• Clinical Research •

Exploring the role of hyperreflective walls as a biomarker for the management of cystoid macular edema

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Abstract

● **AIM:** To investigate the prevalence and clinical implications of hyperreflective walls (HRW) in foveal cystoid spaces in patients with cystoid macular edema (CME) caused by retinal diseases and noninfectious uveitis (NIU).

● **METHODS:** This retrospective cross-sectional study included 443 eyes with CME secondary to diabetic macular edema (DME), retinal vein occlusion (RVO), retinitis pigmentosa (RP), neovascular age-related macular degeneration (nAMD), and NIU. Demographic data, HRW features, and other spectral domain optical coherence tomography (SD-OCT) biomarkers were analyzed.

● **RESULTS:** HRW was observed in 40.9% of DME eyes (present, *n*=77, 38 males, 58.30±12.04y; absent, *n*=111, 50 males, 55.95±10.56y), 32.5% of RVO eyes (present, *n*=49, 22 males, 64.53±11.90y; absent, *n*=102, 42 males, 60.67±11.73y), 31.4% of nAMD eyes (present, *n*=16, 8 males, 70.13±7.75y; absent, *n*=35, 13 males, 73.91±9.11y), 57.1% of RP eyes (present, *n*=12, 4 males, 40.50±12.06y; absent, *n*=9, 4 males, 44.11±14.32y), and 18.8% of uveitic macular edema (UME) eyes (present, *n*=6, 3 males, 30.83±16.23y; absent, *n*=26, 12 males, 43.46±17.58y). HRW was significantly associated with vitreoretinal abnormalities [odds ratio (OR), 2.202; 95% confidence interval (95%CI), 1.342-3.613; *P*=0.002], hyperreflective foci (OR, 3.33; 95%CI, 1.884-5.883; *P*<0.001), inner retinal layer disorganization (OR, 1.816; 95%CI, 1.087-3.035; *P*=0.023), external limiting membrane disruptions (OR, 3.476; 95%CI, 1.839-6.574; *P*<0.001), and disrupted ellipsoid zone length (OR, 1.001; 95%CI, 1.000-1.002; *P*=0.04), and a high HRW height in the foveal cystoid spaces (OR, 1.003; 95%CI, 1.001-1.006; *P*=0.003).

● **CONCLUSION:** HRW in foveal cystoid spaces is a common OCT finding in CME and is associated with more severe retinal structural damage and worse visual acuity. HRW may be utilized as a prognostic OCT biomarker for disease severity and treatment response in patients with CME. This study suggests that early detection of HRW and optimization of treatment strategies may improve patient prognosis.

● **KEYWORDS:** hyperreflective walls; cystoid macular edema; optical coherence tomography; biomarker; Müller glial cell

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INTRODUCTION

Cystoid macular edema (CME) is a common pathological feature in ocular diseases, including diabetic macular edema (DME), retinal vein occlusion (RVO), retinitis pigmentosa (RP), neovascular age-related macular degeneration (nAMD), and noninfectious uveitis (NIU). Optical coherence tomography (OCT) has become an indispensable tool for diagnosing and monitoring CME because of its ability to achieve near-histological *in vivo* imaging of the retinal microarchitecture, providing qualitative and quantitative information in a repeatable manner[1]. Several OCT biomarkers are widely utilized, including CME, subretinal fluid (SF), the status of the ellipsoid zone (EZ) and external limiting membrane (ELM), disorganization of the retinal outer layers[2], intraretinal cysts, the presence of hyperreflective

foci, vitreoretinal interface features, disorganization of retinal inner layers (DRIL), and outer retinal tubulations. Among the numerous OCT biomarkers, hyperreflective walls (HRW) in foveal cystoid spaces have recently emerged as a notable imaging finding in retinal pathology, following the seminal characterization by Terada *et al*[3] who first identified this OCT biomarker. Besides identifying hyperreflective deposits within foveal cystoid spaces, some cystoid spaces are outlined by thick bands (≥40 μm). These bands displayed higher reflectivity levels than the nearby tissue and the same reflectivity levels as the ELM. The HRW was observed at the bottom of the cystoid spaces or in the septa between spaces. In the literature[3], eyes displaying this OCT finding in medium or large foveal cystoid spaces (≥250 μm in horizontal width) within the central 1 mm in either vertical or horizontal retinal sectional images were categorized as eyes with HRW in their foveal cystoid spaces. Although HRW have been reported in DME, their prevalence and significance in other retinal diseases remain underexplored. Therefore, we reviewed medical records pertaining to many cases of retinopathy and NIU in a single center. This study aims to investigate the prevalence of HRW in foveal cystoid spaces across different ocular diseases and to explore their associations with other OCT biomarkers and clinical outcomes.

PARTICIPANTS AND METHODS

Ethical Approval This study strictly adhered to the principles outlined in the Declaration of Helsinki, and received approval from the Ethics Committee of the Tianjin Medical University Eye Hospital [2023KY (L)-33]. Oral informed consent was obtained from all patients; participants did not receive a stipend.

This was a retrospective cross-sectional, observational study conducted at a single center. Medical records of patients diagnosed with DME, RVO, nAMD, and NIU, who visited Tianjin Medical University Eye Hospital between August 1, 2021, and July 31, 2023, were reviewed. As RP is a rare inherited eye disease, patients with RP who visited between August 1, 2018, and July 31, 2023, were specifically selected for inclusion in this study.

Study Participants and Data Collection The inclusion criteria encompassed the following: 1) patients diagnosed with RP or NIU, nAMD, RVO, or DME and over the age of 18 years; 2) the presence of CME observed on horizontal/vertical raster scans using spectral domain OCT (SD-OCT), within 1 mm of the macula and with a width ≥250 μm. Patients with the following criteria were excluded: 1) diagnosed with other retinopathy; 2) CME caused by other vitreoretinal diseases; 3) poor-quality of SD-OCT imaging; 4) history of major ocular surgery in the past 6mo (including cataract extraction, vitrectomy, and any intraocular surgery).

Patient Cohort We retrospectively reviewed 443 eyes with CME caused by ocular diseases, included 188 eyes of 188 patients with DME, 151 eyes of 151 patients with RVO, 51 eyes of 51 patients with nAMD, 21 eyes of 13 patients with RP, and 32 eyes of 29 patients with NIU in this study. After reviewing 362 eyes with DME, 270 eyes with RVO, 256 eyes with nAMD, 85 eyes with RP, and 181 eyes with UME, exclusions were made for those that did not meet the inclusion criteria.

Data Collection Medical records of all patients were meticulously reviewed for baseline demographics, including sex, age, chorioretinopathy duration, diabetes mellitus, hypertension, and any previous ophthalmological history (intravitreal or laser treatment). Baseline ophthalmic examination results, such as best-corrected visual acuity (BCVA) on the logarithm of the minimum angle of resolution (logMAR) scale, DR severity, ischemia in RVO, and CME status, were recorded. Retinal imaging was performed using the RTVue XR Avanti OCT system (Optovue, Inc., Fremont, CA, United States), capturing vertical or horizontal sectional images of the fovea in the cross-hair mode (10°), followed by quantifying the mean central subfield thickness (CST) and other data[4].

Image Analysis Two retinal investigators evaluated the qualitative and quantitative SD-OCT findings. Disagreements were resolved by one of the investigators, who is a specialist. The OCT biomarkers were measured in μm and assessed as follows: 1) Height and width of the foveal cystoid spaces: the largest capsule on the vertical or horizontal sectional image was selected for measurement; 2) CST; 3) Presence of hyperreflective deposits within the cystoid spaces; 4) The length of DRIL, defined as the inability to segment the boundaries of the ganglion cell–inner plexiform layer complex, inner nuclear layer (INL); and outer plexiform layer in the central 1-mm zone on the fovea[5]; 5) Continuity of the ELM, including disrupted and absent; 6) Length of EZ disruption (formerly the inner segment–outer segment photoreceptor junction); 7) Presence of hyperreflective foci, defined as circumscribed dots with reflectivity similar to that of the nerve fiber layer, absence of back-shadowing, and a diameter of <30 μm[6]; 8) Presence of SF; 9) Presence of vitreoretina relationships, including epiretinal membrane and vitreomacular traction[5].

Statistical Analysis Data analyses were performed using IBM SPSS Statistics for Windows version 27. Patient characteristics and study parameters were summarized using descriptive statistics following standard practice. The Kappa (*K*) statistic was used to assess differences in demographics, eye disease severity, classification, and the presence of laser treatment between the two groups. For normally distributed

Table 1 Characteristics of the HRW of patients with DME

Characteristics	HRW in foveal cystoid spaces		*P*
	Present (*n*=77 cystoid spaces)	Absent (*n*=111 cystoid spaces)	
Age (y), mean±SD	58.30±12.04	55.95±10.56	0.166
Sex (male/female)	38/39	50/61	0.665
DM duration, median (IQR), y	17.0 (13.0–20.0)	11.0 (7.0–19.0)	0.013
Duration of DME, median (IQR), mo	13.0 (9.5–24.0)	6.0 (3.0–12.0)	<0.01
DR severity stage (NPDR/PDR)	71/6	100/11	0.811
Intravitreal, median (IQR)	2.0 (0–4.0)	1.0 (0–4.0)	0.207
Laser treatment (yes/no)	33/44	31/80	0.003
VA logMAR, median (IQR)	0.8 (0.54–1.0)	0.4 (0.3–0.7)	<0.01

HRW: Hyperreflective walls; DME: Diabetic macular edema; SD: Standard deviation; IQR: Interquartile range; DR: Diabetic retinopathy; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; DM: Diabetes mellitus; VA: Visual acuity.

Table 2 Characteristics of the HRW of the patients with RVO

Characteristics	HRW in foveal cystoid spaces		*P*
	Present (*n*=49 cystoid spaces)	Absent (*n*=102 cystoid spaces)	
Age (y), mean±SD	64.53±11.90	60.67±11.73	0.070
Sex (male/female)	22/27	42/60	0.665
Hypertension duration, median (IQR), y	2.0 (0.8–5.0)	1.5 (0–4.0)	0.073
Duration of RVO, median (IQR), mo	18.0 (6.5–36.0)	7.0 (2.0–18.0)	<0.001
RVO severity (non-ischemic/ischemic)	9/40	68/34	<0.001
RVO type (CRVO/BRVO)	36/13	48/54	0.04
Intravitreal, median (IQR)	4.0 (1.5–8.0)	3.0 (0–4.0)	0.011
Laser treatment (yes/no)	21/28	16/86	<0.001
VA logMAR, median (IQR)	1.0 (0.8–1.3)	0.54 (0.3–0.8)	<0.001

HRW: Hyperreflective walls; RVO: Retinal vein occlusion; SD: Standard deviation; IQR: Interquartile range; VA: Visual acuity; CRVO: Central retinal vein occlusion; BRVO: Branch retinal vein occlusion; VA: Visual acuity.

variables, mean and standard deviation were used for quantitative variables, and an independent sample *t*-test was used for group comparisons. For data that were not normally distributed, median and interquartile ranges were used, and a nonparametric test of two independent samples was performed between the groups. Statistical significance was set at $P<0.05$, and binary logistic regression was conducted to explore the associations between the presence or absence of HRW in SD-OCT features and BCVA, another OCT biomarker.

RESULTS

Characteristics of the HRW of Patients with DME HRW was observed in 77 (40.9%) of 188 foveal cystoid spaces in those with DME. The OCT imaging were typically located at the bottom of the foveal cystoid spaces or within the septa between the spaces (Figure 1). In DME, *K* statistics and nonparametric tests confirmed no association between age, sex, DR severity, or number of intraocular injections. In the univariate analysis, HRW in the foveal cystoid spaces was associated with diabetes duration ($P=0.013$), DME duration ($P<0.01$), retinal photocoagulation ($P=0.003$), and worse VA ($P<0.01$; Table 1).

Characteristics of the HRW of Patients with RVO HRW was observed in 49 (32.5%) of 151 in those with RVO (Figure 1). In RVO, *K* statistics and nonparametric tests confirmed no association between age, sex, and hypertension duration. In the univariate analysis, HRW was associated with RVO duration ($P<0.001$), degree of RVO ischemia ($P<0.001$), RVO type ($P=0.04$), number of intraocular injections ($P=0.011$), retinal photocoagulation ($P<0.001$), and poor VA ($P<0.001$; Table 2).

Characteristics of the HRW of Patients with nAMD HRW was observed in 16 (31.4%) of 51 in those with nAMD (Figure 1). In nAMD, *K* statistics and nonparametric tests confirmed no association between age and sex. In the univariate analysis, HRW was associated with nAMD duration ($P<0.001$), number of intraocular injections ($P=0.011$), and worse VA ($P<0.001$; Table 3).

Characteristics of the HRW of Patients with RP HRW was observed in 12 (57.1%) of 21 in those with RP (Figure 1). We also evaluated the demographics and median logMAR VA of the patients with RP. *K* statistics and nonparametric tests confirmed no association between age and poor VA, which was reasonable given the inherently worse VA in patients with RP. In the univariate analysis, HRW was associated with RP duration ($P=0.033$; Table 4).

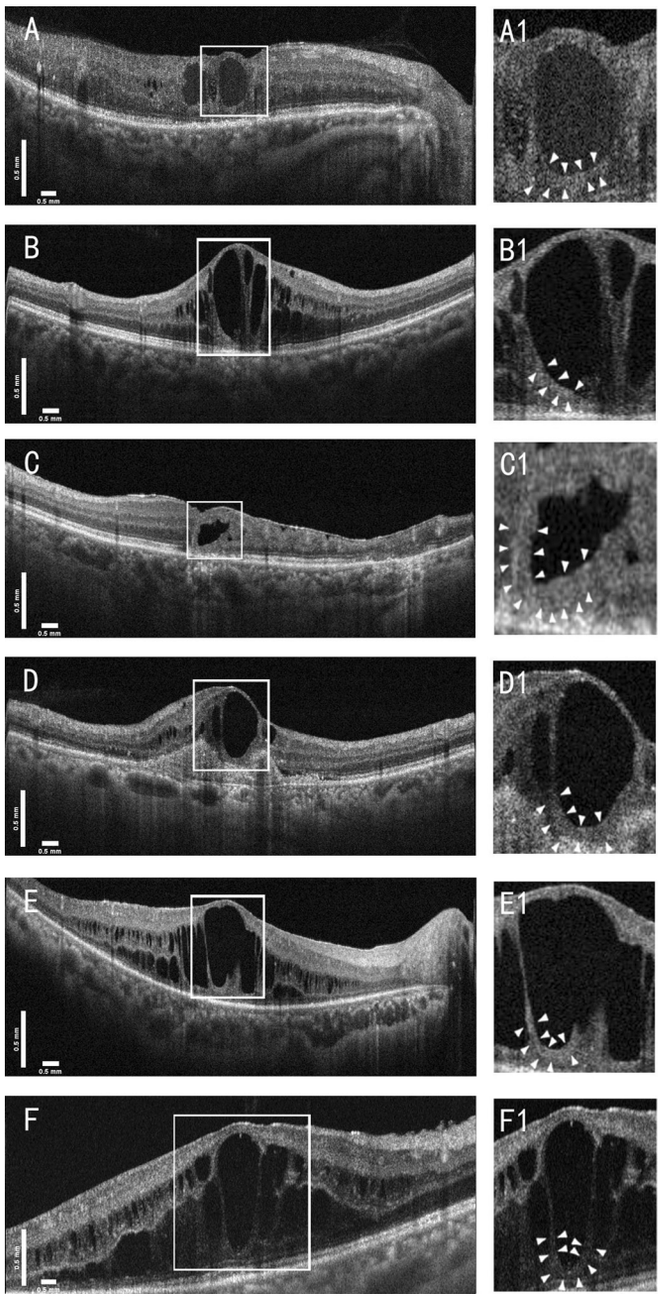

Figure 1 HRW of the foveal cystoid space on SD-OCT image A: HRW of the foveal cystoid spaces in a 50-year-old male patient with NPDR; B: HRW at the bottom of foveal cystoid spaces in a 64-year-old female patient with ischemic CRVO; C: HRW of the foveal cystoid spaces in a 71-year-old female patient with BRVO; D: HRW of the foveal cystoid spaces in a 77-year-old female patient with nAMD; E: HRW of the foveal cystoid spaces in a 33-year-old female patient with RP; F: HRW of the foveal cystoid spaces in a 42-year-old male patient with non-infectious posterior uveitis. A1–F1 are magnified images of the rectangles in A–F. White arrows indicate HRW. HRW: Hyperreflective walls; SD-OCT: Spectral domain optical coherence tomography; NPDR: Non-proliferative diabetic retinopathy; CRVO: Central retinal vein occlusion; BRVO: Branch retinal vein occlusion; nAMD: Neovascular age-related macular degeneration; RP: Retinitis pigmentosa.

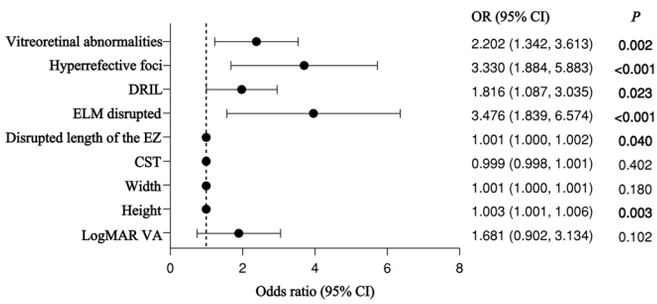

Figure 2 OCT biomarkers as predictors of HRW in diseases OCT: Optical coherence tomography; HRW: Hyperreflective walls; OR: Odds ratio; CI: Confidence interval; DRIL: Disorganization of retinal inner layers; ELM: External limiting membrane; EZ: Ellipsoid zone; CST: Central subfoveal thickness; VA: Visual acuity.

Characteristics of the HRW of Patients with NIU HRW was observed in 6 (18.8%) of 32 in those with UME (Figure 1). In UME, *K*-statistics and nonparametric tests confirmed no association with age. In the univariate analysis, HRW was associated with posterior uveitis duration (P=0.042) and poor VA (P<0.01; Table 5).

Table 6 demonstrates the differences between the presence or absence of HRWs in logMAR VA, HRW characteristics, and other OCT imaging biomarkers. Nonparametric tests revealed the following as significant factors: logMAR VA (P<0.001), HRW height in the foveal cystoid space (P<0.001), HRW width in the foveal cystoid space (P<0.001), CST (P<0.001), DRIL (P<0.001), ELM disruption (P<0.001), disrupted length of the EZ (P<0.001), hyperreflective foci (P<0.001), and vitreoretinal abnormalities (P=0.003).

Association Between HRW and logMAR VA, SD-OCT Biomarkers According to binary logistic regression analysis, several SD-OCT biomarkers were significantly associated with HRW in foveal cystoid spaces (Figure 2). Specifically, vitreoretinal abnormalities (P=0.002), hyperreflective foci (P<0.001), DRIL (P=0.023), ELM disruption (P<0.001), disrupted EZ (P=0.04), and HRW height in the foveal cystoid space (P=0.003) were significant. The odds ratios (OR) and 95% confidence intervals (95%CI) were as follows: 2.202 (95%CI, 1.342–3.613) for vitreoretinal abnormalities, 3.33 (95%CI, 1.884–5.883) for hyperreflective foci, 1.816 (95%CI, 1.087–3.035) for DRIL, 3.476 (95%CI, 1.839–6.574) for ELM disruption, 1.001 (95%CI, 1.000–1.002) for the length of EZ disruption, and 1.003 (95%CI, 1.001–1.006) for the HRW height in the foveal cystoid spaces. However, other biomarkers, including logMAR VA, CST, and width in the foveal cystoid space, showed no significant association with HRW.

DISCUSSION

Despite the rapid advancements in ophthalmology, retinal diseases are the leading cause of irreversible blindness worldwide, resulting in vision loss, visual field defects, and

Table 3 Characteristics of the HRW of the patients with nAMD

Characteristics	HRW in foveal cystoid spaces		*P*
	Present (*n*=16 cystoid spaces)	Absent (*n*=35 cystoid spaces)	
Age (y), mean±SD	70.13±7.75	73.91±9.11	0.108
Sex (male/female)	8/8	13/22	0.576
Duration of nAMD, median (IQR), mo	27.5 (8.2–48.2)	24.0 (6.0–38.0)	<0.001
Intravitreal	4.0 (0.3–9.8)	3.0 (0–8.0)	0.011
VA logMAR, median (IQR)	1.0 (0.7–1.5)	0.9 (0.6–1.3)	<0.001

HRW: Hyperreflective walls; nvAMD: Neovascular age-related macular degeneration; SD: Standard deviation; IQR: Interquartile range; VA: Visual acuity.

Table 4 Characteristics of the HRW of the patients with RP

Characteristics	HRW in foveal cystoid spaces		*P*
	Present (*n*=12 cystoid spaces)	Absent (*n*=9 cystoid spaces)	
Age (y),	40.50±12.06	44.11±14.32	0.948
Duration of RP, median (IQR), mo	120.0 (84.0–216.0)	72.0 (24.0–120.0)	0.033
VA logMAR, median (IQR)	0.8 (0.7–1.2)	0.54 (0.4–0.9)	0.113

HRW: Hyperreflective walls; RP: Retinitis pigmentosa; IQR: Interquartile range; VA: Visual acuity.

Table 5 Characteristics of the HRW of the patients with UME

Characteristics	HRW in foveal cystoid spaces		*P*
	Present (*n*=6 cystoid spaces)	Absent (*n*=26 cystoid spaces)	
Age (y), mean±SD	30.83±16.23	43.46±17.58	1.000
Duration of UME, median (IQR), mo	38.0 (9.0–72.0)	14.5 (6.0–18.2)	0.042
VA logMAR, median (IQR)	0.54 (0.4–1.0)	0.3 (0.2–0.4)	<0.01

HRW: Hyperreflective walls; UME: Uveitic macular edema; SD: Standard deviation; IQR: Interquartile range; VA: Visual acuity.

Table 6 Ocular characteristics and SD-OCT-based measures of foveal cystoid spaces in 443 eyes median (IQR)

Characteristics	HRWs in foveal cystoid spaces		*P*
	Present (*n*=160 cystoid spaces)	Absent (*n*=283 cystoid spaces)	
VA logMAR	0.9 (0.6–1.2)	0.54 (0.3–0.8)	<0.001
Height (μm)	356.0 (250.0–517.0)	267.0 (185.0–337.0)	<0.001
Width (μm)	476.5 (382.0–698.5)	429.0 (324.0–530.0)	<0.001
CST (μm)	576.5 (399.3–716.8)	401.0 (313.0–535.0)	<0.001
Hyperreflective deposits (present/absent)	37/123	70/213	0.791
DRIL (present/absent)	81/79	68/215	<0.001
Disrupted length of the EZ (μm)	1000.0 (353.5–1000.0)	236.0 (28.0–755.0)	<0.001
ELM disrupted (present/absent)	138/22	133/150	<0.001
Hyperreflective foci (present/absent)	59/101	36/247	<0.001
Subretinal fluid (present/absent)	51/109	71/212	0.154
Vitreoretinal abnormalities (present/absent)	95/65	125/158	0.003

SD-OCT: Spectral domain optical coherence tomography; HRW: Hyperreflective walls; VA: Visual acuity; IQR: Interquartile range; CST: Central subfoveal thickness; DRIL: Disorganization of retinal inner layers; EZ: Ellipsoid zone; ELM: External limiting membrane.

potential blindness. Maintaining a relatively dehydrated and transparent state is crucial for the retina's health under physiological conditions. The blood-retinal barrier, composed of tight junctions between vascular endothelial cells, plays a pivotal role in preserving this physiological status[7]. Beyond the blood-retinal barrier, recent insights have expanded our understanding to include the drainage functions of the retinal pigment epithelium and retinal Müller glia (RMG) as additional contributors to maintaining the retina's dehydrated and transparent state[8]. RMGs are unique macroglial cells found in the retina, extending throughout the tissue thickness, with the end feet reaching the inner limiting membrane, forming their basal membrane, and continuing down to the ELM, establishing contact with the vitreous cavity, all neural cell types, and retinal vessels. Neurovascular units, comprising neurons, glial cells, vascular smooth muscle cells, pericytes,

and vascular endothelial cells, establish a functional link between neurons and blood vessels, provide nutritional support to neurons, and regulate homeostasis of the neuronal, vascular, and extracellular environments (water, ions, and pH). RMGs express numerous K^+ channels and aquaporins[9]. CME is the final common pathway for numerous ocular diseases and systemic insults[10]. Extracellular fluid may infiltrate the inner retinal layers in the macular area, forming intraretinal cystoid edema known as CME. Alternatively, fluid accumulation in the subretinal space is known as SF[9]. The major causes of CME are DR, RVO, nAMD, RP, NIU, and pseudophakic CME[7,10]. The pathophysiology of foveal cystoid edema is complex and involves ischemia, hypoxia, inflammation, exudation, vitreoretinal traction, intracytoplasmic swelling of the RMGs, and degeneration[6,11]. A reduction in K^+ conductance has been observed in DR, RVO, various forms of retinal degeneration, and posterior uveitis[9]. Dysfunction of water channels and ion imbalance leads to intracellular edema in RMG cells, causing neuronal toxicity and liquefaction necrosis[12].

In this study, a high incidence of HRWs in foveal cystoid spaces was observed in CME caused by common chorioretinal diseases, including DME (40.9%), RVO (32.5%), AMD (31.4%), RP (57.1%), and UME (18.8%). HRWs in foveal cystoid spaces detected by SD-OCT have rarely been reported previously; thus, the significance of this sign remains underappreciated. This study established strong correlations between HRW histology and both vitreoretinal abnormalities and ELM disruption. As the inner limiting membrane is the endplate of the RMGs, and the ELM is their basal membrane, vitreoretinal abnormalities and damage are localized to the RMGs. Additionally, HRW is highly correlated with DRIL in this study. Proteomic analysis of the aqueous humor has recently shown a significant correlation between the DRIL observed in OCT changes in DME and RMG dysfunction[13], indirectly confirming the strong correlation between HRW and RMGs. Third, hyperreflective foci identified on OCT imaging have been established as reliable biomarkers of active inflammatory cells[14]. Research shows inflammatory cytokines are expressed after DR, RVO, nAMD, RP, and NIU, leading to microglial activation and the appearance of hyperreflective foci[15-19]. In this study, a strong correlation was observed between HRW and hyperreflective foci. Inflammatory cytokines and ischemia have been implicated in accelerating RMG cell degeneration[11]. The strong association between HRW and Müller glial cell dysfunction highlights the potential role of HRW in reflecting chronic retinal damage[1]. Further longitudinal studies are needed to explore the temporal changes in HRW and their implications for treatment outcomes.

Electron microscopy and photonics examination revealed swelling and widespread necrosis of RMGs in three eyes with CME, indicating that foveal cysts resulting from RMG cell degeneration manifested as hyporeflective cystoid edema within the intraretinal layers on SD-OCT. Excessive RMG gliosis during the reparative process may lead to the proliferation of retinal glial scars, hypothesized to contribute to the formation of HRW observed in foveal cysts on SD-OCT[20]. HRW may signify a reparative response formed by RMG cell degeneration[21]. Photoreceptor undergoes progressive structural damage through a pathological cascade initiated by RMG dysfunction, wherein edema formation, necrotic processes, and apoptotic degeneration collectively trigger retrograde neurotoxic effects, results in EZ line disruption[20]. EZ integrity has been emerged as a critical imaging biomarker for prediction of visual acuity outcomes[22-24]. These changes corresponded to the unfavorable visual outcomes observed in patients with HRW in this study.

Recent studies have also highlighted the role of HRW in predicting treatment response in DME[1]. For instance, Sardana *et al*[25] demonstrated that HRW in foveal cystoid spaces are associated with poorer visual outcomes and non-resolution of central macular thickness (CMT) after intravitreal ranibizumab treatment. Similarly, Park *et al*[26] observed that RP-associated CME were linked to Müller cell dysfunction and slower resolution of cystoid spaces following dexamethasone treatment. These findings align with our results, further supporting the role of HRW as a prognostic biomarker in CME. HRW, as depicted using SD-OCT, may offer novel insights into the damage to RMGs and help visualize changes in eye diseases. Therefore, HRW can serve as a valuable reference for the rational treatment of fundus diseases, contributing to the preservation and enhancement of patient vision.

In conclusion, HRW in foveal cystoid spaces are a common OCT finding in CME and are associated with more severe retinal structural damage. The presence of HRW suggests prolonged duration of ocular diseases, poorer vision, greater height compared to cysts without HRW, and a history of more intravitreal and laser treatments in fundus vascular diseases. HRW may serve as a prognostic biomarker for disease severity and treatment response in patients with CME. As the field progresses, more ophthalmologists are expected to appreciate and adopt this biomarker for clinical assessment.

The limitations of this study stem from its retrospective cross-sectional observational design and the absence of pathological findings. HRW is predominantly derived from imaging observations *via* SD-OCT, and further investigations are warranted to elucidate the correlation between pathophysiology and this OCT imaging biomarker. This cross-sectional study did not observe this biomarker at various stages of ocular disease, so further longitudinal studies are needed to explore

the temporal changes in HRW and their implications for treatment outcomes.

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Data Availability Statement: All data generated or analyzed during this study are included in this published article and its supplementary information files.

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