral buckling. Higher rEZR values were significantly associated with a better BCVA (coefficient estimate [CE] = 0.3009 [0.1620; 0.4398], $P < 0.001$) and scleral buckling (CE = 12.20 [0.33; 24.07], $P < 0.044$).

Conclusions. This study supports the functional relevance of outer retinal impairment, as quantified by rEZR, and its association with surgery-related variables in the early postoperative period after RRD repair. Further research is needed to better understand the importance of longitudinal rEZR changes to finally achieve the best visual outcomes for RRD patients.

Keywords: photoreceptor health, ellipsoid zone reflectivity, rhegmatogenous retinal detachment repair

Although tremendous innovations in surgical devices have enriched vitreoretinal (VR) techniques and opportunities over the past decades, VR surgeons and patients are still frequently faced with a disappointing recovery of visual function following surgical repair for rhegmatogenous retinal detachment (RRD).[1–3] Moreover, discrepancies between the "obvious" anatomical success of a reattached retina and visual outcome can challenge VR surgeons.[1,2]

Because high-resolution retinal imaging allows for the assessment of the retinal structure and even ultra-structure, increasing evidence has emerged that microstructural changes in the outer retina occur during the process of retinal reattachment.[4–6] Moreover, studies demonstrated the association between outer retinal alterations and postoperative visual acuity and therefore highlighted their functional relevance after retinal surgery.[3,7–17] In a post-hoc analysis of the PIVOT trial, Muni et al. explored the microstructural integrity of the outer retina one year after surgery focusing on the external limiting membrane (ELM) and the ellipsoid zone (EZ).[10] Herein, the authors found significantly more discontinuities of the ELM and the EZ in eyes treated with vitrectomy (instead of pneumatic retinopexy [PnR]) and

that continuity of either layer presented with better visual acuity.[11]

Thus it seems to be convincing that the postoperative success exceeds the mere surgical act of retinal reattachment. It is, however, not yet understood whether impairment of outer retinal health occurs simply during the anatomical process of retinal reattachment or even as a result of surgical techniques.

The relative EZ reflectivity (rEZR), defined as the ratio of the EZ to the ELM peak reflectivity in underlying reflectivity profiles of SD-OCT image data, was introduced as a novel and reliable biomarker for photoreceptor integrity.[18–21] Because the EZ reflectivity signal derives from the mitochondria-rich ellipsoid part of the photoreceptor inner segments, EZ analysis is considered a surrogate for retinal photoreceptor assessment, which was recently highlighted by the Food and Drug Administration accepting the assessment of EZ loss as an endpoint in age-related macular degeneration.[22]

The ELM, on the other hand, represents the tight junctions between photoreceptors and glial Müller cells, that are crucial for photoreceptor health and survival.[23–28] Therefore, as a quantitative measure for the "photoreceptor-support-complex," analysis of the rEZR is a promising approach for gaining new insights into outer retinal ultrastructure and visual outcomes after RRD repair.

Although also other biomarkers in OCT-imaging exist, determination of the rEZR shows advantages in its quantitative nature, which is much more refined than the mere assessment of presence/absence of EZ or ELM structure. Furthermore, it allows to a spatially-resolved analysis of outer retinal structure in a semi-automated manner, as described already previously by Thiele et al.,[18,19] Goerdt et al.,[21] and Sassmannshausen et al.,[22] which makes its application feasible also in the context of longitudinal and large data sets.

This study aims to evaluate the rEZR in the early postoperative phase (i.e., six weeks after RRD repair) concerning its association with visual function, as well as with surgery-related characteristics in a European tertiary eye care setting. Ultimately, this analysis aims at a better understanding of outer retinal alterations following retinal reattachment which is crucially relevant to eventually achieve better functional outcomes for patients undergoing surgery for RRD repair.

Material and Methods

Study Cohort

For this analysis, patients were retrospectively identified as having received treatment for primary RRD at the Department of Ophthalmology, University of Bonn, Germany, between April 2021 and April 2023. All patients with first-time RRD were included regardless of the extent or location of retinal breaks, and independent of the presence of proliferative vitreoretinopathy (PVR), vitreous hemorrhage, or giant retinal tears. Besides a complete anatomical reattachment of the retina, further inclusion criteria were the absence of any confounding ocular condition affecting either eye, the study, or the fellow eye, at the time of surgery, as well as at the first follow-up (FU1) visit approximately six weeks after the surgery. This implies that only RRD patients were included in which no obvious abnormalities of the macula were detected at the FU1 visit neither in clinical examination nor in high-resolution SD-OCT imaging. For instance, this included the absence of a clinically significant cataract, cystoid macular edema, outer retinal folds, epiretinal membrane, or any other ocular disorder in either eye and at any time of assessment. Because the study presented here is a retrospective analysis of data exclusively obtained in clinic routine care at an academic university setting, no ethics approval was required according to the guidelines of the local ethics committee at the University of Bonn.

Clinical Assessment and Determination of Intraoperative/Perioperative Characteristics

As part of routine clinical care, all patients presenting with primary RRD were thoroughly examined after pupils' dilation with tropicamide 0.5% and phenylephrine 2.5% eye drops. This included an assessment of the (preoperative) best-corrected visual acuity (BCVA [decimal]) and duration of presenting symptoms (days). The retinal detachment was further characterized concerning its macula involvement (i.e., if the fovea was attached or detached [macula-on vs. macula-off]).

Surgery for primary RRD repair was conducted by senior consultants highly experienced in vitreoretinal (VR) surgery. The choice of surgical procedure, either scleral buckling or 23-gauge (g) primary pars plana vitrectomy (PPV), was left to the discretion of the surgeon, based on factors such as macula-on versus macula-off RRD or the presence of multiple retinal tears. For scleral buckling procedures, only cases with a single-hole retinal detachment were selected. Consequently, radial buckling was performed in all scleral buckling cases, and no subretinal fluid drainage was required. This applies also to the applied intraoperative measures during retinal reattachment, such as the use of cryopexy or laser photocoagulation, the use of heavy liquid (Perfluorocarbon liquids (PFCL), F-Decalin, Geuder, Heidelberg, Germany) to assist for retinal reattachment during the surgical procedure or peeling of the internal limiting membrane (ILM). ILM peeling was selectively performed in cases with evident or suspected PVR, based on the intraoperative judgment of the surgeon. In none of the included cases, a retinotomy was performed to achieve subretinal fluid drainage. In all vitrectomy cases, subretinal fluid was drained through the original retinal break when possible, or heavy liquid was used to assist retinal reattachment. Accordingly, either gas (sulfur hexafluoride [SF6]; Alcon Laboratories, Fort Worth, TX, USA; hexafluoroethane [C2F6]; MedTech, Mömbris, Germany; perfluoropropane [C3F8]; Alcon Laboratories) or silicone oil (light (Siluron2000; Geuder, Heidelberg, Germany) or heavy oil (Siluron5000; Geuder) was used as endotamponades after PPV surgery. In some cases, when considered clinically beneficial, primary PPV was combined with cataract surgery, which encompassed phacoemulsification and implant of an intraocular lens (IOL) into the capsular bag. No combined procedures (i.e., primary PPV combined with scleral buckling) were performed in this cohort during the study period.

At the postoperative FU1 visit, another thorough ophthalmologic examination was performed. This included an assessment of the postoperative BCVA, as well as a slit-lamp and dilated fundus examination. In each patient, high-resolution retinal imaging was performed using the

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Spectralis HRA2+OCT device (Heidelberg Engineering, Heidelberg, Germany) for combined confocal scanning laser ophthalmoscopy and spectral-domain optical coherence tomography (SD-OCT). SD-OCT volume raster scanning encompassed a scanning field of at least 30° × 25° centered to the fovea and consisted of at least 31 and up to 121 serial OCT B-Scans in high-speed acquisition mode.

Determination of the rEZR

As a quantitative measure for outer retinal integrity, more precisely for the photoreceptor-support-complex, the rEZR was defined as the peak reflectivity ratio of the EZ and the ELM in underlying reflectivity profiles (see Supplementary Fig. S1).[20,21,23] Briefly, a semi-automated approach was applied to assess the rEZR in the raw SD-OCT image data using Python version 3.9 with the NumPy, SciPy, and scikit-image packages (Python Software Foundation, Wilmington, DE, USA). This allowed for analysis of the linearly-displayed, "native" reflectivity data of the SD-OCT images. Automated retinal layer segmentation was executed using the Heidelberg Eye Explorer software V.2.5.6 (Heidelberg Engineering) and manually corrected if needed. For every pixel along the image x-axis, the rEZR was determined in the corresponding reflectivity profiles allowing for both global (i.e., within the entire SD-OCT volume scan) and spatially-resolved rEZR determination. For the latter, the Early Treatment Diabetic Retinopathy Study (ETDRS) grid was applied and the rEZR was determined within each of the nine ETDRS subfields.[29]

The assessment of a reflectivity ratio allows for avoiding potentially confounding factors on the reflectivity of single retinal bands. Of note, only is little known regarding the optical and thus shadowing effects of a silicone oil tamponade on retinal bands in SD-OCT imaging. However, as both retinal bands are directly adjacent to each other and only a few microns apart, any assumed effect of a silicone oil tamponade is assumed to be neglectable as recently highlighted by Ha et al.[30] For transparency and reproducibility, the annotated Python code used for rEZR analysis is openly available at: https://github.com/bisselma/relEZIquantification.

Statistical Analysis

The data was tested for normality using the Shapiro-Wilk test. The mean (± standard deviation [SD]) and the median (interquartile range [IQR]) are given for normally and non-normally distributed data, respectively. Patient characteristics are presented as absolute and relative frequencies for categorical variables. The rEZR was determined for the study eye, as well as the healthy fellow eye in high-resolution SD-OCT retinal imaging at FU1 visit as the mean per the entire volume scan (globally) and per any of the ETDRS grid subfields (topographically). A linear mixed-effects model was used to compare the mean rEZR in the study and fellow eyes considering patients as random effects to account for the nested data structure (varying number of pixels per patient).

In the study eyes, separate univariable linear models were further applied to evaluate the association between the postoperative BCVA (dependent variable) and the mean rEZR for the entire SD-OCT volume scan (global rEZR), the topographically-resolved rEZR values (according to the ETDRS grid subfields), the preoperative BCVA, macula-on versus -off RD, as well as the reported duration of symptoms (structure-function analysis). Herein, the models were corrected for patients' age, sex, and laterality (right or left eye affected with RRD), as well as the presence of PVR, which was included as a marker of disease severity. The averaging over the different ETDRS subfields also accounts for the effects of the eccentricity on rEZR. Given the retrospective nature of this study, BCVA was measured in decimals as part of a routine clinical care assessment and for this analysis also converted to the logarithm of the minimum angle of resolution (logMAR) values.[31–33] In the case of statistical significance, the cross-validated r^2 acted as a measure of variable importance signifying the capability of individual factors to explain the variability in postoperative BCVA.

Subsequently and to investigate associations between the rEZR and intraoperative/perioperative characteristics, separate linear mixed-effects models were used with the pixel-wise rEZR (arbitrary unit [AU]) determined in each dense SD-OCT volume raster scan as the dependent variable. The patient entered as a random intercept term and the models were again adjusted for laterality, age, sex, and eccentricity, with eccentricity entering the model as a B-spline of 2° of distance to the center.[21]

The analyses were performed with the software R, version 4.1.2, using the package lme4.[34] P values < 0.05 were considered significant.

Results

Cohort Characteristics

A total of 187 eyes with primary RRD of 187 participants (60 female [32.1%]) with a median age of 70.0 years (IQR = 9.7) were included in this study, 75 (40.1%) of the patients presented with macula-off detachment (cf., Table 1). At first presentation, median preoperative BCVA was 0.35 (IQR = 1.2) logMAR (20/45 Snellen; 0.45 decimal), and the median time of reported symptoms before presenting to the Department of Ophthalmology/Bonn was 3.5 days (IQR = 5.25). 171 patients (91.4%) were treated with primary vitrectomy for RRD repair. In vitrectomy cases, heavy liquid was used to assist with retinal reattachment during the surgery in 99 patients (52.9%). Gas was chosen as the postoperative tamponade in 149 (87.1%) and silicon oil in 22 (12.9%)

Table 1. Descriptive Analysis of Cohort Characteristics

Determinants	
Number of patients	187
Sex (total)	68% (127) male
Age (years), [median]	60.95 [9.71]
Macula-on RD (total)	60% (112)
Preoperative BCVA (logMAR) [median]	0.35 [1.2]
Postoperative BCVA (logMAR) [median (logMAR)]	0.20 [0.3]
rEZR (AU), mean/entire volume scan	28.86 ± 16.49
Duration of symptoms (days) [median]	3.50 [5.25]
Determinants of the surgery	
Scleral buckling instead of vitrectomy (total)	9% (16)
Silicone oil tamponade (total)	12% (22)
Gas tamponade (total	81% (125)
Usage of heavy liquids (total)	53% (99)
Combined cataract surgery (total)	26% (48)
Cryopexy (total)	65% (122)
Laser photocoagulation (total)	46% (86)
Inner limiting membrane peeling (total)	4% (8)

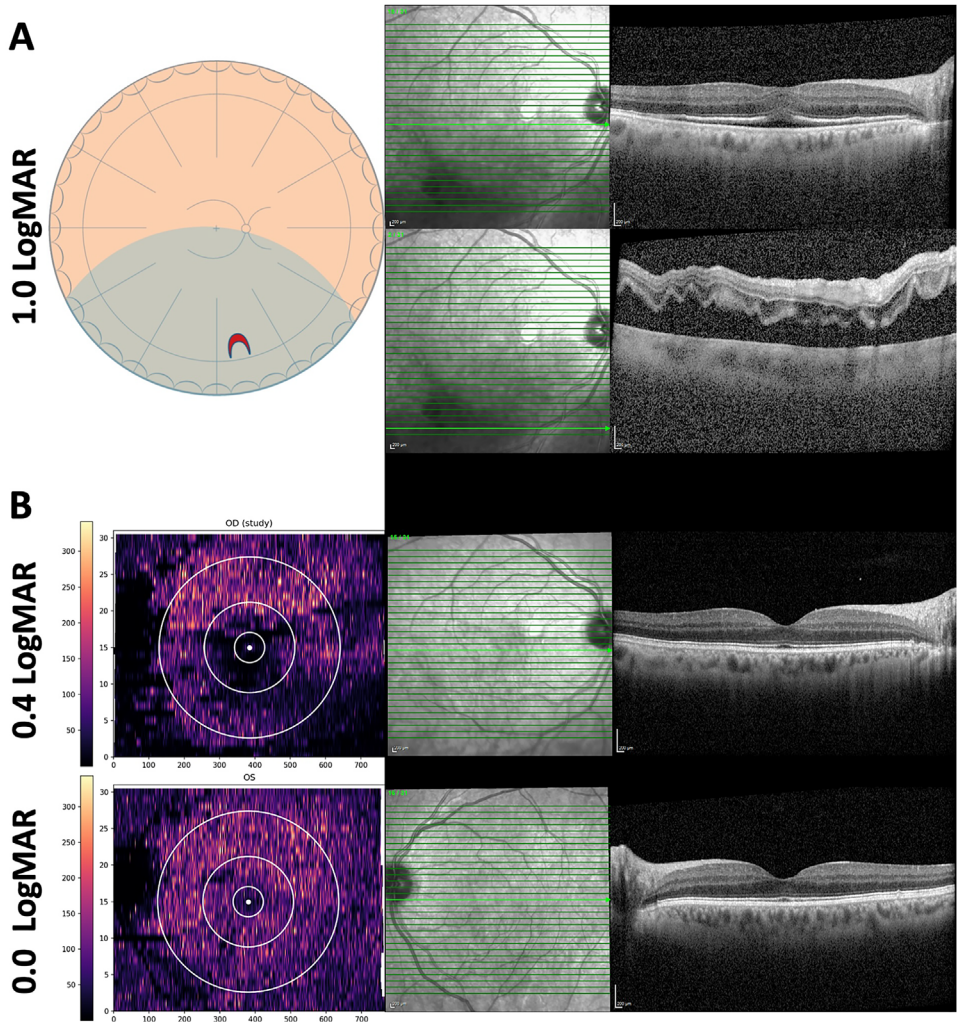

Figure. Exemplary patient. Representative (pseudophakic) patient with macula-off RRD in the right eye (**A**, see sketch) presenting with a preoperative BCVA of 1.0 logMAR (20/200 Snellen, 0.2 decimal) in the right and 0.0 logMAR (20/20, 1.0 decimal) in the fellow eye. SD-OCT line scans demonstrate the extent of the retinal detachment with foveal involvement (**A**, *right column*). Surgical RRD repair was performed on the day of the first presentation with 23g PPV, laser photocoagulation, and gas endo tamponade (no intraoperative use of heavy liquid). Retinal reattachment was demonstrated at a postoperative FU1 visit six weeks after surgery (**B**). Furthermore, the normal macular configuration was present in clinical assessment and SD-OCT imaging (**B**, *first row*). Postoperative BCVA was 0.4 logMAR (20/50 Snellen, 0.4 decimal). An en-face heat-map representation of the rEZR (color-coded from *black* to *yellow* indicating lower to higher rEZR values) demonstrates, despite complete retinal reattachment and the absence of any other macular pathology, worse outer retinal integrity in the study eye (**B**, *first row*) compared to the healthy fellow eye (**B**, second row).

cases. Scleral buckling was performed in 16 patients (9%). Herein, an additional gas bubble (SF6) was injected in two cases. For the descriptive characteristics of the scleral buckling or vitrectomy mac on/off subgroups, see Supplementary Table S1.

The median time for the first postoperative review (FU1) at the Department of Ophthalmology Bonn was 6.1 (IQR = 1.9) weeks at which the postoperative BCVA was 0.2 (IQR = 0.3) logMAR (20/30 Snellen, 0.63 decimal). Descriptive analysis revealed a mean rEZR per SD-OCT volume scan of 28.9 ± 16.5 AU in the study and 41.4 ± 19.8 AU in the fellow eyes, respectively. The rEZR was significantly reduced in the study eyes compared to the fellow eyes (coefficient estimate [CE] = −11.9; 95% confidence interval [CI], [−11.9; −11.8]; $P < 0.001$). Table 1 provides a detailed overview of the cohort characteristics. An exemplary case of a patient at first presentation (A) and six weeks after the surgery (B) with SD-OCT imaging and color-coded rEZR en-face map representation is provided in the Figure.

Association Between the Postoperative BCVA and the rEZR (Structure-Function Analysis)

Univariable analyses revealed a significant association of the postoperative BCVA with the rEZR both in global (e.g., total ETDRS grid) and topographical (ETDRS subfields) analysis ($P < 0.001$) with strongest associations for the mean rEZR of the entire SD-OCT volume scan (CE = 0.0026 [0.0004; 0.0048], $r^2 = 0.08$) and the mean rEZR of the central ETDRS subfield (CE = 0.0039 [0.0016; 0.0063], $r^2 = 0.16$). Additionally, patients with macula-on RD as well as patients with better pre-operative BCVA ($P < 0.001$) demonstrated a significantly better postoperative BCVA given CEs of 0.2534

Table 2. Univariable Analyses to Assess the Association of the Postoperative BCVA and the rEZR, as Well as Other Patients' Characteristics

Determinants*	Coefficient Estimate	95% CI	*P* Value	Cross-Validated r^2
Global rEZR assessment, mean rEZR[AU]	0.0026	0.0004; 0.0048	<0.001	0.08
Topographical rEZR assessment (ETDRS grid) [AU], mean rEZR				
All ETDRS subfields	0.0023	0.0006; 0.0039	<0.001	0.09
Central subfield	0.0039	0.0016; 0.0063	<0.001	0.16
All inner subfields	0.0028	0.0011; 0.0044	<0.001	0.14
All outer subfields	0.0019	0.0003; 0.0035	<0.001	0.07
Preoperative BCVA [logMAR]	0.3009	0.1620; 0.4398	<0.001	0.32
Macula-on RD	0.2534	0.1801; 0.3268	<0.001	0.26
Duration of symptoms (days)	−0.0031	−0.0059; 0.0003	0.195	NA
Age (years)	−0.0001	−0.0005; 0.0004	0.897	NA

NA, not applicable.
* Corrected for patients' age, sex, macula-on versus -off, proliferative vitreoretinopathy and laterality of the retinal detachment.

Table 3. Univariable Analyses to Assess the Association Between the rEZR and Surgery-Related Variables

Determinants*	Coefficient Estimate	95% CI	*P* Value
Cryopexy	−1.28	−8.72; 6.16	0.735
Laser photocoagulation	−0.17	−7.10; 6.76	0.961
Silicone oil tamponade	−6.83	−17.67; 4.01	0.216
Usage of heavy liquids	−6.17	−13.79; −0.21	0.034
Scleral buckling instead of vitrectomy	12.20	0.33; 24.07	0.044
Combined cataract surgery	0.84	−6.83; 8.51	0.830

* Corrected for patients' age and sex, for laterality, proliferative vitreoretinopathy and macula-on versus -off RD of the retinal detachment. Because these models' purpose is not to predict the pixel-wise computed rEZR but to determine its association with surgical variables, we did not calculate the R^2 for them.

([0.1801; 0.3268]; $r^2 = 0.26$) and of 0.3009 ([0.1620; 0.4398]; $r^2 = 0.32$), respectively. For a detailed overview of univariable results, please see Table 2.

Association Between the rEZR and Surgery-Related Variables

Six weeks after surgery for RRD repair, eyes after scleral buckling demonstrated a significantly higher rEZR (CE = 12.20 [0.33; 24.07]; $P = 0.044$) as compared to eyes after vitrectomy. In vitrectomy eyes, the rEZR was significantly lower (CE = −6.17 [−13.79; −0.21], $P = 0.034$) following the intraoperative usage of heavy liquids. In contrast, neither the application of cryopexy (CE = −1.28 [−8.72; 6.16]) nor of laser photocoagulation (CE = −0.17 [−7.10; 6.76]) and neither the use of silicone oil (instead of gas) for postoperative endotamponade (CE = −6.83 [−17.67; 4.01]) nor combined cataract surgery in vitrectomy cases (CE = 0.84 [−6.83; 8.51]) exhibited a significant association with the rEZR. A detailed representation of the univariable analyses is provided in Table 3.

Discussion

This study demonstrates the functional relevance of early photoreceptor alterations in patients after anatomically successful RRD repair and highlights its association with the applied surgical techniques. Herein, a novel structural and quantitative measure for outer retinal integrity, the rEZR, was revealed to be significantly lower in eyes following RRD surgery compared to healthy fellow eyes. Furthermore, higher rEZR values were significantly associated with better postoperative visual acuity as well as with the procedure of scleral buckling, while significantly lower rEZR values were detected in vitrectomy eyes, in which heavy liquid was used to assist with retinal reattachment. The rEZR as a robust, semi-automated ratio of outer retinal integrity by relating EZ reflectivity to that of the adjacent ELM accounts for interindividual reflectivity variation and OCT signal quality. Previous studies in macular diseases have shown that this ratio correlates well with photoreceptor function and disease severity, offering a reliable single marker rather than analyzing EZ and ELM separately.[18–21]

Recently, the SD-OCT-derived rEZR was evaluated in the context of degenerative retinal conditions and was shown to be a valid and reliably assessable quantitative biomarker for photoreceptor integrity.[18–21] In the work presented here, study eyes demonstrated, compared to healthy fellow eyes, six weeks after RRD repair a significantly lower rEZR given a mean rEZR of 28.9 AU ± 16.5 AU (vs. 41.4 ± 19.8 AU in the fellow eye [FE], $P < 0.001$). Additionally, structure-function analysis revealed not only a significant association of the postoperative BCVA and the rEZR when assessed topographically (e.g., for the mean rEZR in the central ETDRS subfield: (CE = 0.0039 [0.0016; 0.0063], $P < 0.001$) but also when determined in a larger retinal area (e.g., in global assessment: CE of 0.0026 [0.0004; 0.0048], $P < 0.001$). The results therefore suggest postoperative photoreceptor alterations extending beyond the central fovea, even in eyes with initially preserved macular attachment, supporting the notion of a more widespread outer retinal response following RRD. Unsurprisingly, however, the strongest association of the postoperative visual acuity was found with the preoperative BCVA (CE = 0.3009 [0.1620; 0.4398], $P < 0.001$) and explaining its variability to the highest extent (cross-validated $r^2 = 0.32$). Nevertheless, the results presented here are in line with previous works focusing, although mainly in a qualitative manner, on the EZ and ELM integrity after surgery for RRD repair.[10,35] Muni and co-workers[10,36] have

shown in a post-hoc analysis of the PIVOT trial, whose primary objective was to evaluate the different structural outcomes between vitrectomy and PnR, that postoperative continuity of the EZ and the ELM was associated with better visual outcome after RRD repair.[35] Moreover, the authors were able to point out that RRD eyes following vitrectomy were more likely to demonstrate EZ discontinuity (odds ratio [OR] = 3.81; $P = 0.002$) and ELM (OR = 2.21; $P = 0.04$) than eyes which were, at least as the first primary surgical procedure, treated with PnR. This is in agreement with the here presented results of a clinical setting, in which RRD eyes following vitrectomy demonstrated a significantly lower rEZR than eyes treated previously with scleral buckling (CE = 12.20; 95% CI, 0.33–24.07; $P = 0.04$). Muni and colleagues concluded that presumably stronger and less physiological forces act on the reattaching cellular elements during vitrectomy, thus, explaining worse outer retinal integrity following vitrectomy. However, a huge variety of surgical measures, in particular in the context of vitrectomy, exists and it remains unclear which of those might have been causative for the observed differences in retinal microstructure after RRD repair. Also, other surgical determinates, such as a combined epiretinal membrane peeling among others might influence the clinical and anatomical outcome.[37] As an explanatory study, Barca et al.[38] showed that, particularly in macula-off RRD, the integration of OCT-angiography has provided valuable insights where a larger foveal avascular zone area has been associated with worse visual outcomes.

The study presented here further sought to evaluate potential associations of the rEZR with perioperative determinants and surgical measures in the context of primary RRD repair. Herein, the intraoperative use of heavy liquids in vitrectomy cases demonstrated significantly lower rEZR values (CE = −6.17; 95% CI, −13.79 to −0.21; $P = 0.034$), suggesting worse photoreceptor integrity in the early postoperative phase. Of note, this data derives from a clinical care setting in which both primary vitrectomy and the use of heavy liquids might have been favored (against scleral buckling) in more complex and advanced RRD cases that might have gone along with a priori worse photoreceptor integrity. To account for this, however, macula-on versus macula-off RD was in this study regarded as a surrogate for RD severity and therefore considered in statistical analyses allowing a more precise analysis of the actual surgical measures and their association with postoperative photoreceptor integrity.

Nevertheless, our findings can be considered in agreement with the previously referred conclusion from the post-hoc PIVOT analysis, as the primary objective for the use of heavy liquids is to induce a forceful displacement of subretinal fluid for retinal reattachment which takes place not only in a single retinal location but more in a larger retinal area.[35] In addition, because of the retrospective nature of the study, we cannot exclude that other unmeasured variables such as the extent of the detachment, vitreous status, or subtle clinical factors influenced the decision to use specific surgical techniques and thus that may have contributed to observed differences in rEZR.

Several limitations need to be considered in this study. First of all, this is a study of early photoreceptor involvement after RRD repair in a clinical setting and does not aim to draw causative conclusions concerning the use and application of certain surgical techniques and measures for RRD repair. Herein, this study underscores the necessity for prospective analyses in the future. Such analyses should encompass a more nuanced evaluation of surgical techniques, including for example the use of various silicone oil endo tamponades—distinguishing between lighter and heavier oils—and additional surgical procedures such as addressing the presence/peeling of proliferative vitreoretinopathy. Given the nature of our exploratory analysis and thus the tight inclusion criteria, further surgical determinants, like the impact of intraoperative peeling of an epiretinal membrane or the internal limiting membrane, as well as other imaging techniques, like OCT-angiography, need to be also assessed in a larger study cohort.[37,38] In future prospective studies, a more comprehensive evaluation of postoperative visual function should also include additional functional tests such as contrast sensitivity, microperimetry, or visual field analysis, which may detect impairments not captured by BCVA alone. Moreover, a broader spectrum of surgical outcomes should be examined that includes patient-related outcome measures, the incidence of a retinal re-detachment, and thus the requirement of secondary surgical interventions. Importantly, these outcomes should be observed over a more prolonged postoperative period to capture a comprehensive picture of long-term implications after surgery. As an exploratory study, we have focused on evaluating the rEZR in the early postoperative period and at a single follow-up visit. Although this limits the ability to assess postoperative photoreceptor changes over time, we understand the current study as an essential foundation for future prospective investigations into the longitudinal rEZR evolution and its potential prognostic relevance for long-term visual outcomes. Although beyond the scope of the retrospective real-world study presented here, future studies are, however, needed to also assess its clinical applicability in the preoperative context and thus to evaluate its predictive value, which would enhance surgical decision-making and patient counseling before surgery.

Second, this is an exploratory study evaluating the rEZR only at a single postoperative follow-up visit after RRD repair and is therefore not able to determine its postoperative changes over the time of photoreceptor recovery. In many cases of macula-off RRD, preoperative OCT imaging is either technically not feasible or does not provide evaluable reflectivity data because of the detachment itself. Further and as part of routine clinical care, not every patient with primary RRD presenting to our department has undergone retinal imaging (SD-OCT) before surgery (e.g., when patients presented to us on weekends and surgical repair was timely performed). As a result, unfortunately, meaningful preoperative rEZR quantification was not possible or comparable across patients in this study cohort. This limits our ability to determine whether the observed differences in postoperative rEZR between surgical techniques reflect true surgical effects or pre-existing retinal integrity. Further studies of larger sample sizes, however, are warranted to also characterize preoperative rEZR measurements in a RRD subgroup with mac-on situation.

Third and concerning data interpretation, this is a retrospective analysis of data obtained in a clinical care setting encompassing heterogeneous sample sizes and inconsistent imaging protocols hampering more refined statistical analyses. Despite these limitations, this study provides important early data that will serve as the basis for more robust prospective studies designed to evaluate both the longitudinal changes in rEZR and its prognostic relevance for future visual and functional outcomes. Although rEZR assessment has been thoroughly validated and explored already in previous studies, alternative methodological approaches,

such as separate assessments of the EZ and ELM or through other additive models, might yield distinct or complementary insights into outer retinal integrity after RRD repair. These possibilities merit further investigation, particularly in the context of prospective studies with larger patient cohorts.

To conclude, this study aims to demonstrate early outer retinal affection after RRD repair and its association with surgical measures. Considering the rEZR as a novel, quantitative measure for photoreceptor integrity, this study's objective was to go beyond categorical retinal reattachment to achieve deeper insights into photoreceptor health after RRD repair. Given the circumstance that only patients with a normal macular configuration after RRD surgery were included, the here presented results suggest that early postoperative photoreceptor affection, and therefore visual function, seems to depend on the process of retinal reattachment. A refined characterization of changes in the photoreceptor integrity over time and its association with surgical measures as well as surgical (long-term) outcomes are warranted to eventually achieve the best possible visual outcomes for patients with RRD.

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