Clinical science

OCT analysis of preoperative foveal microstructure in recent-onset macula-off rhegmatogenous retinal detachment: visual acuity prognostic factors

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ABSTRACT

Background To evaluate, in patients undergoing macula-off rhegmatogenous retinal detachment surgery (RRD), the correlation between preoperative optical coherence tomography (OCT) morphological features and postoperative visual acuity.

Methods Retrospective interventional non-randomised clinical trial on 89 eyes of 89 patients undergoing pars plana vitrectomy for macula-off primary RRD at Policlinico Universitario Agostino Gemelli from 2020 to 2023. Preoperative 6×6 mm OCT B scans with Nidek Mirante (Nidek, Gamagori, Japan) were performed, collecting the following features: foveal involvement (fovea-on vs fovea-off), subretinal hyper-reflective points (HRPs), outer retinal corrugations (ORCs) and intraretinal cystic spaces (ICS) in the outer nuclear layer. The patients were followed in a 6-month follow-up to evaluate best-corrected visual acuity (BCVA) outcomes.

Results Preoperative mean BCVA was 0.15±0.22 and improved to 0.29±0.3 decimals at 6 months (p<0.001). The presence of subretinal HRPs showed a significant negative impact on BCVA improvement in the univariate regression analysis (r=−0.264, p=0.024), as well as the presence of foveal detachment (r=−0.355, p=0.012). The other OCT features did not show a significant correlation with BCVA improvement: ORCs (r=0.072, p=0.257) and ICS (r=−0.020, p=0.734). In the multivariate regression analysis, the negative impact of foveal detachment was confirmed (r=−0.199, p=0.05) while the statistical significance of subretinal HRPs was lost (r=−0.135, p=0.105).

Conclusions The negative impact of foveal involvement in a macula-off RRD was confirmed. Moreover, the presence of subretinal HRPs, as a possible indirect marker of inflammatory response extent, may act as a negative predictor for postoperative visual recover.

Trial registration number NCT05747144.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Preoperative microstructure of the fovea, analysed with optical coherence tomography, proved to be a crucial element in the determination of the visual prognosis following macula-off rhegmatogenous detachment surgery.

WHAT THIS STUDY ADDS

⇒ This is the first study to assess the presence of subretinal hyper-reflective points (HRPs) as predictive negative biomarker for visual recover in macula-off detachment,

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ If HRPs indirectly represent the extent of subretinal inflammatory status, this parameter could, among others, guide retinal detachment surgery (RRD) surgical timings.

INTRODUCTION

After surgery for macula-off rhegmatogenous retinal detachment (RRD), visual function recovery does not always match morphological recovery. Even when reattachment surgery is successful, the postoperative outcome in terms of best-corrected visual acuity (BCVA) is still mostly not satisfactory. Moreover, a recent meta-analysis of 29 publications highlighted how the classic term 'macula-off' in turn includes a wide variety of retinal detachment morphologies.[1] There is still no officially recognised nomenclature in the literature describing the condition of the fovea in macula-off retinal detachment; indeed, Klaas *et al* highlighted the need, both scientifically and clinically, to establish a label that takes into account the foveal state.[2] The preoperative microstructure of the fovea, analysed with optical coherence tomography (OCT), proved to be a crucial element in the determination of the visual prognosis following RRD surgery.[3] The continuity of the external limiting membrane and the ellipsoid zone (EZ), which is representative of photoreceptor integrity, has been reported to be strongly correlated with postoperative BCVA.[4 5] The presence of outer retinal corrugation (ORC), which shows how much fluid builds up between the outer and inner retina after a detachment, has been linked to younger patients, better vision before surgery and more recent RRD.[6 7] In any case, debates remain on the role of ORC as a prognostic factor for postoperative BCVA.[8 9] Even the presence of

intraretinal cystic spaces (ICS) in the outer nuclear layer (ONL) has been explored as a potential biomarker, negatively impacting preoperative visual morphology and function but apparently not affecting postoperative outcomes.[10] Finally, the height of the retinal detachment in the foveal area has been hypothesised to play a significant role in the visual outcome of macula-off RRD following repair, due to increased tension forces occurring in high RRD.[11]

Less diagnostic insight has been given to the subretinal space in the case of macula-off RRD. In this condition, cells acting as mediators of inflammation, such as neutrophils, monocytes and macrophages, may also migrate along with retinal pigmented epithelium (RPE) cells and with the outer segments of disrupted photoreceptors.[8] Macrophage infiltration of the subretinal space occurs through the RPE and Bruch's membrane and can be demonstrated on immunohistochemical examinations: the upregulation of normally expressed cytokines (CD14, CD31, ICAM-1, Osteopontin and MIF), as well as macrophage secretion factors (Chitinase 3-like 1, IL-8 and MCP-1), are red flags of phagocytic activation and recall of immune cells to the site of damage, determining the establishment of a proinflammatory state.[8 12] Before surgery, OCT scans may show 'hyper-reflectivity points' (HRPs) in the subretinal area.[13] These dots seem to be connected to groups of activated microglia cells, indirect sign of an inflammatory state.[8] Their nature, however, has not yet been precisely elucidated since some authors claimed that the hyper-reflexivity would be due to the presence of leucocytes or RPE cells, indicating retinal inflammation in itself, while others hypothesised that HRPs represent small intraretinal proteins or small lipid deposits, usually after the breakdown of the inner blood–retina barrier seen in patients with diabetic retinopathy and retinal vein occlusion.[3 14]

Studies on mouse models showed that activated microglia are able to travel into the damaged photoreceptor layer within 24 hours post-RD, interacting with infiltrating macrophages and dying photoreceptors.[15] Moreover, a significant proliferative stimulus involves all non-neuronal cell types within the detachment area: this response begins at day 1 post-RD, peaks between days 3 and 4, and then continues at reduced levels for as long as the retina remains detached.[16 17] Similarly, photoreceptor apoptosis peaks between days 3 and 4 and continues at low levels in detached regions.[18]

From a tomographic perspective, Martins Melo *et al* proposed different morphological stages of preoperative RRD, based on the mean duration of the fovea-off condition. The occurrence of ORCs happened on average in the first 2–3 days after RRD, while advanced stages, characterised by the loss of the definition of ORCs and successive patchy ('moth-eaten') aspect of inner and outer segments, were mostly seen after 11–12 days from the detachment. Advanced stages were associated with worse BCVA at 3 months after surgery.[19]

Based on these premises, the aim of our study was to evaluate, in patients developing macula-off RRD and undergoing pars plana vitrectomy (PPV) surgery within 7 days from symptoms occurrence, the existence of a correlation between morphological parameters detected on preoperative OCT images and postoperative BCVA, focusing on the role of subretinal HRPs as a potential predictive biomarker.

MATERIALS AND METHODS

A retrospective review of raw data of patients undergoing PPV for macula-off and macula on-off primary RRD at Policlinico Universitario Agostino Gemelli from January 2020 to October 2023 was conducted. The trial was registered at ClinicalTrials.gov (identifier, NCT05747144).

For each patient, informed consent was collected, and a complete explanation of the target protocol was fully provided, in conformity with the Declaration of Helsinki.

The inclusion criteria were age >18 years, a maximum of 7 days from the beginning of macula-off RRD-related symptoms (sudden visual loss reported as a 'curtain' or shadow over central vision field), uncomplicated RRD surgery with PPV, preoperative pseudophakic status and a duration of the follow-up of at least 6 months.

Exclusion criteria included patients with any other ophthalmological pathology that affects vision, macula-off RRD with symptoms lasting >7 days, recurrent retinal detachment, non-rhegmatogenous aetiology, silicone oil tamponade, combined PPV and scleral buckling surgery, the presence of subretinal or epiretinal proliferative vitreo retinopathy (PVR) affecting the macular area, degenerative myopia, ambient opacities hindering imaging, macula-on RRD and history of ocular surgeries except cataract surgery. Furthermore, patients suffering from RRD recurrence during the study period were excluded from the analysis. Phakic patients were excluded from the study in order to minimise confounding factors affecting visual acuity.

Surgical procedures were performed in all cases by the same experienced vitreoretinal surgeon (SR). 23 or 25-gauge PPV with gas (SF6 or C3F8) endotamponade was performed in all patients.

Scan protocol and definitions

Preoperatively, patients underwent OCT acquisitions, performed with Nidek Mirante (Nidek, Gamagori, Japan), a multimodal imaging platform combining a confocal scanning laser ophthalmoscopy (cSLO) and a spectral domain (SD) OCT. B scan protocol included a 6×6 mm horizontal volume scan centred on the fovea, comprising 512×128 scans. Only patients with available preoperative good-quality OCT-B scan acquisitions (≥7/10 at the in-built quality score) were included. Each B-scan was averaged nine times.

Morphological extent of RRD involvement was performed using an Early Treatment Diabetic Retinopathy Study (ETDRS) grid overlayed on the infrared image and the corresponding OCT scan. In the absence of a validated terminology in literature,[2] 'macula-off' RRD was considered as the presence of infrared image involvement of the 3 mm ring of the ETDRS grid, confirming a visible separation between the RPE and the retina based on OCT B-scan. Moreover, we divided our cohort into 'macula-off fovea-on' detachments, in eyes in which the fovea was still attached at B-scans, and 'macula-off fovea-off', in case of foveal detachment.

Preoperative BCVA assessment with Snellen equivalent (decimals) and slit lamp anterior segment and fundus examination after pupil dilation was also performed. A postoperative examination was performed 6 months after surgery and included a BCVA assessment with a Snellen chart and a slit lamp examination.

Out of 854 medical records of retinal detachment, 89 eyes met the aforementioned inclusion and exclusion criteria.

Outcome measures

One of the outcomes of our study was to determine how foveal detachment impacts patients' visual function. Additional morphological data found on OCT examination of the macular area, as well as objects of our study, were as follows:

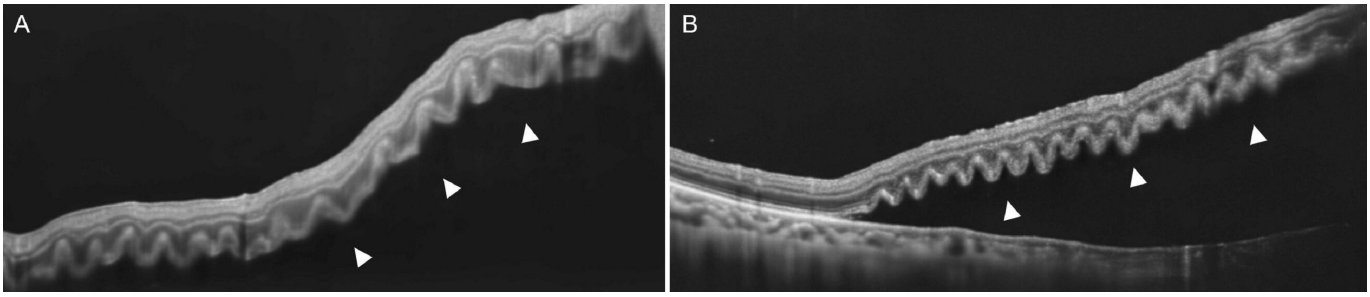

Figure 1 Optical coherence tomography scans of two patients with rhegmatogenous retinal detachment, exhibiting outer retinal corrugations (indicated by white triangles). In these cases, no signs of subretinal hyper-reflective points were visible.

1. Subretinal hyper-reflective points (HRPs): in the absence of a validated cut-off for these parameters, the presence of ≥10 visible hyper-reflective spots in the area between the detached retina and the RPE, in any of the B scans, was defined as suggestive of HRPs.
2. Rippling or corrugation of the outer retina (ORC): as previously defined by Yeo *et al*,[7] the presence of a change in the outer retinal gradient (negative to positive) of ≥3 within the 6 mm diameter of B scans was defined as suggestive of ORCs.
3. ICS in the ONL: the presence of non-reflective cavities in the context of the ONL in any of the B scans was defined as indicative of ICS.

Sample OCT scans highlighting those morphological characteristics are visible in figures 1 and 2. The impact of those preoperative biomarkers on visual outcomes was evaluated, focusing on the improvement between preoperative and postoperative BCVA.

Analyses of all OCT images were performed by three retinal specialists (MCS, MMC and FG), masked to the surgeon (SR).

Statistical analysis

Statistical analysis was performed using IBM SPSS software, V.27.0 (SPSS). The collected data were analysed descriptively, using frequencies and percentages for categorical data and mean and SD for continuous data. For inferential statistics, linear regressions were conducted on the variables related to the presence of HRPs, ORCs and ICS, as well as preoperative BCVA and macula-off fovea-off detachment, to explore the impact on BCVA improvement (delta between preoperative and postoperative BCVA) and postoperative BCVA itself.

Statistical significance was set at values of $p<0.05$. Statistical analysis was performed with STATA V.17 software (Stata).

RESULTS

89 eyes of 89 patients met the inclusion criteria. The study sample was made of 59 (66.29%) males and 30 females (33.71%), with a mean age of 55.6±17.7 years. Among the participants, there were 58 right eyes (65.17%) out of the total and 31 (34.83%) left eyes. Mean duration of symptoms was 3.7±2.4 days. Demographic characteristics of the study cohort, preoperative OCT findings and surgical procedures are summarised in table 1.

The preoperative mean BCVA was 0.15±0.22 decimals (median 0.05, IQR 0.003–0.2), while the postoperative mean BCVA was 0.29±0.3 decimals (median 0.2, IQR 0.02–0.4), showing a significant improvement ($p<0.001$) (figure 3).

OCT features

The morphological data of the study population were examined by the evaluation of retinal OCT pictures and presented

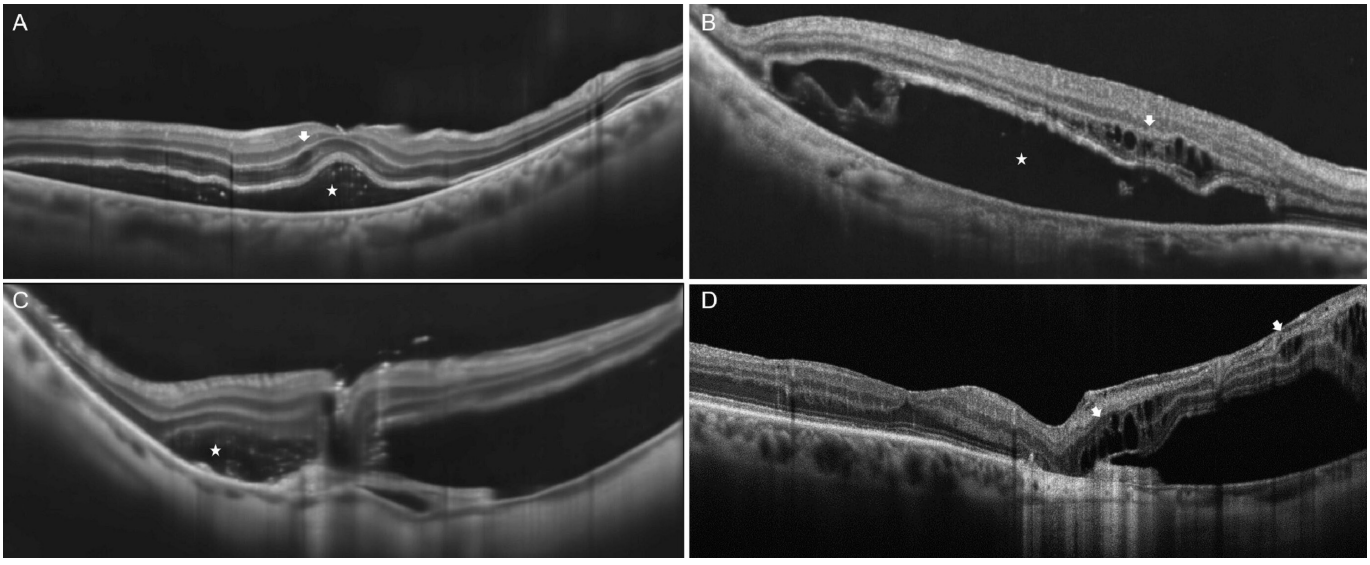

Figure 2 Optical coherence tomography scans of different retinal detachment morphologies in the macular area. (A–B) B scans show signs of subretinal hyper-reflective points (HRPs, white stars), visible as ≥10 hyper-reflective dots in the subretinal spaces and intraretinal cystic spaces (ICS, white arrows) in the outer nuclear layer. (C) B scan showing the presence of sparse hyper-reflective signal in the subretinal area (white star), which was considered in this case non-sufficient to be defined as HRPs. (D) B scan showing ICS (white arrow) but no signs of subretinal HRPs.

Table 1 Baseline demographic and clinical characteristics of the study population, along with surgery type and endotamponade type

Characteristic	Value
Study eye, RE, no	58 (65.2%)
Mean age, years	55.6±17.7
Gender, male, no (%)	59 (66.3%)
Preoperative BCVA±SD, decimals	0.15±0.22
Mean symptoms duration±SD, days	3.7±2.4
Mean IOP±SD; mm Hg	11.0±5.3
Surgery type	
23-gauge	35 (39.3%)
25-gauge	54 (60.7%)
Endotamponade type	
SF6	66 (74.2%)
C3F8	23 (25.8%)
OCT features	
Foveal detachment (macula off–fovea off)	64 (71.2%)
Subretinal hyper-reflective points	20 (22.5%)
Outer retinal corrugation	27 (30.3%)
Intraretinal cystic spaces	38 (42.7%)

BCVA, best-corrected visual acuity; C3F8, perfluoropropane; IOP, intraocular pressure; OCT, optical coherence tomography; RE, right eye; SF6, sulfur hexafluoride.

as categorical binary data. Foveal involvement characterised by fovea off-macula detachment was detected preoperatively in 64 patients (71.9%); 25 of these patients, conversely, had fovea on-macula detachment (28.1%). HRPs were present in 20 patients, accounting for 22.5% of the sample, whereas the remaining 69 patients did not exhibit any signs of inflammation (77.5%). ORCs were detected in the OCT-preoperative images of 27 patients, accounting for 30.3% of the sample. ICSs were found in 38 out of 89 patients (42.7%) (table 1).

The presence of subretinal HRPs showed a significant negative impact on BCVA improvement in the univariate regression analysis (r=−0.264, p=0.024), as well as the presence of foveal detachment (r=−0.355, p=0.012). The other OCT features did not show a significant correlation with BCVA improvement: ORCs (r=0.072, p=0.257) and ICS (r=−0.020, p=0.734) (table 2).

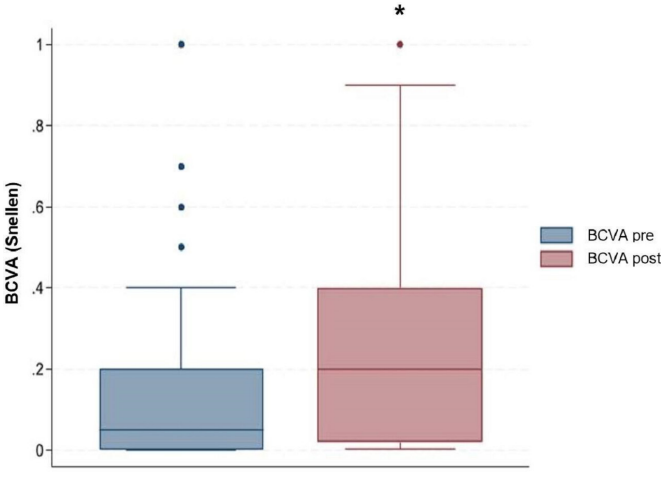

Figure 3 Box plots of best-corrected visual acuity (BCVA), measured in Snellen equivalent, before and after rhegmatogenous retinal detachment repair. Asterisk indicates statistical significance.

However, in the multivariate regression analysis, the statistical significance of subretinal HRPs was lost (r=−0.135, p=0.105) while the negative impact of foveal detachment was confirmed (r=−0.199, p=0.05) (table 2). Similar results are obtained setting the postoperative BCVA as the outcome and adjusting for the preoperative BCVA (table 3).

DISCUSSION

Structural OCT is still considered to have a key tool for the assessment of retinal damage and visual prognosis in patients with RRD. In this study, we investigated OCT preoperative characteristics affecting visual outcome after PPV surgery for early-onset macula-off RRD. As far as we know, this is the first study to assess the role of subretinal HRPs, seen as hyper-reflective dots in the subretinal area, as potential biomarker of worse visual outcome. However, the real origin of HRPs has not been established, potentially being a combination of dying photoreceptors, macrophages and microglia.[8] We hypothesise that the presence of HRPs (with the cut-off of ≥10) could be an indirect biomarker of the extent of the inflammatory response happening when the retina detaches from the RPE. Moreover, the influence of subretinal HRPs turned out to be more significant than the presence of preoperative ORCs and ICS, in terms of visual recovery.

Several studies have already shown a correlation between preoperative imaging data and visual acuity achieved after surgery; among them, Park *et al* were able to identify six morphological parameters (EZ integrity, Henle's fibre layer and ratio of ONL/photoreceptor layer, photoreceptor outer segment length ratio, photoreceptor outer segment length ratio/photoreceptor inner segment length ratio, photoreceptor layer thickness ratio between detached eye and healthy eye, and photoreceptor outer segment length ratio between detached eye and healthy eye) that would act as predictive factors in patients operated on for macula-off RRD.[3] Wolfensberger and Gonvers also showed how the presence of macular oedema frequently correlates with worse postoperative visual acuity.[20] In contrast, Cho *et al* found that the presence of ORCs on preoperative OCT is a sign of worsening vision after surgery, indicating its role as a predictive biomarker.[9] However, this correlation has not been confirmed in other studies.[21–23] Similarly, in our research, the presence of ORCs in macula-off retinal detachments did not show any predictive value. Neither did the presence of ICS in the ONL nor the fovea's involvement in the detachment, in contrast with the study of Klaas *et al*, in which centre involvement in retinal detachment was associated with significantly worse visual function at 3 months after surgery.[24]

Subretinal HRPs, on the other hand, suggesting the presence of degradation material and/or a state of proinflammatory activation, have been recognised in our study as a biomarker that can predict a poor functional prognosis after surgery. It is well known that inflammation may interfere with cells growth and abnormal proliferation, making the vitreoretinal interface more likely to have problems.[2] Undoubtedly, in defining the visual prognosis of these patients, the concurrence of numerous other factors must always be considered, including individual (eg, age, duration of symptoms, pre-existing retinal pathology), perioperative (eg, timing and type of surgery, surgeon's experience, appropriateness of follow-up) and anatomical (eg, foveal involvement, extent of detachment) factors.

Furthermore, in the management of an RRD, an important data point to consider is the timing of surgery. Many studies indeed claimed that the lack of functional recovery may depend

Table 2 Univariate and multivariate regression analysis highlighting the predictive value of preoperative OCT biomarkers on BCVA improvement

	Univariate analysis		Multivariate analysis	
OCT features	**Coeff (95% CI)**	**P value**	**Coeff (95% CI)**	**P value**
Foveal detachment (macula off–fovea off)	−0.355 (−0.478 to −0.239)	0.012*	−0.199 (−0.256 to −0.103)	0.05*
Subretinal hyper-reflective points	−0.264 (−0.305 to −0.224)	0.024*	−0.135 (−0.299 to 0.029)	0.105
Outer retinal corrugations	0.072 (−0.545 to 0.199)	0.257	0.064 (−0.080 to 0.210)	0.376
Intraretinal cystic spaces	−0.020 (−0.143 to 0.102)	0.734	−0.002 (−0.133 to 0.128)	0.972

*Statistically significant p value.
BCVA, best-corrected visual acuity; OCT, optical coherence tomography.

on the time elapsed between the diagnosis of the detachment and the surgical procedure of reattachment. In fact, the duration of detachment was shown to be a negative factor in the visual prognosis of a patient operated on for macula-off retinal detachment.[25 26] The morphofunctional outcome of vision in these patients is time-dependent. For example, Hassan *et al* showed that the achievement of better visual acuity correction is possible in patients undergoing surgery in an interval of less than 10 days after the occurrence of RRD[25]; in contrast, a German study recognised that starting treatment after 6 days after the event is associated with a progressively worse visual outcome.[26]

The main explanation is that photoreceptor cells undergo necrosis after a certain amount of time when physically separated from the EPR and the choroidal vessels that support their metabolic function. Various studies on experimental models and patients have shown that photoreceptor death begins approximately 12 hours after detachment occurs, with a peak between days 2 and 3.[18 27–29] It follows that postponing the reattachment surgery is necessarily associated with a worsening of photoreceptor function and, consequently, a poor postoperative visual outcome.[30] Many data points still remain unknown regarding the mechanisms of postoperative visual rehabilitation, but according to some researchers, possible hypothesis lie in the operative-induced iatrogenic damage to the photoreceptors or the blood–retinal barrier disruption.[31]

The permanent functional damage following a macula-involving detachment implies that in surgical practice, macula-off retinal detachments are not given emergency treatment, which is the case with macula-on detachments. Although, from a surgical point of view, macula-off detachments are considered to be of lower priority, an article published by Grabowska *et al* showed that in cases of detachment occurring less than 72 hours before, postoperative visual improvement is only marginally lower than that obtained by patients who underwent surgery for macula-on detachment.[32] Starting from this assumption, the preoperative morphology of macular, and in particular foveal, structure, may act as a guidance for the surgeon in order to choose the best surgical timings. Among the proposed OCT biomarkers presented in literature, we suggest the role of subretinal HRPs as possible marker of inflammation: dealing with an RRD surgery in these subgroup of patients may result in worse visual outcomes.

This study has some limitations, due to the inherent weaknesses of a retrospective study. The duration of symptoms was retrieved from medical records, thus not being as precise as it could be in a prospective research. Furthermore, even though OCT was done just before surgery in the majority of the cases in our research, it is still possible that some patients' macular status altered between the time of admission and the operation. Moreover, obtaining an OCT B scan in the presence of RRD is not always simple, particularly when dioptric media opacity (ie, vitreous haemorrhage) and complete RRD are present. In addition, the cut-off of 10 HRPs was proposed by our group but has no matching in current literature, thus needing validation with further studies and bigger cohorts. One other restriction is the short follow-up period of 6 months after surgery, which may be insufficient to draw firm conclusions regarding the ultimate functional outcome, thus requiring future implementations. In addition, despite the fact that metamorphopsia is a well-known functional parameter—particularly in eyes with foveal detachment—it was not evaluated in our work.[33] Similarly, we did not evaluate the role of RRD height as a prognostic biomarker in our cohort and we hope to implement this aspect in further prospective research. Finally, we only analysed recent RRD with a strict time window of 7 days. Further studies including long-lasting RRD could be useful to assess the role of HRPs on surgical timing.

In conclusion, our research confirmed the negative impact of foveal detachment on postoperative visual outcomes. Moreover, we found out that the evidence of subretinal HRPs in a macula-off retinal detachment correlates with worse postoperative visual improvement and may therefore be considered a negative predictor; in contrast, the other OCT parameters under study (ORCs and ICS) showed no significant correlation with visual improvement. Undoubtedly, further studies aimed to identify new biomarkers will be needed, and certainly the advent

Table 3 Univariate and multivariate regression analysis highlighting the predictive value of preoperative OCT biomarkers on postoperative BCVA, adjusted for preoperative BCVA

	Univariate analysis (BCVA post)		Multivariate analysis (BCVA post)	
OCT features	**Coeff (95% CI)**	**P value**	**Coeff (95% CI)**	**P value**
Foveal detachment (macula off–fovea off)	−0.255 (−0.368 to −0.179)	0.031*	−0.219 (−0.325 to 0.109)	0.043*
Subretinal hyper-reflective points	−0.194 (−0.305 to −0.104)	0.044*	−0.141 (−0.288 to 0.014)	0.126
Outer retinal corrugations	0.105 (−0.176 to 0.385)	0.211	0.088 (−0.106 to 0.258)	0.376
Intraretinal cystic spaces	0.031 (−0.143 to 0.102)	0.764	−0.004 (−0.113 to 0.98)	0.984

*Statistically significant p value.
BCVA, best-corrected visual acuity; OCT, optical coherence tomography.

of recent technologies, such as artificial intelligence, may also provide great help in this regard, in order to apply a quantitative rather than a qualitative method, in the evaluation of OCT parameters. The hope is to achieve a consistent and reproducible description of preoperative biomarkers, which should act as a guidance for surgical timing and become predictive values of functional recovery.

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Competing interests None declared.

Patient consent for publication Not applicable.

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