Clinical Characteristics and Outcomes in Central Serous Chorioretinopathy With Subretinal Hyper-Reflective Material: MICRoN Report 6

NIROJ KUMAR SAHOO, NASIQ HASAN, NINAN JACOB, JESSICA CAO, CHARLES C. WYKOFF, PRIYA SHAH, PANISA SINGHANETR, ELIZABETH J. ROSSIN, LORENZO FERRO DESIDERI, FELICIA HERTKORN, MARION R. MUNK, SAMER KHATEB, JAY WANG, RAHUL N. KHURANA, YUSUF ASHFAQ, ZACHARY KROEGER, MICHAEL ZHANG, MAURIZIO BATTAGLIA PARODI, GABRIELE PICCOLI, STELA VUJOSEVIC, MIN KIM, CARMEN ANTÍA RODRÍGUEZ-FERNÁNDEZ, LUIS ARIAS BARQUET, KENT SMALL, PAISAN RUAMVIBOONSUK, PERANUT CHOTCOMWONGSE, LUIZ H. LIMA, ADRIAN T. FUNG, LIHTEH WU, AND JAY CHHABLANI, FOR THE MACULA SOCIETY INTERNATIONAL CSCR RESEARCH NETWORK (MICRON)

• PURPOSE: To evaluate the clinical features and longitudinal outcomes of chronic central serous chorioretinopathy (CSCR) presenting with subretinal hyperreflective material (SHRM).

• DESIGN: Retrospective, multicenter clinical cohort study from the Macula Society CSCR Study Group.

• PARTICIPANTS: This study included consecutive patients with a diagnosis of CSCR, with and without SHRM.

• METHODS: Baseline and final best-recorded visual acuity (BRVA) and multimodal imaging parameters were compared between SHRM and non-SHRM groups.

• MAIN OUTCOME MEASURES: Longitudinal changes in BRVA and imaging parameters in both groups; factors affecting subretinal fluid (SRF) persistence, and change in BRVA.

• RESULTS: A total of 503 eyes (103 with SHRM and 400 eyes without SHRM) were analyzed. The SHRM group showed poorer baseline BRVA (0.4 ± 0.3 logMAR; 20/50) compared to the non-SHRM group (0.2 ± 0.3 logMAR; 20/30) ($p = .006$). SHRM eyes demonstrated greater RPE alteration ($p = .04$), higher neurosensory retinal detachment ($p < .001$), more photoreceptor irregularities ($p = .004$), hyperreflective foci ($p < .001$), and double-layer sign ($p < .001$). The incidence of concurrent macular neovascularization ($p = .01$) and persistent subretinal fluid ($p < .001$) was higher in the SHRM group. Despite visual improvement in both groups, final height of neuro-sensory detachment ($p < .001$) remained higher in SHRM eyes. Eyes with a history of steroid exposure and ellipsoid zone (EZ) loss (post-resolution) were greater in higher SHRM grades. Logistic regression revealed non-SHRM status, and combination therapy had lower odds of SRF persistence.

• CONCLUSION: CSCR with SHRM presented with worse initial vision. Although vision improved after treatment, persistent SRF and EZ loss (in resolved cases) remain more frequent in SHRM eyes. (Am J Ophthalmol 2026;286: 152–162.

The members of the MICRoN Study Group are listed in the Acknowledgment section.

Accepted for publication February 23, 2026.

From the Anant Bajaj Retina Institute (N.K.S., N.J.), Kode Venkatadri Chowdary Campus, LV Prasad Eye Institute, Vijayawada, Andhra Pradesh, India; University of Pittsburgh Medical Center (N.H., J.C.), Pittsburgh, Pennsylvania, USA; Retina Consultants of Texas (J.C., C.C.W.), Houston, Texas, USA; Harvard Medical School Department of Ophthalmology within Massachusetts Eye and Ear (MEE) (P. Shah, P.S., E.R.), Boston, Massachusetts, USA; Inselspital, University Hospital Bern (L.F.D., M.R.M.), Bern, Switzerland; Augenarzt Praxisgemeinschaft Gutblick (F.H., M.R.M.), Pfäffikon, Switzerland; Department of Ophthalmology (M.R.M.), Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA; Department of Ophthalmology (S.K.), Hadassah Medical Center, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel; Northern California Retina Vitreous Associates (J.W., R.N.K.), Mountain View, California, USA; Casey Eye Institute at Oregon Health and Science University (Y.A., Z.K.), Portland, Orlando, USA; The Canberra Hospital (M.Z.), Yamba Dr, Garran, Australia; Sydney and Sydney Eye Hospital (M.Z.), Sydney New South Wales, Australia; Ophthalmology Department (M.B.P.), IRCCS San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy; Eye Clinic IRCCS MultiMedica (G.P., S.V.), Milan, Italy; Department of Biomedical, Surgical and Dental Sciences (S.V.), University of Milan, Milan, Italy; Yonsei University College of Medicine (M.K.), Seoul, Republic of Korea; Department of Ophthalmology (C.A.R-F., L.A.B.), Hospital Universitari de Bellvitge, Carrer de La Feixa Llarga, S/N, L'Hospitalet de Llobregat, Catalunya, Spain; Macula and Retina Institute (K.S.), Glendale and Los Angeles, California, USA; Molecular Insight Research Foundation (K.S.), Glendale and Los Angeles, California, USA; Vitreoretina Unit (P.R., P.C.), Department of Ophthalmology, Rajavithi Hospital, Rungsit University, Bangkok, Thailand; Department of Ophthalmology (L.H.L.), Federal University of São Paulo/Paulista School of Medicine, São Paulo, Brazil; Save Sight Institute (A.T.F.), Specialty of Clinical Ophthalmology and Eye Health, The University of Sydney, Sydney, New South Wales, Australia; Department of Ophthalmology (A.T.F.), Westmead Hospital, Sydney, New South Wales, Australia; Department of Ophthalmology (A.T.F.), Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia; Zhongshan Ophthalmic Centre (A.T.F.), Sun Yat-sen University, Guangzhou, China; Asociados de Macula Vitreo y Retina de Costa Rica (L.W.), San José, Costa Rica; University of Pittsburgh School of Medicine (J.C.), Pittsburgh, Pennsylvania, USA

Inquiries to Jay Chhablani, Faculty – Clinician, University of Pittsburgh, UPMC Eye Center, Pittsburgh, Pennsylvania, USA.; e-mail: jay.chhablani@gmail.com

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2026.02.037

INTRODUCTION

Central serous chorioretinopathy (CSCR) is characterized by the accumulation of subretinal fluid (SRF) in the posterior pole.[1] The rate and extent of SRF resolution are influenced by several factors, including age, central macular thickness (CMT), sub-foveal choroidal thickness (SFCT), and retinal pigment epithelium (RPE) changes.[2,3] In most cases, the fluid resolves spontaneously or after treatment, but varying degrees of structural and functional impairment may persist.[1,4] Therefore, identifying clinical biomarkers associated with poor prognosis may be valuable for guiding patient education and also for informing both the choice and timing of therapy.[5,6] While SRF is usually optically clear, optical coherence tomography (OCT) may reveal hyperreflective foci (HRF) or subretinal hyperreflective material (SHRM) in some cases.

SHRM is defined as the accumulation of medium- to high-reflectivity material in the subretinal space.[7] Although frequently observed in CSCR, it is not specific to the disease and may also occur in macular neovascularization, high myopia, posterior uveitis, macular dystrophies, etc.[7] In these conditions, SHRM has been recognized as a marker of disease severity and poor visual prognosis. The term has been used broadly to describe different lesions, including blood, exudates, fibrosis, and neovascular complexes. The precise composition of SHRM in CSCR, however, remains uncertain. Some studies suggest that it represents fibrin derived from choroidal structures,[8,9] while others propose that it may consist of shed photoreceptor elements.[10,11] Several previous studies have described the presence and clinical implications of SHRM in CSCR. Maruko et al. and our earlier work reported associations between SHRM and visual outcomes in relatively small cohorts.[10,11] Irrespective of its origin, the presence of SHRM is clinically significant, as it may be associated with visual decline,[12] particularly when accompanied by outer retinal disruption.[11] More recently, using multimodal cross-sectional imaging, Pu et al. [12] categorized SHRM into 3 subtypes and demonstrated correlations with choroidal vascular alterations, RPE changes, and the extent of SRF, with these associations varying according to SHRM grade. However, their work did not include longitudinal follow-up, limiting insights into progression and long-term sequelae. Other studies have been limited by small sample sizes, short follow-up periods, or lack of comprehensive control groups, restricting the ability to perform robust prognostic evaluations or meaningful subgroup analyses.[8-10]

In this study, we aim to utilize a large multicentric cohort to fill these gaps by evaluating functional outcomes and morphological changes related to SHRM over a long-term follow-up. We also aim to directly compare SHRM and non-SHRM CSCR cases to evaluate SHRM's independent prognostic value and perform grade-specific analyses to detect differential outcomes among SHRM subtypes. Such information may ultimately support the development of patient-specific treatment strategies for this subset of CSCR.

METHODS

• **STUDY DESIGN:** This was a retrospective, multicenter, clinical cohort study evaluating eyes with a diagnosis of CSCR with SHRM. All cases were gathered through a collaborative effort by the Macula Society members to create a cohort of CSCR patients with multimodal imaging data. Local institutional review board clearance was obtained from individual institutions, and the study adhered to the tenets of the Declaration of Helsinki. The project has previously published details on data-sharing agreements among collaborators, as well as procedures for collecting and analyzing demographic, clinical, and imaging data.[13] All cases were collected from January 2010 to December 2023. The inclusion criteria were: (a) patients older than 18 years, (b) a confirmed diagnosis of CSCR (c) presence of SHRM between the neurosensory retina and the RPE (in patients with both eyes meeting this criterion, only the right eye was analyzed). The exclusion criteria were: (a) eyes with inadequate or incomplete records, (b) coexisting inflammatory ocular conditions (like VKH) that can present with SHRM, and (c) eyes showing macular neovascularization (MNV) at baseline, diagnosed using OCT angiography or indocyanine green angiography, depending on availability. A control group was also selected from the multicentric cohort, consisting of eyes with CSCR but without SHRM. Information regarding the baseline demographics, best recorded visual acuity (BRVA), systemic co-morbidities, history of psychiatric or sleep disorders, medication use, smoking status, symptom duration, and prior treatment for CSCR was also obtained.

• **IMAGING EVALUATION:** Imaging data were collected at both baseline and final visits, including fundus autofluorescence (FAF), optical coherence tomography (OCT), and fluorescein angiography (FFA). FAF assessment included: (a) the extent of retinal pigment epithelium (RPE) changes quantified in disc areas [including both hypo- and hyperautofluorescent lesions, in disc areas (DA)]; (b) focal vs multifocal RPE alterations; (c) presence of gravitational tracts; and (d) peripapillary RPE changes. CSCR cases were further classified based on the extent of RPE involvement and the presence of multifocal lesions into simple or complex

CSCR. Simple CSCR referred to disease limited to 2 or fewer disc areas of RPE alteration, whereas complex CSCR included eyes with multifocal involvement or changes extending more than 2 DA.[14]

Other OCT parameters evaluated included CMT and the height and width of the neurosensory retinal detachment (NSRD). CMT was obtained automatically from the macular cube scan generated by the OCT device. The height of the NSRD was measured from the innermost surface of the elevated neurosensory retina at its highest point to the inner border of the RPE at the fovea. Choroidal measurements included SFCT, Haller vessel diameter, and inner choroidal thickness. SFCT was determined within a 500 µm radius of the fovea using the OCT caliper, extending from the outer surface of the RPE to the choroid–sclera junction. Haller vessel thickness was measured by identifying the largest choroidal vessel lumen within 750 µm of the foveal center. The inner choroid, comprising the choriocapillaris and Sattler's layer, was measured from the inner margin of the largest Haller vessel to the outer surface of the RPE. Pigment epithelial detachments (PEDs) were identified on OCT as dome-shaped elevations of the RPE. Their number was confirmed using fundus fluorescein angiography (FFA), infrared imaging, or en-face OCT. The tallest PED within the scanned volume was selected for height measurement, defined as the vertical distance from Bruch's membrane to the apex of the RPE elevation. PED width was measured horizontally between the points where the RPE contour returned to normal, using Bruch's membrane as a reference. Fovea-involving RPE atrophy was also recorded, defined as focal or diffuse areas of hyper-transmission on OCT, with any portion located within 200 µm of the foveal center. Loss of the ellipsoid zone (EZ) was defined as a discontinuity in the EZ extending over an area of at least 100 microns. EZ integrity was analyzed only in eyes with SRF resolution at the final visit. Assessment (as a categorical variable) was performed by reviewing the entire macular cube to identify EZ disruptions corresponding to regions of prior NSRD. The double-layer sign (DLS) was recorded when shallow, irregular PEDs with internal hyperreflective, hyporeflective, or mixed signals were observed. Hyperreflective dots (HRDs) in the choroidal stroma were also noted. Photoreceptor outer segment (PROS) thickening was defined as an increased distance between the inner boundary of the ellipsoid zone and the outer surface of the neurosensory retina in the presence of SRF. Any irregularities in the PROS layer in any of the OCT B-scans of the macular cube were also recorded. Detection of macular neovascularization (MNV) was based on findings from OCT angiography or indocyanine green angiography (ICG-A), when available.

OCT images were acquired using Heidelberg Spectralis HRA and OCT (Heidelberg Engineering, Heidelberg, Germany), Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA), and Triton SS-OCT device (Topcon Corporation, Tokyo, Japan). FFA /ICG/FAF images were acquired using Heidelberg Spectralis HRA and OCT (Heidelberg Engineering, Heidelberg, Germany), Zeiss FF 450 plus IR (Carl Zeiss Meditec AG, Jena, Germany), and Optos California device (Optos plc, Dunfermline, UK).

• **SHRM GRADING:** SHRM was identified on OCT and was defined by the presence of medium to high reflectivity material in the sub-retinal space. The SHRM group was further classified into 3 grades using Fiji software (ImageJ, version 2.16.0) based on the methods described in a previous study by Pu et al.[12] The areas of SHRM were manually delineated by an experienced grader (NH). The proportion of SHRM area relative to the total subretinal fluid (SRF) area was subsequently calculated. An initial attempt to quantitatively assess SHRM by binarizing the images was deferred due to suboptimal detection of finer SHRM reflectivities. Grade 1 consisted of occupying less than 20 % of the subretinal space (Figure 1B); Grade 2 represented SHRM occupying 20–50 % of the subretinal space (Figure 1C); and Grade 3 indicated extensive SHRM involving more than 50 % of the subretinal area, often showing layered or onion-like reflectivity on OCT (Figure 1C). Few modifications were made to the classification: the grades were assigned based on the area occupied, irrespective of the configuration [adherent to the neurosensory retina, suspended within subretinal fluid, or appearing as filamentous strands beneath the photoreceptor outer segments (PROS)]. The mean SHRM area was calculated as the average of 3 horizontal OCT scans within the macular cube. The 3 horizontal OCT scans for evaluation were selected as follows: one mandatory scan through the foveal center, and 2 additional non-consecutive scans positioned superior and inferior to the fovea, ensuring that at least one scan captured the region of maximum SHRM accumulation based on review of the entire macular cube. This standardized protocol enabled consistent evaluation across all cases, regardless of leakage-point identification or angiographic availability. This approach also minimized overestimation that could occur when SHRM appeared extensive on a single scan through a shallow detachment segment.

For all measurements, including SHRM grading, data were collected from each center and evaluated collectively by a senior grader (NH) who was masked for the clinical outcomes.

• **OUTCOME MEASURES:** The primary outcome measures were factors affecting the change in BRVA from baseline to the final visit, and the factors associated with persistence of subretinal fluid at the final follow-up. Similarly, the secondary outcomes were changes in CMT, NSRD height, and SFCT; disease course (resolution, recurrence, or persistence); development of MNV; EZ loss in resolved cases; subretinal scar formation; and change in SHRM grade.

• **STATISTICAL ANALYSIS:** All analyses were conducted using R Studio (version 2025.09.1 + 40), R Foundation for Statistical Computing, Vienna, Austria. The cohort

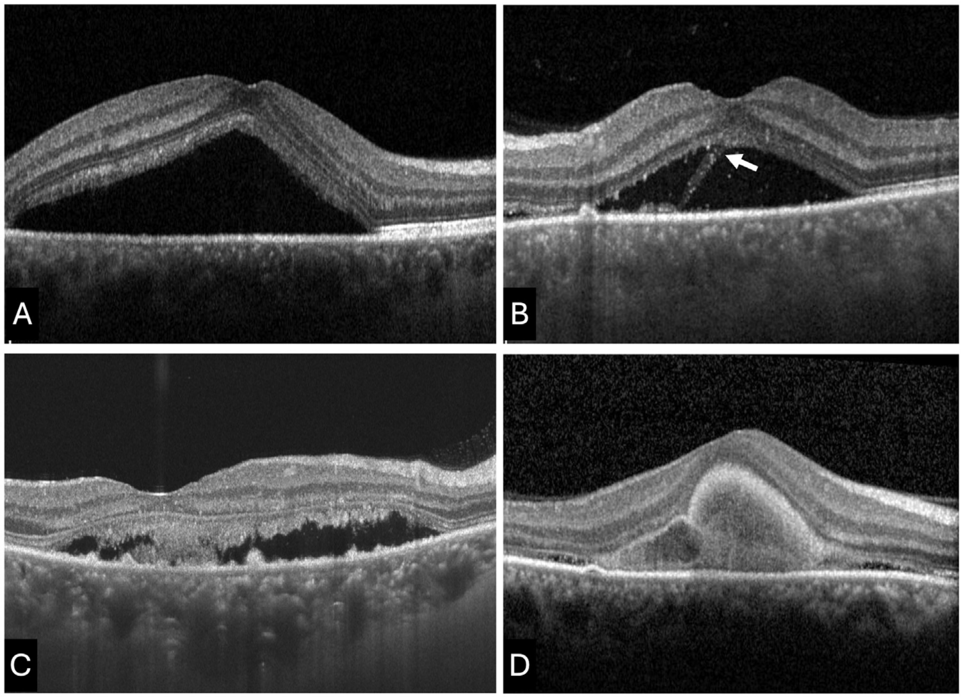

FIGURE 1. Example of (A) Central serous chorioretinopathy (CSCR) with no subretinal hyper-reflective material (SHRM), (B) CSCR with Grade-1 SHRM, showing continuity of the material with the elongated photoreceptor outer segment (PROS)(*white arrow*), (C) CSCR with Grade-2 SHRM with broad attachments to the PROS, and (D) CSCR with Grade-3 SHRM showing layering.

consisted of 2 groups according to the presence or absence of SHRM . Continuous variables were summarized as mean ± SD or median (IQR), while categorical variables were expressed as counts and percentages. The normality of data distribution was examined using the Shapiro-Wilk test. Comparisons between groups were made using the independent-samples t-test or Mann-Whitney U test for continuous variables, and the chi-square or Fisher's exact test for categorical data. To explore determinants of persistent SRF, logistic regression analysis was performed; and to analyze the factors affecting change in BRVA [expressed in logarithm of minimum angle of resolution (logMAR)], linear regression analysis was performed. Each baseline factor was first evaluated in a univariate model, and variables showing a p-value < .10 were subsequently entered into a multivariable logistic regression model. A manual stepwise approach was then applied, where variables were iteratively added or removed. Results were presented as odds ratios (OR) or Regression coefficients with 95% CIs (CI). A 2-sided $p < .05$ was considered statistically significant.

RESULTS

A total of 103 eyes of 103 patients (76 males and 27 females) with SHRM and 400 eyes of 400 patients (297 males and 103 females) without SHRM], were included in the study. The mean age of the cohort was 47.1 ± 11.2 years. The median duration of symptoms was 2 months (IQR 0.5 to 6 months). A history of previous treatment was present in 36 patients (17.5%) [26 (25.2%) in the SHRM group and 67 (16.5%) in the non- SHRM group, $p = .04$]. A summary of baseline characteristics of the 2 groups is mentioned in Table 1.

• **COMPARISON BETWEEN SHRM AND NON-SHRM GROUPS:** The baseline BRVA was worse in the SHRM group (0.4 ± 0.3 logMAR, Snellen equivalent 20/50), compared to the non-SHRM group (0.2 ± 0.3 logMAR, Snellen equivalent 20/30) ($p = .001$). In terms of imaging parameters, the amount of RPE alterations ($p = .04$), number of simple CSCR ($p = .001$), height of NSRD ($p < .001$), eyes with PROS irregularities ($p = .004$), eyes with HRF in PROS ($p < .001$), presence of DLS ($p < .001$), were significantly higher in the SHRM group (Table 1). The patients were followed up for a median of 20 months (IQR 8 to 56 months). A total of 68 (66%) eyes received treatment after the baseline visit in the SHRM group [4 were on mineralocorticoid receptor antagonist (MRA) drugs, nine underwent PDT, 14 received anti-VEGF injections, 29 underwent subthreshold micropulse laser (STML)/conventional laser, and 12 had combination therapy]; while 255 (63.8%) eyes received treatment in the

TABLE 1. Baseline Characteristics of All Groups.

Parameter	CSCR without SHRM) [n = 400]	CSCR with SHRM) [n = 103]	p-value (SHRM versus non-SHRM groups)	Grade-1 SHRM [n = 38]	Grade-2 SHRM [n = 55]	Grade-3 SHRM [n = 10]	Overall p-value among SHRM grades*
Age, years	46.7 ± 10.9	47.7 ± 11.9	.53	47.9 ± 14.6	47.7 ± 10.5	47 ± 8.6	.97
Gender, Males (%)	297 (74.3)	76 (73.8)	.92	26 (68.4)	43 (78.2)	7 (70)	.55
History of treatment for CSCR	67 (16.5)	26 (25.2)	.04	10 (26.3)	12 (21.8)	4 (40)	.46
Systemic co-morbidities(%)	197 (49.3)	54 (52.4)	.62	19 (50)	28 (50.9)	7 (70)	.51
Smoking (%)	52 (13)	21 (20.4)	.09	6 (15.8)	12 (21.8)	3 (30)	.56
Steroid exposure (%)	95 (23.8)	28 (27.2)	.52	4 (10.5)	20 (36.4)	4 (40)	.01 (.03, .24,0.9)
Sleep/psychiatric disturbance (%)	47 (11.8)	16 (15.5)	.38	6 (15.8)	10 (18.2)	0 (0)	.34
Duration of symptoms [Median (IQR)], months	2 [0.5 to 6]	2 [0.75 to 4]	.67	1.25 [1.25 to 3]	3 [1 to 6]	2 [0.9 to 18]	.04 (.9,0.57,.1)
Ocular parameters							
BRVA, logMAR	0.2 ± 0.3	0.4 ± 0.3	.001	0.4 ± 0.33	0.3 ± 0.3	0.5 ± 0.5	.57
Simple CSCR (%)	258 (64.5)	41 (39.8)	.001	17 (44.7)	23 (41.8)	1	.14
Area of RPE alterations, disc areas	1.9 ± 1.9	3.2 ± 3.9	.04	2.4 ± 3.4	3.2 ± 3.7	6.1 ± 5.6	.05 (.9, .4, .1)
Gravitational tract (%)	17 (4.3)	5 (4.9)	.76	0 (0)	4 (7.3)	1 (10)	.3
Peripapillary RPE alterations (%)	44 (11)	8 (7.8)	.36	2 (5.2)	4 (7.3)	2 (20)	.26
OCT							
CMT, microns	350.7 ± 139.7	391.7 ± 190.2	.04	481.7 ± 201.9	345.1 ± 167.6	305.4 ± 133.5	.001 (.003, .9, .06)
NSRD height, microns	123.6 ± 126.1	270.7 ± 202.1	<.001	367.9 ± 220.1	205.1 ± 155.9	264.7 ± 228.7	.001 (<.001, .9, .84)
Irregular PROS (%)	115 (28.8)	48 (46.6)	.004	16 (42.1)	28 (50.9)	4 (40)	.64
HRF in PROS (%)	238 (59.5)	102 (99)	<.001	36 (94.7)	55 (100)	9 (90)	.42
Hyper-reflective deposits on RPE/RPE nodularity (%)	144 (36)	53 (51.5)	.04	16 (42.1)	21 (38.2)	6 (60)	.44
DLS (%)	128 (32)	58 (56.3)	.001	23 (60.5)	29 (52.7)	6 (60)	.89
Length of DLS, microns	1220.1 ± 807.9	1185.8 ± 1033.9	.82	1090.6 ± 1318.9	1161.2 ± 808.8	1669.5 ± 736.9	.47
SFCT, microns	380.5 ± 103.7	394.5 ± 105.7	.23	409.5 ± 117.3	380.2 ± 98.6	415.9 ± 94.1	.34
Haller vessel thickness, microns	288.4 ± 99.4	296.8 ± 103.4	.47	310.5 ± 113.9	283 ± 97.5	320.1 ± 91.1	.34
Inner choroidal thickness, microns	111.8 ± 92.1	99.7 ± 49.2	.08	96.8 ± 34.2	103 ± 58.8	92.5 ± 41.6	.75
Pachyvessels (present) (%)	271 (67.8)	81 (78.6)	.11	29 (76.3)	44 (80)	8 (80)	.9
Number of PEDs	1.4 ± 1.7	1.7 ± 1.1	.41	1.8 ± 1.9	1.7 ± 0.8	1.4 ± 0.5	.79
Maximum height of PEDs, microns	120.5 ± 95.8	128.5 ± 110.8	.71	179.9 ± 161.1	100.3 ± 62.9	143.9 ± 132.2	.16
Maximum width of PEDs, microns	461.1 ± 281.2	589.4 ± 420.8	.16	739.9 ± 680.3	531.8 ± 485.8	547.3 ± 374.3	.57

BRVA: Best recorded visual acuity; CSCR: Central serous chorioretinopathy; CMT: Central macular thickness; SFCT: Sub-foveal choroidal thickness; NSRD: Neurosensory detachment; RPE: Retinal pigment epithelium; DLS: Double layer sign; PROS: Photoreceptor outer segments; PED: Pigment epithelium detachment.

*Pairwise p-values (Grade 1 vs 2, Grade 2 vs 3, Grade 1 vs 3) have been provided in variables having significant overall comparisons.

non-SHRM group (24 were on MRA drugs, 73 underwent PDT, 46 received anti-VEGF injections, 53 underwent STML/conventional laser, and 59 had combination therapy). The number of eyes developing concurrent MNV was higher in the SHRM group [25 eyes, 24.3% (16 eyes using ICG and 9 eyes using OCTA)], compared to the non-SHRM group [50 eyes, 12.5%(30 using ICG and 20 using OCTA)] (p = .01). Similarly, in terms of course of the disease, 36 eyes (34.9%) resolved, 25 eyes (24.3%) had recurrence, and 42 eyes (40.8%) had persistent SRF in the SHRM group; while 206 eyes (51.5%) resolved, 124 eyes (31%) had recurrence, and 70 eyes (17.5%) had persistence in the non-SHRM group. The overall distribution differed significantly between the 2 groups (p < .001). Pairwise comparison in individual disease courses demonstrated a significantly higher number of persistent cases in the SHRM group (adjusted p-value < 0.001). The mean number of recurrences was similar in the 2 groups (2.3 ± 1.5 and 2.1 ± 1.2, in SHRM and non-SHRM groups respectively, p = .7)

At the final visit, both groups showed significant improvement in BRVA (p < .001). Mean BRVA improved to 0.2 ± 0.3 logMAR (Snellen equivalent 20/30) in the SHRM group and 0.2 ± 0.3 logMAR (Snellen equivalent 20/25) in the non-SHRM group, with no significant difference between groups at the final visit (p = .67). Similarly, both groups demonstrated significant reductions in CMT, NSRD, and SFCT during follow-up (Table 2). However, final NSRD height (p < .001) was significantly higher in the SHRM group. At the end of follow-up, residual SRF was observed in 106 eyes (26.5%) in the non-SHRM group and in 47 eyes (45.6%) in the SHRM group (p < .001), of which 36 eyes (34.9%) also had residual SHRM. On comparison of eyes with or without residual (persistent or increased) SHRM at the end of follow-up, although the baseline BRVA was not significantly different (0.4 ± 0.3 and 0.4 ± 0.4 logMAR, respectively, p = .45), there was a significantly better vision in eyes with no residual SHRM (0.4 ± 0.4 and 0.1 ± 0.3 logMAR, respectively, p = .02). Among eyes with complete resolution, well-defined EZ loss at final visit (corresponding to areas of previous NSRD) was seen in 82 of 294 eyes (27.8%) in the non-SHRM group and in 25 of 56 eyes (44.6%) in the SHRM group (p = .01).

• **COMPARISON OF SHRM GRADES AND MORPHOLOGICAL CHANGES:** Out of all eyes with SHRM, 38 eyes (36.9%) had grade-1 SHRM, 55 (53.4%) had grade-2 SHRM, and 10 eyes had grade-3 SHRM. A higher number of patients had a history of steroid exposure in the Grade-2 SHRM group compared to the Grade-1 SHRM. Although the percent was high even in the Grade-3 group, the p-value did not reach statistical significance. In terms of imaging parameters, Grade-1 SHRM had significantly higher CMT (p = .003) and NSRD (p < .001) values compared to Grade-2 SHRM. There was no significant difference in other parameters (Table 1). At the end of follow-up, BRVA

TABLE 2. Ocular Parameters in All Groups At the Final Visit.

Parameter	Control Group (CSCR without SHRM) [n = 400]	P-value (compared to baseline)	Study Group (CSCR with SHRM) [n = 103]	P-value (compared to baseline)	p-value (SHRM versus non-SHRM groups)	Grade-1 SHRM [n = 38]	P-value (compared to baseline)	Grade-2 SHRM [n = 55]	P-value (compared to baseline)	Grade-3 SHRM [n = 10]	Grade-3 SHRM [n = 10]	Overall p-value among SHRM grades (ANOVA)
BRVA, logMAR	0.2 ± 0.3	<.001	0.2 ± 0.3	<.001	.67	0.2 ± 0.3	.008	0.2 ± 0.4	.04	0.2 ± 0.2	0.2	.87
CMT, microns	234.5 ± 84.4	<.001	226.4 ± 69.4	<.001	.26	225.8 ± 50.8	<.001	233.7 ± 74.6	<.001	189.3 ± 92.3	0.03	.23
NSRD height, microns	47.8 ± 82.1	<.001	52.7 ± 76.6	<.001	<.001	55.2 ± 91.4	<.001	54.2 ± 68.7	<.001	35.8 ± 60.9	0.03	.76
SFCT, microns	351.4 ± 90.1	<.001	371.7 ± 104.1	.03	.07	364.4 ± 104.2	.03	367.9 ± 97.8	.27	420.5 ± 133.6	0.9	.29

BRVA: Best recorded visual acuity; CMT: Central macular thickness; SFCT: Sub-foveal choroidal thickness; NSRD: Neurosensory detachment.

TABLE 3. Factors Affecting Subretinal Fluid Persistence At Final Visit and Change in Visual Acuity.

Logistic regression (Persistence of subretinal fluid as dependent variable)			
Variables	Odds ratio	95 % CI of OR	*p*-value*
Group (non-SHRM compared to SHRM group)	0.36	0.19 to 0.77	.001
Duration of symptoms	1	0.9 to 1.01	.55
Baseline BRVA (logMAR)	2.64	0.98 to 7.44	.06
Baseline RPE alteration area	1.13	1 to 1.29	.05
Simple compared to complex CSCR	1.42	0.78 to 2.58	.24
CMT at baseline	0.9	0.9 to 1	.6
Linear regression [Change in BRVA as dependent variable]			
Variables	**Regression co-efficient**	**95 % CI of OR**	***p*-value***
Age (years)	0.003	0.001 to 0.005	.003
Duration of symptoms	0.001	0.0004 to 0.003	.004
Baseline BRVA (logMAR)	−0.53	−0.61 to − 0.45	<.001
CMT at baseline	−0.0001	−0.0003 to 0	.06
Group (non-SHRM/SHRM group)	0.07	0.02 to 0.13	.01
Treatment after baseline (Laser compared to Observation)	−0.05	−0.11 to 0.001	.05
Persistent course (compared to resolution)	0.21	0.15 to 0.27	<.001
Recurrent course (compared to resolution)	0.07	0.02 to 0.13	.004

SHRM: Subretinal hyper-reflective material; PROS: Photoreceptor outer segment; BRVA: Best recorded visual acuity.

improved significantly in the Grade-1 and Grade-2 groups; CMT and NSRD reduced significantly in all groups; and SFCT reduced significantly in the Grade-1 SHRM group. There were no significant between-group differences at the final visit (Table 2). The proportion of eyes with persistence of SRF (39.4%, 43.6%, 30% respectively) was not significantly different in the 3 groups. However, there was a significant difference in the proportion of eyes with well-defined EZ loss (in resolved cases) in the area of past SRF ($p = .002$). Pairwise comparison showed a greater proportion of eyes with EZ loss in Grade 3 SHRM compared to Grade-1 (adjusted $p = .009$) and Grade-2 (adjusted $p = .009$). Four eyes (10.5%) in the Grade-1 SHRM group transformed to Grade-2, while 6 eyes (10.9%) in the Grade-2 SHRM group were seen to transform into Grade-3 SHRM at the last visit [median follow-up of 48 months (IQR 10 to 57.3 months)]. Eight eyes (7.8%) [2 eyes (20%) from Grade-3 and 6 eyes (10.3%) from Grade-2 SHRM group] were seen to have residual subretinal scar in the area of previous SHRM, by the end of follow-up [median follow-up of 4.6 (IQR 3.9 to 112 months)].

• **FACTORS AFFECTING PERSISTENCE AND VISUAL ACUITY CHANGE:** Logistic regression analysis showed that non-SHRM group status ($p = .001$) and lower RPE alteration area ($p = .05$) at baseline visit, were associated with lower odds of persistence of SRF. Similarly, in terms of improvement in BRVA, higher age ($p = .04$), higher duration of symptoms ($p = .004$), better baseline BRVA ($p < .001$), non-SHRM status ($p = .01$), observation (compared to laser) ($p = .05$), persistence of SRF ($p < .005$), and recurrence of SRF ($p = .004$), were associated with lesser BRVA improvement (Table 3).

DISCUSSION

While previous studies on SHRM in CSCR have primarily focused on cross-sectional observations or limited longitudinal cohorts, our study used a large, multicentric dataset to highlight distinct clinical patterns in eyes with SHRM compared to non-SHRM CSCR controls. At baseline, the SHRM group showed a significantly higher frequency of PROS irregularity, HRF within the PROS, DLS, and greater NSRD height. Although both groups demonstrated significant improvement in BRVA and NSRD during follow-up, NSRD height remained greater in the SHRM group at the final visit. SHRM presence and higher RPE alteration area at baseline were associated with a higher likelihood of disease persistence, whereas poorer baseline BRVA, younger age, lesser duration of symptoms, SHRM at baseline, laser treatment (compared to observation), and disease resolution (compared to persistence and recurrence), correlated with better visual recovery.

Pu et al. reported several distinguishing clinical and imaging characteristics in CSCR eyes with SHRM compared to those without, including higher choroidal vascularity index (CVI), greater NSRD height, presence of PED, more eyes with RPE defects, certain FAF patterns, and larger areas of choroidal vascular hyperpermeability (CVH).[12] Although our study did not assess CVI or CVH, we observed a significantly greater NSRD height

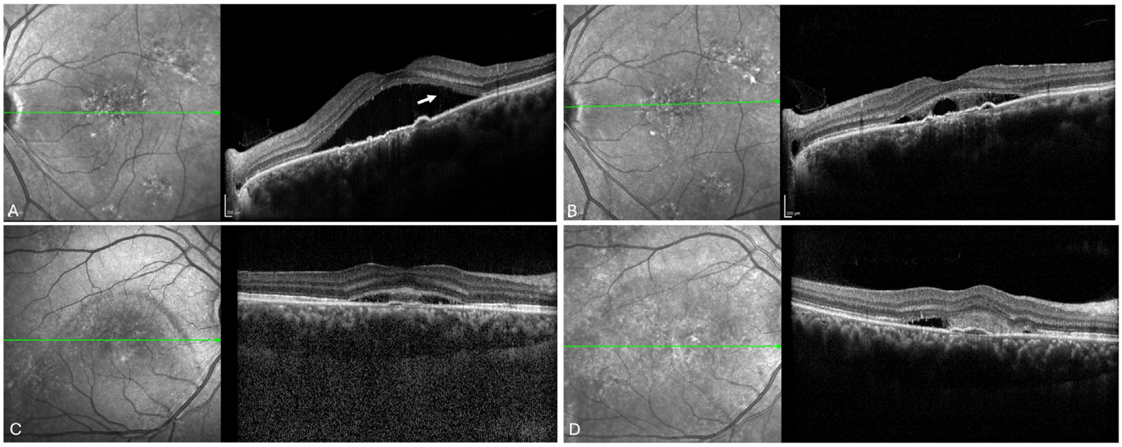

FIGURE 2. Examples showing (A) Central serous chorioretinopathy with Grade-1 subretinal hyper-reflective material (SHRM) (*white arrow shows the filamentous deposits*), that was treated with focal laser. (B) The subretinal fluid (SRF) reduced over a follow-up of 8 months, with an increase in the grade of SHRM. (C) A 44-year-old male presenting with CSCR with Grade-2 SHRM was observed after the baseline visit. After 6 months, the patient presented with a mild increase in SRF and SHRM grade (D).

in the SHRM group, supporting the notion of heightened choroidal activity in these eyes. Moreover, at the final follow-up, both NSRD and SFCT (although non-significant) remained higher in the SHRM group. When the SHRM group was further categorized by grade, the highest NSRD height was observed in Grade 1 SHRM. Interestingly, 10.5% of Grade 1 and 10.9% of Grade 2 cases showed progression to a higher grade both with resolution and an increase in SRF, suggesting that SHRM deposits may undergo structural organization over time (Figure 2). Additionally, although the overall frequency of prior steroid exposure did not differ significantly between SHRM and non-SHRM groups, higher proportions of steroid use were noted in Grade 2 ($p = .03$) and Grade 3 (not statistically significant) compared with Grade 1 SHRM. Whether this association reflects a causal role of increased choroidal permeability contributing to higher SHRM grades remains to be determined through further investigation.

In terms of visual prognosis, Pu et al. reported that the presence of SHRM in CSCR was associated with poorer visual outcomes in their cross-sectional analysis.[12] Our findings were consistent, as eyes with SHRM showed significantly worse baseline visual acuity compared with those without SHRM. However, in line with our earlier observations,[11] both groups demonstrated significant improvement in BRVA over longitudinal follow-up. Although the SHRM group continued to have a lower mean BRVA at the final visit, the difference was not statistically significant, suggesting that despite poorer vision at presentation, substantial visual recovery can occur over time. Regression analysis using change in BRVA as the dependent variable also showed that SHRM presence resulted in improvement in visual acuity. Also, lesser visual recovery was predicted by older age, higher duration of symptoms, observation at baseline (compared to laser), good baseline BRVA, and disease persistence/recurrence. These factors have been consistently recognized in earlier studies as key determinants of visual outcome in CSCR.[4-6]

A key aspect of CSCR management is addressing the recurrence and persistence of SRF. In our study, eyes in the SHRM group had a significantly higher rate of persistent SRF compared to the non-SHRM group. Multivariable analysis confirmed that the presence of SHRM remained a significant predictor for persistence of SRF, suggesting that SRF associated with SHRM may be more resistant to resolution. Whether this resistance is due to intrinsic differences in the properties of the subretinal fluid or reflects heightened choroidal activity leading to reduced fluid clearance remains unclear. Even in eyes achieving resolution, several structural changes were more pronounced in the SHRM group. We observed that EZ loss at final visit (corresponding to areas of previous SRF) was significantly more frequent in the SHRM group, with the highest frequency seen in Grade 3 SHRM. (Figure 3) Furthermore, 20% of eyes in Grade 3 had residual scar (Figure 4), indicating that this subgroup is prone to unfavorable structural outcomes, even after fluid resolution.

The exact nature of subretinal hyperreflective material (SHRM) in CSCR remains uncertain. While some authors attribute it to fibrin from the choroidal circulation [8,9] others suggest it represents shed photoreceptor elements.[10,11] Both mechanisms likely contribute. However, several imaging findings favor a predominant photoreceptor origin. These accumulations were frequently continuous with PROS (Figure 1B, *white arrow*), and typically exhibited broad attachments to the photoreceptor layer (Figure 1C).

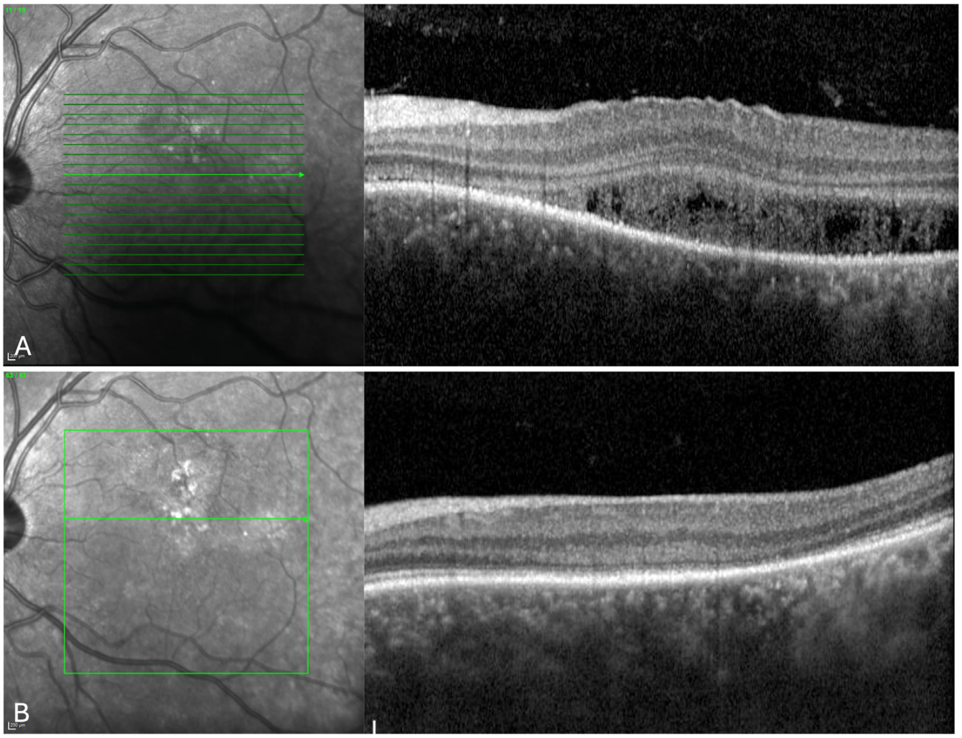

FIGURE 3. Example of a 46-year-old male presenting with Central serous chorioretinopathy and Grade-3 subretinal hyper-reflective material (A). The eye was treated with sub-threshold micropulse laser, which resulted in complete resolution of subretinal fluid (SRF). However, a large area of ellipsoid zone loss was seen at the site of the previous SRF (*white arrow*).

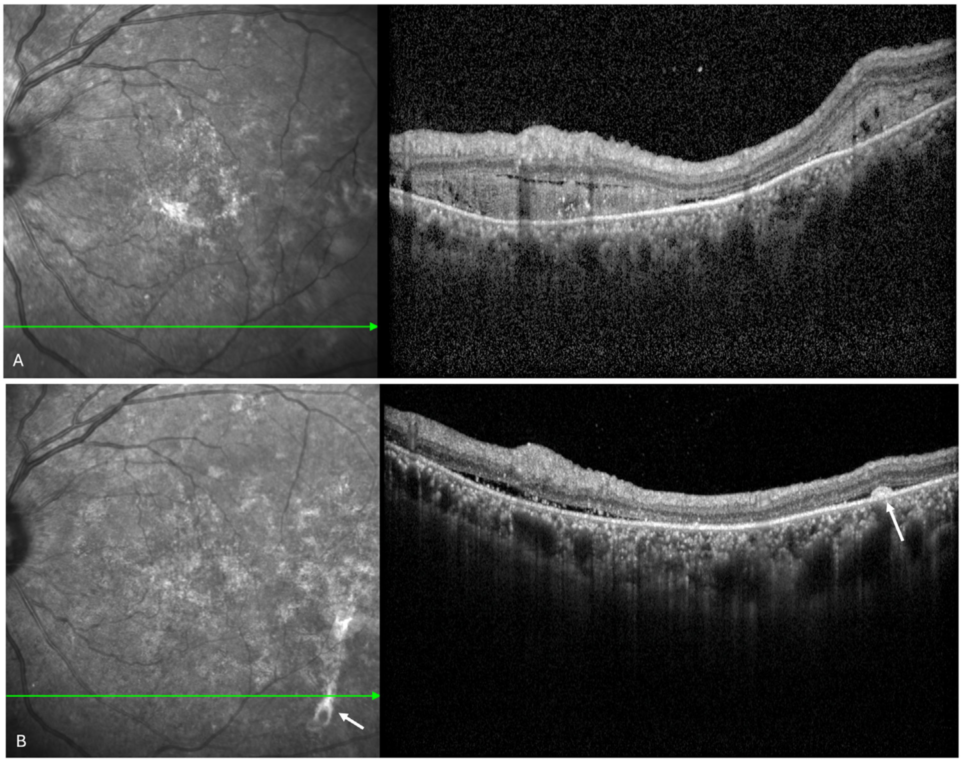

FIGURE 4. Example showing a case with Central serous chorioretinopathy and Grade-3 subretinal hyper-reflective material (SHRM) (A). The patient was treated with a focal laser. After 13 months, the subretinal fluid and SHRM had reduced, with the formation of a subretinal scar infero-temporally (*white arrow*).

A higher incidence of irregular PROS in the SHRM group further supports the possibility of photoreceptor shedding. Moreover, the presence of clear SRF spaces and the "vacuole sign" is against a purely choroidal source, as a fibrinous material would be expected to uniformly fill the detachment. The greatest NSRD height in Grade 1 SHRM and its progressive reduction in higher grades, along with conversion of lower to higher grades during follow-up (with increase or decrease of SRF), further indicates that SHRM formation/progression is not directly linked to SRF volume or active leakage. Nevertheless, imaging indicators of increased choroidal activity,[12] and their proximity to leakage sites suggest a possible additional choroidal contribution. Proteinaceous material from a hyperpermeable choroid may accumulate beneath the photoreceptors in a "stalactite-like" fashion, particularly around the leakage zone, which initiates a cascade involving elongation of PROS, migration of macrophages or other cellular elements (consistent with the higher frequency of PROS-HRF in SHRM eyes), and eventual breakdown of photoreceptor elements into fluorophore-rich by-products that contribute to the observed autofluorescence.

In addition to its retrospective design, a key limitation of this study was the absence of uniformly collected dye-angiography data and CVI analysis, both of which could have offered deeper insights into baseline disease severity. The differential availability of OCTA vs ICGA across centers could affect their sensitivities for MNV detection, as SHRM can attenuate the OCTA signal and mask underlying neovascularization. Additionally, the variability in imaging equipment across different facilities could have reduced the accuracy of the comparison. While grading, a manual delineation of the SHRM margins was performed instead of binarization, which could have introduced error. We acknowledge that SHRM grading may vary with the timing of the examination and fluctuations in SRF volume. Unlike the approach by Pu et al.[12], who correlated SHRM with angiographic leakage points, our standardized protocol evaluated SHRM in the foveal region and in areas of maximum accumulation, regardless of leakage location. While this approach allowed consistent assessment across all cases, including those without identifiable leakage or available angiography, it may not have captured the relationship between SHRM and specific sites of RPE dysfunction. Moreover, the area-based grading system employed in our study is reproducible, but it does not distinguish between SHRM of potentially varying compositions, such as fibrinous material vs shed photoreceptor elements. Future research could shed light on how these differences uniquely affect visual outcomes. Another limitation was the lack of intervening follow-up visits, which prevented assessment of the exact timing of SRF resolution or recurrence. Moreover, the uneven distribution of eyes across treatment groups limited our ability to evaluate treatment-specific effects on disease outcomes. Despite these constraints, this remains one of the largest longitudinal studies examining CSCR with SHRM and its clinical course over time.

In conclusion, CSCR eyes with SHRM demonstrated a higher frequency of PROS irregularity, hyperreflective foci within the PROS, DLS, and greater NSRD height compared to those without SHRM, findings consistent with earlier reports and indicative of increased choroidal activity. Although both groups showed significant improvement in BRVA and NSRD over time, the presence of SHRM was linked to greater disease persistence and a higher rate of EZ loss in resolved cases. These features may help refine disease characterization and may suggest that earlier or more intensive treatment might benefit this subgroup. Nonetheless, future prospective studies with balanced treatment allocation are needed to validate these observations.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Niroj Kumar Sahoo: Writing – original draft, Visualization, Validation, Resources. **Nasiq Hasan:** Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Ninan Jacob:** Formal analysis, Data curation. **Jessica Cao:** Formal analysis, Data curation. **Charles C. Wykoff:** Writing – review & editing, Resources. **Priya Shah:** Formal analysis, Data curation. **Panisa Singhanetr:** Formal analysis, Data curation. **Elizabeth J. Rossin:** Writing – review & editing, Resources. **Lorenzo Ferro Desideri:** Formal analysis, Data curation. **Felicia Hertkorn:** Formal analysis, Data curation. **Marion R. Munk:** Writing – review & editing, Resources. **Samer Khateb:** Writing – review & editing, Resources. **Jay Wang:** Formal analysis, Data curation. **Rahul N. Khurana:** Writing – review & editing, Resources. **Yusuf Ashfaq:** Formal analysis, Data curation. **Zachary Kroeger:** Writing – review & editing, Resources. **Michael Zhang:** Writing – review & editing, Resources. **Maurizio Battaglia Parodi:** Writing – review & editing, Resources. **Gabriele Piccoli:** Formal analysis, Data curation. **Stela Vujosevic:** Writing – review & editing, Resources. **Min Kim:** Writing – review & editing, Resources. **Carmen Antía Rodríguez-Fernández:** Formal analysis, Data curation. **Luis Arias Barquet:** Writing – review & editing, Resources. **Kent Small:** Writing – review & editing, Resources. **Paisan Ruamviboonsuk:** Formal analysis, Data curation. **Peranut Chotcomwongse:** Writing – review & editing, Resources. **Luiz H. Lima:** Writing – review & editing, Resources, Formal analysis, Data curation. **Adrian T. Fung:** Writing – review & editing, Resources. **Lihteh Wu:** Writing – review & editing, Resources. **Jay Chhablani:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization.

Acknowledgments: MICRoN Study Group: Nasiq Hasan, Arman Zarnegar, Carmen Antia, Yusuf Ashfaq, Luis Aria Barquet, Elodie Bousquet, Jessica Cao, Lisa Checchin, Peranut Chotcomwongse, Andrea Corletti, Lorenzo Ferro Desideri, Adrain T. Fung, Priyank Gandhi, Sunir Garg, Manjot Gill, Giulia Gregori, Felicia Hertkorn, Naoya Imanaga, Ninan Jacob, Samer Khateb, Rahul N Khurana, Min Kim, Hideki Koizumi, Zachary Kroeger, Timothy Lai, Luiz Lima, Marco Lupidi, Bita Momenaei, Marion R. Munk, Roselind Ni, Maurizio Battaglia Parodi, Gabriele Piccoli, Lorenzo Pili, Francisco Rodriguez, Elizabeth Rossin, Paisan Ruamviboonsuk, Niroj Kumar Sahoo, Stanley Saju, Priya Shah, Rufino Silva, Panisa Singhanetr, Kent Small, Lucia Sobrin, Carol Villafeurte, Stela Vujosevic, Jay Wang, Halit Winter, Lihteh Wu, Charles C. Wykoff, Glenn Yiu, Arman Zarnegar, Micheal Zhang and Jay Chhablani.
Declaration of competing interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.Funding Support: No funds, grants, or other support was received. Financial Disclosures: No financial disclosures. All authors attest that they meet the current ICMJE criteria for authorship.
Declaration of generative ai and ai-assisted technologies in the writing process: The authors declare that no utilization of any AI-based technology was done in the course of this work.

REFERENCES

1. Daruich A, Matet A, Dirani A, et al. Central serous chorioretinopathy: recent findings and new physiopathology hypothesis. *Prog Retin Eye Res*. 2015;48:82–118 2015/09/01/. doi:10.1016/j.preteyeres.2015.05.003.
2. Daruich A, Matet A, Marchionno L, et al. Acute Central serous chorioretinopathy: factors influencing episode duration. *Retina*. 2017;37(10):1905–1915. doi:10.1097/iae.0000000000001443.
3. Parajuli A, Joshi P. Factors influencing the episode duration and the anatomical and functional outcome in cases of acute central serous chorioretinopathy. *BMJ Open Ophthalmol*. 2020;5(1):e000540. doi:10.1136/bmjophth-2020-000540.
4. Sahoo NK, Ong J, Selvam A, et al. Longitudinal follow-up and outcome analysis in central serous chorioretinopathy. *Eye (Lond)*. 2023;37(4):732–738. doi:10.1038/s41433-022-02044-z.
5. Loo RH, Scott IU, Flynn Jr HW, et al. Factors associated with reduced visual acuity during long-term follow-up of patients with idiopathic Central serous chorioretinopathy. *Retina*. 2002;22(1). doi:10.1097/00006982-200202000-00004.
6. Da Pozzo S, Iacono P, Arrigo A, Battaglia Parodi M. The role of imaging in planning treatment for central serous chorioretinopathy. *Pharmaceuticals*. 2021;14(2). doi:10.3390/ph14020105.
7. Feo A, Stradiotto E, Sacconi R, Menean M, Querques G, Romano MR. Subretinal hyperreflective material in retinal and chorioretinal disorders: a comprehensive review. *Surv Ophthalmol.*. 2024;69(3):362–377 2024/05/01/. doi:10.1016/j.survophthal.2023.10.013.
8. Ie D, Yannuzzi LA, Spaide RF, Rabb MF, Blair NP, Daily MJ. Subretinal exudative deposits in central serous chorioretinopathy. *Br J Ophthalmol*. 1993;77(6):349–353. doi:10.1136/bjo.77.6.349.
9. Yu J, Jiang C, Xu G. Study of subretinal exudation and consequent changes in acute central serous chorioretinopathy by optical coherence tomography. *Am J Ophthalmol*. 2014;158(4):752–756 e2. doi:10.1016/j.ajo.2014.06.015.
10. Maruko I, Iida T, Ojima A, Sekiryu T. Subretinal dot-like precipitates and yellow material in central serous chorioretinopathy. *Retina*. 2011;31(4):759–765. doi:10.1097/IAE.0b013e3181fbce8e.
11. Sahoo NK, Govindhari V, Bedi R, et al. Subretinal hyperreflective material in central serous chorioretinopathy. *Indian J Ophthalmol*. 2020;68(1):126–129. doi:10.4103/ijo.IJO_265_19.
12. Pu J, He G, Zhang X, et al. Multimodal imaging biomarkers of subretinal hyperreflective material accumulation in Central serous chorioretinopathy. *Photodiagnosis Photodyn Ther*. 2025:104595. doi:10.1016/j.pdpdt.2025.104595.
13. Hasan N, Zarnegar A, Jacob N, et al. Clinical characteristics and progression of pachychoroid macular atrophy in central serous chorioretinopathy. *Ophthalmol Retina*. 2025;9(10):984–993 2025/10/01/. doi:10.1016/j.oret.2025.04.005.
14. Chhablani J, Cohen FB, Aymard P, et al. Multimodal imaging-based central serous chorioretinopathy classification. *Ophthalmol Retina*. 2020;4(11):1043–1046. doi:10.1016/j.oret.2020.07.026.