Demography, Clinical Characteristics and Long-Term Outcomes of Central Serous Chorioretinopathy in Women. MICRoN Report Number Fourteen

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• PURPOSE: To evaluate the characteristics and longitudinal outcomes of chronic central serous chorioretinopathy (CSCR) in women compared to an age-matched cohort of men with CSCR.

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

• PARTICIPANTS: This study included 426 eyes (213 women and 213 age-matched men) with a diagnosis of CSCR.

• METHODS: Baseline and final best-recorded visual acuity (BRVA) and multimodal imaging parameters such as area of retinal pigment epithelium (RPE) alterations, choroidal macular thickness (CMT), sub-foveal choroidal thickness (SFCT), subretinal fluid (SRF), pigment epithelium detachment (PED), double layer sign (DLS), hyperreflective dots (HRD), as well as the presence of choroidal neovascularization (CNV) and subretinal hyperreflective material (SHRM) were assessed. Regression analysis was used to evaluate baseline predictors of final visual acuity.

• MAIN OUTCOME MEASURES: Longitudinal changes in BRVA and imaging parameters in men and women stratified for age; factors affecting subretinal fluid (SRF) persistence, and change in BRVA.

• RESULTS: A total of 426 eyes (213 women and 213 age-matched men) with CSCR were analyzed. Women showed better BRVA at presentation (0.25 ± 0.24 vs 0.31 ± 0.35 logMAR; $P = .05$), and exhibited smaller areas of RPE alterations (2.37 ± 2.64 vs 1.59 ± 1.55 disc areas; $P = .003$), less frequent peripapillary RPE changes (13.6% vs 7.5%; $P < .001$), shorter DLS (1353.9 ± 970.2 vs 1071.6 ± 888.7 μm; $P = .039$), and smaller PEDs (644.9 ± 546.4 vs 442.1 ± 278.9 μm; $P = .022$). During follow-up, women exhibited higher rates of complete SRF resolution ($P = .001$) while persistence and the number of recurrences were significantly more common in men ($P = .006$ and $P = .02$, respectively). Logistic regression analysis revealed that persistent SRF was independently associated with complex CSCR, male gender, baseline PROS irregularities, worse BRVA, SHRM, and CNV, while PDT was protective.

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• CONCLUSION: **Women had better visual outcomes and more favorable structural evolution while men tended to present with more complex anatomical alterations and experience higher rates of persistent SRF.**

INTRODUCTION

Central serous chorioretinopathy (CSCR) is a chorioretinal disorder characterized by serous detachment of the neurosensory retina with or without a pigment epithelial detachment (PED).[1] Although the natural history of the disease is favorable, with most eyes resolving spontaneously, some patients tend to develop a chronic disease, which results in a recurrent or persistent course that can lead to permanent vision loss.[2,3] Even though risk factors for CSCR including male gender, corticosteroid use, psychological stress, and pregnancy have been described [4,5], its associations with gender have not been fully investigated.[6] Quantitative measurements of the choroid and retina are known to differ by gender in healthy eyes.[7] Several hypotheses have been proposed to explain these divergences. A leading theory implicates dysregulation of the mineralocorticoid pathway in the pathogenesis of CSCR.[8] From this perspective, hormonal differences may contribute to gender-specific disease behavior; in particular, progesterone, a natural antagonist of the mineralocorticoid receptor, may confer a degree of protection in women by delaying onset or mitigating disease severity. [9] In contrast, genetic predisposition appears to play a lesser role in explaining gender differences.[10] Studies evaluating risk variants such as complement factor H (CFH) have not demonstrated meaningful disparities in allele frequencies between male and female patients.[11] While these observations provide valuable insights, they remain largely fragmented, focusing on isolated imaging characteristics rather than offering a comprehensive assessment of gender-related differences in disease severity, progression, and prognosis. The recent multimodal imaging–based classification of CSCR offers a structured framework to categorize some gender-specific differences in CSCR.[6] However, this work did not include long-term longitudinal follow-up, limiting insights into progression and long-term sequelae. In this study, we aim to address this gap by evaluating the functional outcomes and morphological changes, comparing men vs women during long-term follow-up. Such information may ultimately support the development of patient-specific treatment strategies for CSCR.

METHODS

This was designed as a retrospective, multicenter center study that was part of the Macula Society CSCR project-Macula Society International CSCR Research Network (MICRoN). The patients recruited were affected by acute or chronic CSCR. The study adhered to the tenets of the Declaration of Helsinki and was approved by the local institutional review boards or Ethics Committee of each participating center. Data sharing agreements among collaborators and the procedures for demographic, clinical, and imaging data collection and analysis have been detailed in prior publications of the project.[12] Inclusion criteria consisted of: (1) women older than 18 years, (2) a confirmed diagnosis of CSCR, and (3) presence of follow-up imaging (in patients with bilateral disease meeting this criterion, only the right eye was analyzed).

Exclusion criteria were: (1) eyes with inadequate or incomplete records, or (2) coexisting retinal diseases, such as high myopia, diabetic retinopathy, glaucomatous optic neuropathy or retinal vasculopathies. Men were selected from the multicentric cohort and were age-matched using a nearest-neighbor matching algorithm.

Baseline demographic and systemic information was obtained, including age, gender, medical comorbidities, smoking status, symptom duration, and prior treatment for CSCR. Gender was recorded as gender assigned at birth (male or female) based on medical records. Baseline and follow-up best recorded visual acuity (BRVA) was documented and was expressed in logMAR. The groups were further stratified into those $\geq$ 50 years and $<$ 50 years, for sub-group analysis. CSCR was categorized as either acute or chronic based on the duration of serous retinal detachment (SRD); eyes with SRD persisting for more than 3 to 6 months are described as having chronic CSCR.[13] Disease course was classified into three categories based on longitudinal OCT findings: resolution was defined as complete disappearance of subretinal fluid (SRF) with no evidence of recurrence at the final follow-up visit; recurrence was defined as complete SRF resolution followed by reappearance of SRF at any time during the follow-up period; and persistence was defined as continuous presence of SRF from baseline through the final follow-up visit.

Imaging data were also collected at both baseline and final visits, including fundus autofluorescence (FAF), optical coherence tomography (OCT), and fluorescein angiography (FFA). FAF assessment included: (1) identifying gravitational tracts; (2) assessing peripapillary changes in the retinal pigment epithelium (RPE); (3) measuring the extent of RPE alterations, quantified in disc areas (DA) including both hypo and hyperautofluorescent lesions; and (d) distinguishing between focal and multifocal RPE changes. CSCR cases were further categorized based on the degree of RPE involvement and whether multifocal

lesions were present. Simple CSCR referred to cases where the disease was unifocal and confined to two or fewer DA of RPE alteration, while complex CSCR included cases with multifocal changes or lesions extending beyond 2 DA.[13] OCT parameters assessed included central macular thickness (CMT) as well as the height and width of the neurosensory retinal detachment (NSRD). CMT was measured automatically from the macular cube scan produced 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. Pigment epithelial detachments (PEDs) were detected on OCT as dome-shaped elevations of the RPE. 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.[14] The double-layer sign (DLS) was noted when shallow, irregular PEDs with internal hyperreflective, hyporeflective, or mixed signals were observed. [15] The presence of hyperreflective dots (HRDs) in the choroidal stroma and irregularities in the photoreceptor outer segment (PROS) layer were also recorded. Choroidal measurements included SFCT, Haller vessel diameter, and the thickness of the inner choroid. Subfoveal choroidal thickness (SFCT) was measured 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 determined by identifying the largest choroidal vessel lumen within 500 μm of the foveal center. The inner choroid, which includes the choriocapillaris and Sattler's layer, was measured from the inner margin of the largest Haller vessel to the outer surface of the Bruch's membrane.[16] Detection of choroidal neovascularization (CNV) was based on findings from OCT angiography, FFA or indocyanine green angiography (ICG-A), when available. All images were meticulously analyzed by an experienced retina specialist (NH) and 10% of the sample images were independently reviewed and validated by another masked grader (AZ) to ensure accuracy and consistency. In case of disagreements, the measurements and segmentations were adjudicated by the senior author (JC).

• **STATISTICAL ANALYSIS:** All analyses were conducted using R Studio (version 2025.09.1 + 40), R Foundation for Statistical Computing, Vienna, Austria. The groups were matched (1:1 nearest neighbor matching) by age to minimize baseline differences. 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, linear regression analysis was performed. Inter-class coefficient was calculated between the masked graders (NH and AZ) for thickness measurements including CMT and SFCT and lesions (NSRD height, PED, DLS) of randomly selected 10% of the OCT volumes from the cohort.

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 co-efficient with 95% CIs (CI). The matching variables (age and duration of symptoms) were included as covariates in the model to adjust for potential confounding. Additionally, duration of follow-up was included as a covariate to account for differences in observation time between participants. A two-sided $P < .05$ was considered statistically significant.

RESULTS

A total of 426 patients [213 women and 213 age-matched men] with CSCR were analyzed. The mean age of the cohort was 50.2 ± 10.8 years and the median duration of symptoms was 2 months for women (IQR 1 to 6 months) and 2 months for men (IQR 0.52 to 7 months). A history of previous treatment was present in 59 (27.7%) women and 51(23.9%) men. Baseline characteristics of the two groups has been summarized in Table 1 .

The overall male cohort consisted of 348 CSCR patients derived from a multicenter dataset. The mean age was 46.8 ± 11.8 years, with a baseline mean BRVA of 0.29 ± 0.32 logMAR. Overall, 42% of patients presented with a simple CSCR phenotype. At presentation, the mean central macular thickness (CMT) was 348.9 ± 156.7 μm, and the mean neurosensory detachment (NSD) was 191.1 ± 141.0 μm. Regarding initial management, 210 patients (60.3%) were observed, 30 (8.6%) underwent photodynamic therapy (PDT), 47 (13.5%) received subthreshold micropulse laser (SMPL), 38 (11%) were treated with anti-VEGF injections, and 23 (6.6%) underwent combination therapy. During follow-up, 85 patients (24.4%) experienced recurrence and 80 (23.0%) demonstrated persistent subretinal fluid, while the remaining cases achieved complete resolution. For the 10% of volumes that were analyzed by a masked second grader (AZ) the ICC was 0.97 (95% CI: 0.95-0.98, $P < .001$).

• **COMPARISON BETWEEN THE WOMEN AND MEN GROUPS:** At presentation, women had better BRVA than men (0.25 ± 0.24 logMAR, Snellen equivalent of 20/32 vs 0.31 ± 0.35 logMAR, Snellen equivalent of 20/40, respectively; $P = .05$). In addition, simple CSCR

TABLE 1. Baseline Characteristics of All Groups

Parameter	CSCR Women [$n = 213$] Baseline	CSCR Men [$n = 213$] Baseline	Overall *P*-Value* Between Women and Men
Age, years	50.2 ± 10.8	50.2 ± 10.8	1
Systemic co-morbidities(%)	94 (44.1%)	127 (59.6%)	.018
Smoking (%)	25(11.7%)	48 (22.5%)	.004
Corticosteroid use(%)	59 (27.7%)	57 (26.8%)	.82
Duration of symptoms [Median (IQR)], months	2 [1 to 6]	2 [0.52 to7]	.09
BRVA, logMAR	0.25 ± 0.24	0.31 ± 0.35	.05
Simple CSCR (%)	127 (59.6%)	99(46.5%)	.04
Area of RPE alterations, disc areas	1.59 ± 1.55	2.37 ± 2.64	.003
Gravitational tract (%)	9 (4.2%)	11 (5.2%)	.009
Peripapillary RPE alterations (%)	16 (7.5%)	29 (13.6%)	<.001
OCT			
CMT, microns	335.9 ± 125.1	334.4 ± 143.7	.90
Simple	332.82 ± 147.14	326.46 ± 162.8	.80
Complex	334.86 ± 108.37	344.66 ± 138.1	.55
NSRD height, microns	180.0 ± 164.1	182.9 ± 155.8	.86
Simple	163.13 ± 146.6	180.29 ± 164.33	.45
Complex	194.30 ± 186.62	191.76 ± 159.62	.93
Irregular PROS (%)	158 (74.2%)	151(70.9%)	.32
Simple	92 (58.2%)	71 (47.02%)	.48
Complex	66 (41.7%)	80 (52.98%9	.52
HRD in choroidal stroma (%)	52 (24.4%)	54 (25.3%)	.82
Simple	20 (38.46%)	22 (40.74%)	.8
Complex	32 (61.54%)	32 (59.26%)	.9
DLS (%)	93 (43.7%)	93 (43.7%)	.86
Simple	25 (26.88%)	32 (34.41%)	
Complex	68 (73.12%)	61 (65.59%)	
Length of DLS, microns	1071.6 ± 888.7	1353.9 ± 970.2	.039
Simple	831.59 ± 495.48	1180.46 ± 1042.89	.04
Complex	1507.72 ± 1268.6	1499 ± 931.37	.97
Max height of DLS, micron	48.3 ± 20.1	46.3 ± 19.6	.49
Simple	49.4 ± 20.4	42.8 ± 15.99	.08
Complex	48.38 ± 22.94	49.09 ± 23.1	.89
SFCT, microns	363.6 ± 95.1	375.9 ± 113.7	.23
Simple	356.0 ± 92.2	365.2 ± 112.7	.50
Complex	385.56 ± 100.34	390.43 ± 118.95	.78
Haller vessel thickness, microns	265.2 ± 92.4	280.1 ± 100.7	.05
Simple	259.8 ± 92.05	275.03 ± 99.34	.24
Complex	271.04 ± 102.18	287.37 ± 105.07	.37
Inner choroidal thickness, microns	95.6 ± 45.9	99.4 ± 53.6	.21
Simple	94.61 ± 63.40	94.80 ± 52.76	.98
Complex	107.26 ± 90.80	103.64 ± 54.03	.77
Pachyvessels (present) (%)	144 (67.61%)	164 (77%)	.74
Simple	58 (40.28%)	67 (40.85%)	.8
Complex	86 (59.72%)	97 (59.15%)	.57
Number of PEDs	1.9 ± 2.8	1.4 ± 1.1	.31
Simple	1.22 ± 0.90	1.16 ± 0.62	.8
Complex	2.95 ± 4.08	1.75 ± 1.38	.23
Maximum height of PEDs, microns	111.8 ± 70.0	131.7 ± 95.8	.24
Simple	95.9 ± 56.4	154 ± 113.2	.03
Complex	114.17 ± 75.17	127 ± 81.2	.59
Maximum width of PEDs, microns	442.1 ± 278.9	644.9 ± 546.4	.022
Simple	358.2 ± 197.0	629 ± 478.8	.02
Complex	490.11 ± 317.4	693.1 ± 638.8	.2
SHRM	7 (3.3%)	5 (2.4%)	<.001

(*continued on next page*)

TABLE 1. (*continued*)

Parameter	CSCR Women [$n = 213$] Baseline	CSCR Men [$n = 213$] Baseline	Overall *P*-Value* Between Women and Men
Simple	5 (71.43%)	2 (40%)	<.001
Complex	2 (28.57%)	3 (60%)	.01
CNV after baseline	32 (15%)	39 (18%)	.36
Simple	13 (40.63%)	17 (43.59%)	.93
Complex	19 (59.38%)	22 (56.41%)	.22

CSCR: Central serous chorioretinopathy; BRVA: Best recorded visual acuity; 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, HRF: Hyperreflective foci; CNV: choroidal neovascularization, SHRM: Subretinal hyperreflective material.
*Pairwise *P*-values.

was more frequent in women (59.6%; $P = .04$) and women exhibited smaller areas of RPE alterations (1.59 ± 1.55 vs 2.37 ± 2.64 disc areas respectively; $P = .003$), lower frequency of peripapillary RPE changes (7.5% vs 13.6% respectively; $P < .001$), shorter DLS (1071.6 ± 888.7 vs 1353.9 ± 970.2 μm respectively; $P = .039$), and narrower PEDs (442.1 ± 278.9 vs 644.9 ± 546.4 μm respectively; $P = .022$) compared to men. Central macular thickness (CMT), subfoveal choroidal thickness (SFCT), inner choroidal thickness, Haller vessel thickness, and pachyvessel prevalence were comparable between genders (Table 1).

• **COMPARISON BETWEEN THE AGE LESS THAN 50 AND THE AGE EQUAL TO OR MORE THAN 50 YEARS COHORTS:** Age-stratified analysis showed that baseline BRVA was better in females < 50 years (0.20 ± 0.22 logMAR, Snellen equivalent 20/32), compared to men < 50 years (0.28 ± 0.34 logMAR, Snellen equivalent 20/40) ($P = .031$). In terms of imaging parameters, men < 50 years showed a greater extent of RPE alterations ($P = .003$), PROS irregularities ($P = .003$) and maximum width of PEDs ($P = .05$). Among patients ≥ 50 years, females were more likely to present with simple CSCR (73.8% vs 45%, $P = .003$), while peripapillary RPE alterations ($P = .029$) as well as the length of DLS ($P = .005$), the maximum width of PED ($P = .04$), and the overall amount of RPE alterations ($P = .02$) were more common in men ≥ 50 years. (Table 2)

Women were followed for a median of 19.5 months (IQR 8 to 60 months) compared to 27 months for men (IQR 8.25 to 58.75 months). A total of 94 (44%) eyes in women and 81 eyes (37.9%) in men received treatment after the baseline visit. Among women group, 37 eyes (17.4%) received Subthreshold Micro pulse Laser (SMPL), 29 eyes (13.6%) Photodynamic Therapy (PDT), 17 eyes (8%) anti-VEGF injections and 11 eyes (5.2%) had combination therapy. For men, 37 eyes (17.4%) received SMPL, 13 eyes (6.1%) underwent PDT, 24 eyes (11.3%) received anti-VEGF injections and 7 eyes (3.3%) had combination therapy. Among patients managed with observation only ($n = 245$), 120 were females (56%) and 133 were males (62.1%). In this subgroup, females showed a significantly greater mean BRVA change compared with males (−0.07 ± 0.23 vs 0.02 ± 0.30; $P = .007$). No significant gender differences were observed in the recurrences ($P = .333$) or regarding the persistence of SRF ($P = .09$).

• **FOLLOW-UP CHANGES:** In women, 121 (56.8%) eyes resolved, 69 eyes (32.4%) had recurrence, and 23 eyes (10.8%) had persistent SRF while in men 109 eyes (51.2%) resolved, 58 eyes (27.2%) had recurrence, and 46 eyes (21.6%) had persistence (overall $P = .02$). Pairwise comparison in individual disease courses demonstrated a significantly higher number of persistent cases in the male group over 50 (adjusted $P = .006$).

At the final visit women achieved better BRVA than men (0.18 ± 0.23 logMAR, Snellen equivalent 20/32 vs 0.29 ± 0.45 logMAR, Snellen equivalent 20/40; $P = .002$). Similarly, in women < 50 years there was a significant improvement in mean BRVA (0.2 ± 0.22 logMAR, Snellen equivalent 20/30, $P = .048$), whereas no significant change was observed in men of the same age group, $P = .039$. No significant difference in the incidence of CNV after baseline was observed between women and men, both in the group under 50 years ($P = .29$) and in the group over 50 years ($P = .28$).

Among group over 50 years, BRVA improvement remained significant in women ($P = .005$) an even more pronounced gender-related difference ($P < .001$). The presence of DLS and the DLS length decreased significantly in women < 50 years ($P < .001$ and $P = .040$, respectively) and in women ≥ 50 years ($P = .04$), while a moderate reduction of DLS was present in men under 50 years ($P = .049$).

NSRD height showed a highly significant reduction in women under 50 ($P < .001$) while in groups over 50 years, the reduction was significant in both women ($P = .002$) and men ($P < .001$). Finally, subfoveal choroidal thickness (SFCT) did not show significant changes in subjects < 50 years. In women ≥ 50, SFCT significantly decreased ($P = .016$), whereas men over 50 showed no significant

TABLE 2. Baseline Characteristics of the Age-Stratified Groups

Parameter	CSCR Women < 50 [*n* = 109] Baseline	CSCR Men < 50 [*n* = 113] Baseline	*p*-Value	CSCR Women ≥ 50 Baseline [*n* = 104]	CSCR Men ≥ 50 Baseline [*n* = 100]	*P*-Value
Age, years	41.9 ± 6.6	42.2 ± 6.2	.3	59 ± 6.7	59.3 ± 6.9	.4
Systemic co-morbidities(%)	34 (31,2%)	55 (48.7%)	.009	60 (57.7%)	72 (72%)	.04
Smoking (%)	11 (10.1%)	18 (15.9%)	.09	14 (13.5%)	30 (30%)	.006
Duration of symptoms [Median (IQR)], months	2 [0.86 to 6]	1.45 [0.75 to 6]	.18	3 [1 to 6]	2 [0.7 to 6]	.11
Ocular parameters						
BRVA, logMAR	0.20 ± 0.22	0.28 ± 0.34	.031	0.29 ± 0.25	0.33 ± 0.35	.16
Simple CSCR (%)	56 (51.4%)	54 (52%)	.31	71(73.8%)	45 (45%)	.003
Area of RPE alterations, disc areas	1.65 ± 1.69	2.15 ± 1.56	.003	1.5 ± 1.4	2.5 ± 2.3	.027
Gravitational tract (%)	5 (5.4%)	8 (9%)	.21	4 (4.16%)	3 (3%)	.14
Peripapillary RPE alterations (%)	9 (9.8%)	14 (15.8%)	.16	7 (7.2%)	15 (15%)	.029
OCT						
CMT, microns	336.7 ± 134.5	351.6 ± 137.9	.21	335.0 ± 115.07	314.8 ± 148.11	.13
NSRD height, microns	190.14 ± 137.2	194.5 ± 168.3	.42	157.2 ± 112.59	156.0 ± 130	.47
Irregular PROS (%)	79 (86.1%)	80(90.4%)	.28	79(82.2%)	71 (71%)	.42
HRF in PROS (%)	27 (29.4%)	34 (38.4%)	.42	25(26%)	20 (20%)	.05
DLS (%)	40 (43.65)	48 (54.2%)	.23	53(55.1%)	45 (45%)	.17
Length of DLS, microns	1096.2 ± 1159.7	1256.5 ± 1052.7	.24	1052.4 ± 614.1	1459.8 ± 876.6	.005
Max height of DLS, micron	46.19 ± 17.0	46.2 ± 19.43	.49	50.0 ± 23.34	46.35 ± 20.05	.20
SFCT, microns	386.9 ± 97.69	403.8 ± 102.84	.10	339.0 ± 86.24	344.2 ± 117.57	.36
Haller vessel thickness, microns	283.4 ± 95.4	301.7 ± 97.5	.07	255.2 ± 85.5	245.9 ± 93.1	.23
Inner choroidal thickness, microns	97.5 ± 44.3	104.3 ± 56.4	.16	93.9 ± 49.9	93.6 ± 47.6	.48
Pachyvessels (present) (%)	78 (85%)	98 (86.7%)	.18	66(63.5%)	66 (66%)	.32
Number of PEDs	1.7 ± 2.51	1.6 ± 0.67	.40	2.1 ± 3.3	1.4 ± 1.3	.21
Maximum height of PEDs, microns	122.8 ± 74.6	135.8 ± 98.8	.28	90.6 ± 56.4	126.7 ± 93.9	.14
Maximum width of PEDs, microns	445.5 ± 299.5	621.7 ± 516.8	.05	435.0 ± 240.9	674.1 ± 592.1	.04
SHRM	2(1.8%)	3(2.7%)	.34	5(4.8%)	2(2%)	.08
CNV after baseline	8 (7.3%)	11 (9.7%)	.29	24(23.1%)	27(27%)	.28

CSCR: Central serous chorioretinopathy; BRVA: Best recorded visual acuity; 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; HRF: hyperreflective foci, CNV: choroidal neovascularization, SHRM: Subretinal hyperreflective material.
*Pairwise *P*-values.

variation. No gender-related differences were observed in the ≥ 50 group. (Table 3)

At the end of follow-up, residual SRF was observed in 69 eyes (32.3%) in the female group, 31 (28.4%) in women under 50 and 38 (36.5%) in women over 50; residual SRF was observed in 93 eyes (43.7%) between the male group, 46 (21.5%) in men under 50 and 47(47%) in men over 50 ($P = .12$).

• **FACTORS AFFECTING PERSISTENCE OF SUBRETINAL FLUID:** The logistic regression analysis identified several independent predictors significantly associated with the outcome.

Patients in the complex group exhibited a higher odd of persistence of SRF compared to those in the simple group, in the univariate analysis (OR = 1.93; 95% CI: 1.28–2.91; $P = .002$). Male gender and worse baseline BRVA (higher logMAR) were also associated with an increased risk of persistent subretinal fluid (OR = 1.62; 95% CI: 1.09–2.40; $P = .017$ and OR = 2.24; 95% CI: 1.16–4.34; $P = .017$, respectively).

Moreover, baseline PROS irregularities significantly predicted SRF persistence, nearly doubling the odds in both the univariate and multivariate analysis (OR = 1.93; 95% CI: 1.21–3.07; $P = .006$ OR: 2.24; 95% CI: 1.0 to 5.01; $P = .05$ respectively) as well as the presence of SHRM at baseline (OR = 1.64; 95% CI: 1.10–2.45; $P = .016$).

In addition, both in the univariate and multivariate analysis PDT treatment was associated with significantly lower odds of SRF persistence (OR = 0.42; 95% CI: 0.18–0.99; $P = .04$) using observation as the reference. Worse baseline BRVA (OR 2.24, 95% CI 1.16–4.34; $P = .017$), longer symptom duration (OR 1.03 per month, 95% CI 1.00–1.06; $P = .032$), and development of CNV after baseline (OR 1.75, 95% CI 1.04–2.92; $P = .033$) were also significantly linked to higher SRF persistence (Table 4).

TABLE 3. Ocular Parameters in All Groups At the Final Visit

Parameter	FU Women $N = 213$	FU men $N = 213$	Overall *P*-Value (Compared to baseline)	FU Women < 50 $N = 109$	*P*-Value (Compared to baseline)	FU Men < 50 $N = 113$	*P*-Value (Compared to baseline)	*p*-value FU men vs women < 50	FU Women ≥ 50 $N = 104$	*P*-Value (Compared to baseline)	FU men ≥ 50 $N = 100$	*P*-Value (Compared to baseline)	*P* Value men vs women ≥ 50
BRVA, logMAR	0.18 ± 0.23	0.29 ± 0.45	0.002	0.15 ± 0.22	.048	0.23 ± 0.45	.22	.039	0.20 ± 0.25	.005	0.35 ± 0.44	.37	.0019
DLS	84(39.4%)	96(45.1%)	0.34	34 (31.1%)	<.001	48(42.4%)	.049	.35	50(48.1%)	.37	48(48%)	.33	<.001
Length of DLS	1071.6 ± 888.7	1353.9 ± 970.2	0.039	1096.2 ± 1159.7	.040	1370.5 ± 796.35	.24	.011	1281.8 ± 751	.04	1629.9 ± 923.8	.18	.022
NSRD height, microns	104.4 ± 9.2	92.7 ± 65.4	0.38	113.41 ± 68.8	<.001	93.23 ± 65.5	.07	.18	96.97 ± 120.4	.002	87.2 ± 67.6	<.001	.30
SFCT, microns	337.4 ± 101.8	357.5 ± 103.9	0.057	362.3 ± 111.9	.066	385.3 ± 95.28	.08	.037	313.7 ± 83.7	.016	325.9 ± 104.5	.12	.18

FU: Follow-up; BRVA: Best recorded visual acuity; DLS: double-layer sign; SFCT: Sub-foveal choroidal thickness; NSRD: Neurosensory detachment.

• **FACTORS ASSOCIATED WITH CHANGES IN VISUAL ACUITY:** A linear regression model was used to assess predictors of improvement in BRVA. Several anatomical and clinical factors at baseline correlated with worse functional recovery. Greater baseline CMT was associated with reduced visual improvement ($B = –0.11$; 95% CI, –0.004 to –0.12; $P = .023$), as was poorer baseline BRVA ($B = –0.28$; 95% CI, –0.38 to –0.19; $P < .001$), PROS irregularities ($B = –0.10$; $P = .03$) and baseline HRD in stroma ($B = –0.14$; $P = .005$). Eyes with a persistent course of fluid demonstrated significantly less improvement ($B = –0.18$; 95% CI, –0.17 to –0.04; $P = .002$) both in the univariate and multivariate analysis. Interestingly, gender itself did not emerge as an independent predictor of BRVA improvement in either the univariable or multivariable linear regression analyses ($P > .05$). Longer symptom duration was associated with less improvement in BRVA in both univariable and multivariable analyses ($P = .002$ and $P = .01$, respectively) (Table 4).

DISCUSSION

While previous studies on women in CSCR primarily focused on cross-sectional observations or limited longitudinal cohorts, our study used a large, multicentric dataset to highlight distinct clinical patterns in women compared to age-matched CSCR men.

At presentation, women demonstrated better visual acuity than men, consistent with earlier studies reporting milder baseline dysfunction in female patients with CSCR.[17]

Men, on the other hand, showed a more complex structural phenotype, characterized by larger areas of RPE alteration, greater frequency of peripapillary RPE changes, longer DLS, and broader PEDs. These findings are in agreement with the study by Hanumunthadu et al., who recently described higher rates of diffuse RPE alterations, diffuse leakage and RPE tracts in men.[18] Similar patterns have been associated with increased choroidal vascular hyperpermeability and more aggressive disease behavior in previous imaging-based analyses of CSCR and pachychoroid disease spectrum disorders. [19]

Age-stratified analyses confirmed that these disparities persisted across age groups, with men both < 50 and ≥ 50 years exhibiting more extensive RPE abnormalities and PROS irregularities. The higher frequency of simple CSCR in women ≥ 50 years may reflect a lower burden of choroidal structural alterations, in line with reports suggesting gender-related differences in choroidal vascularity index and hormonal influences on choroidal regulation. [20] These differences may also help explain the more favorable functional baseline profile observed in women.

During follow-up, significant gender-dependent differences emerged in both anatomical resolution and func-

TABLE 4. Factors Affecting Subretinal Fluid Persistence at Final Visit and Change in Visual Acuity

	Univariable Logistic Regression (Persistence of Subretinal Fluid as Dependent Variable)			Multivariable Logistic Regression (Persistence of Subretinal Fluid as Dependent Variable)		
Variables	Odds Ratio	95% CI of OR	*P*-Value*	Odds Ratio	95% CI of OR	*P*-Value*
Group (Baseline simple/complex)	1.93	1.28 to 2.91	.002	1.41	0.71 to 2.77	.32
Group(Female/Male)	1.62	1.09 to 2.40	.017	0.54	0.19 to 1.57	.25
Baseline PROS irregularities (Yes/no)	1.93	1.21 to 3.07	.006	2.24	1.0 to 5.01	.05
Treatment after baseline (PDT /Observation)	0.42	0.18 to 0.99	.04	4.46	1.46 to 13.60	.009
Baseline BRVA (logMAR)	2.24	1.16 to 4.34	.017	4.15	1.17 to 14.76	.03
Baseline SHRM (Yes/no)	1.64	1.10 to 2.45	.016	2.71	0.95 to 7.76	.06
CNV after baseline (Yes/no)	1.75	1.04 to 2.92	.033	1.97	0.90 to 4.31	.08
Duration of symptoms (months)	1.03	1.0 to 1.06	.032	1.04	1.01 to 1.08	.01
	Univariable Linear regression (Improvement in BRVA as dependent variable)			Multivariable Linear regression (Improvement in BRVA as dependent variable)		
Variables	Regression coefficient	95% CI of OR	*P*-value*	Regression coefficient	95% CI of OR	*P*-value*
Baseline CMT, micron	−0.11	−0.004 to 0.12	.023	−0.11	−0.43 to −0.22	.03
Baseline BRVA (logMAR)	−0.28	−0.38 to −0.19	<.001	−0.32	−0.43 to −0.22	<.001
Persistent course (compared to resolution)	−0.18	−0.17 to −0.04	.002	−0.14	−0.09 to −0.01	.01
Baseline HRD (Present/absent)	−0.14	−0.16 to −0.03	.005	0.01	−0.08 to 0.09	.9
Duration of symptoms (months)	0.22	0 to 0.01	.002	0.14	0 to 0.01	.01

PDT Photodynamic therapy: SHRM: Subretinal hyper-reflective material; PROS: Photoreceptor outer segment; BRVA: Best recorded visual acuity, PED: pigment epithelium detachment, CNV: choroidal neovascularization, CMT: central macular thickness, HRD: hyperreflective dots.
*Adjusted for matching variables (age).

tional recovery. Women achieved greater improvement in BRVA across both age groups, whereas male patients, particularly those ≥ 50 years, showed a higher rate of persistent SRF and more frequent recurrences. The higher persistence rate in men is consistent with Sahoo et al. study demonstrating that more complex choroidal and RPE phenotypes correlate with chronicity and reduced fluid clearance.[6]

Moreover, in women, both DLS length and NSRD height significantly decreased, whereas reductions in these biomarkers were less pronounced or absent in men, especially in the older age group. These findings parallel earlier reports that structural biomarkers such as DLS, PROS irregularities, and PED width are strong predictors of activity and chronicity in CSCR.[21] Importantly, residual SRF at the end of follow-up was notably more common in men, especially those ≥ 50 years linking again male gender with a higher likelihood of chronic CSCR.

In logistic regression analysis, several anatomical and demographic factors independently predicted SRF persistence. Complex CSCR morphology nearly doubled the risk of persistence, confirming the prognostic value of structural disease classification.[22]

PROS irregularities at baseline, a marker previously associated with outer retinal compromise and more severe disease expression, also emerged as a strong predictor of chronic fluid retention. Additionally, men exhibited significantly higher odds of persistent subretinal fluid compared with women in univariate analysis. [23] (Figure 1) Interestingly, gender was not an independent predictor in multivariate models highlighting the predominant role of anatomical disease features in determining fluid persistence and treatment decisions rather than gender alone.

The development of CNV during follow-up substantially increased the likelihood of persistent SRF, aligning with Bonino Filho et al. demonstrating that choroidal neovascu-

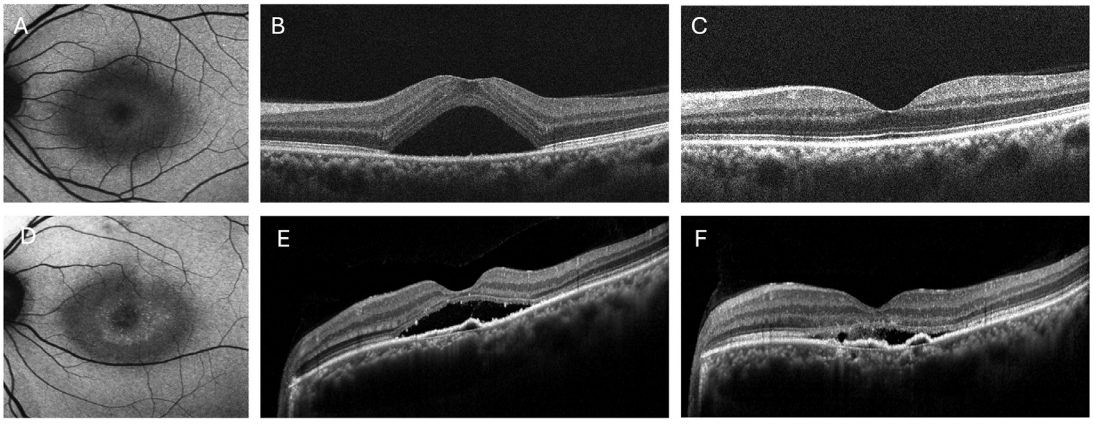

FIGURE 1. Example comparing the multimodal imaging of two patients, a 52-year-old woman (A-C) and a 52-year-old man (D-F), both presenting with central serous chorioretinopathy (CSCR). In the female patient, baseline autofluorescence (A) shows hypofluorescence without any RPE alterations suggestive of simple CSCR; the corresponding Optical Coherence Tomography (OCT) (B) shows the presence of dome-shaped subretinal fluid (SRF), which completely resolves at follow-up after 2 months with no gross abnormalities in the outer retinal layers (C). In contrast, the male patient shows multifocal RPE alterations, both hypofluorescence and hyperfluorescence suggestive of complex CSCR at autofluorescence (D) with SRF, pigment epithelium detachment (PED), and a double-layer sign (DLS) on OCT (E). At 2-month follow-up (F), his OCT still shows persistent SRF, Subretinal hyperreflective material (SHRM) and DLS.

larization in chronic CSCR represents a major driver of prolonged fluid and poorer outcomes.[24] Notably, no significant difference was observed between men and women. Among treatment modalities, PDT significantly reduced the odds of persistent SRF, underscoring its utility in promoting resolution consistent with literature findings.[25,26]

Visual improvement was strongly influenced by baseline anatomy. Higher CMT, poorer initial BRVA, and the presence of HRD in the choroidal stroma or PROS irregularities were all associated with limited functional recovery, emphasizing that outer retinal integrity particularly at the PROS and EZ level is the strongest determinant of visual prognosis in CSCR.[27] Furthermore, a longer duration of symptoms was likewise associated with reduced visual improvement and with an increased risk of persistent subretinal fluid, underscoring the importance of early diagnosis and timely management.[28] Persistent SRF markedly hindered visual gain, further highlighting the importance of timely fluid resolution. Interestingly, gender itself did not emerge as an independent predictor of BRVA improvement, suggesting that the superior outcomes observed in women are mediated through more favorable baseline structural characteristics rather than gender-specific biological mechanisms. Several hypotheses have been proposed to explain gender-specific patterns. One of the leading theory implicates that hormonal differences may contribute to gender-specific disease behavior; in particular, progesterone, a natural antagonist of the mineralocorticoid receptor, may confer a degree of protection in women by delaying onset or mitigating disease severity.[9] Of note, men are consistently reported to have a higher lifetime risk of developing CSCR[29], whereas women typically manifest the disease later in life.[30] Interestingly, in our cohort, women aged ≥ 50 years, despite the presumed reduction in estrogen-mediated hormonal protection, were more likely to present with simple forms of CSCR compared with age-matched men. This apparent paradox suggests that hormone–mediated mineralocorticoid receptor modulation may not represent the primary driver of gender disparities in CSCR and instead supports the contribution of intrinsic anatomical factors including scleral thickness and vortex vein outflow resistance as well as gender-related differences in choroidal hemodynamics and vascular remodeling within the pachychoroid spectrum.[31] On average, men have been shown to possess thicker sclera, a characteristic that may predispose them to choroidal congestion and pachyvessel development—key elements in the pachychoroid disease spectrum, including CSCR.[32] Finally, genetic predisposition such as complement factor H (CFH) appears to play a lesser role in explaining gender differences.[10]

There are several limitations to this study. First, it is a retrospective study from disparate groups with different treatment and follow-up patterns limited our ability to evaluate treatment-specific effects on disease outcomes. In particular, differences in treatment allocation, including the higher use of PDT in women, and differential follow-up duration may have partially influenced anatomical and functional outcomes, limiting the ability to attribute observed differences exclusively to gender-related biological factors. Moreover, systemic comorbidities and smoking status were not uniformly or systematically recorded across participating centers, precluding reliable adjustment for these potential confounders and potentially influencing the interpretation of gender-related differences in disease course and outcomes. Another limitation was the absence of dye-angiography data and choroidal vascularity index analy-

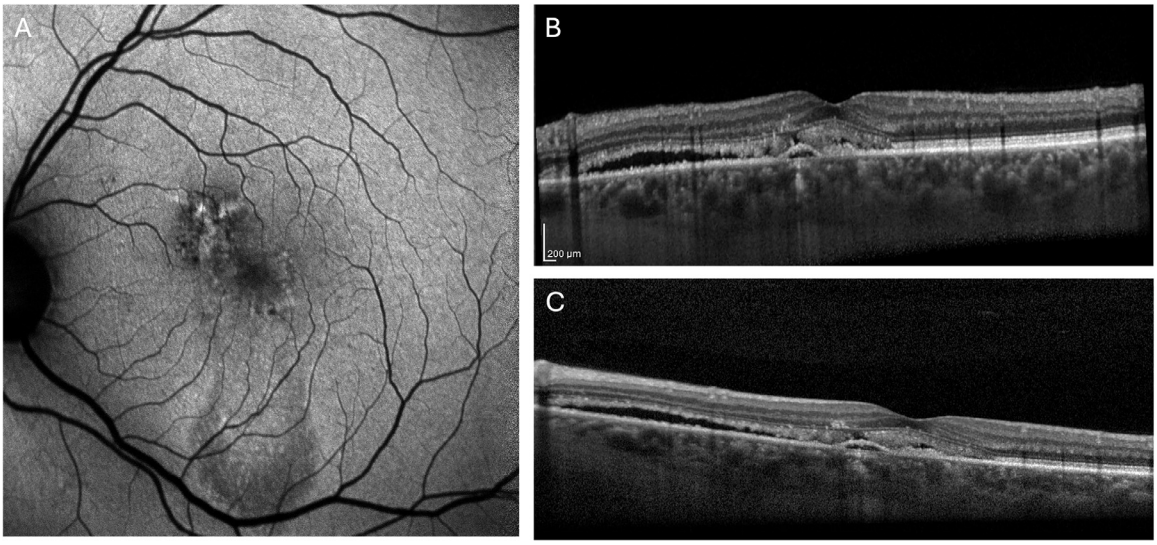

FIGURE 2. Example illustrating the case of a 48-year-old man presenting with CSCR. Baseline fundus autofluorescence (A) shows multifocal RPE alterations, both hypofluorescence and hyperfluorescence more than 2 disc areas (DA) suggestive of complex CSCR. The corresponding baseline OCT (B) shows subretinal fluid (SRF) along with photoreceptor outer segment (PROS) irregularities, pigment epithelium detachment (PED), and a double-layer sign (DLS). At 2-month follow-up (C), the OCT demonstrates persistent SRF, indicating incomplete resolution of the disease.

sis, both of which could have offered deeper insights into baseline disease severity and differential diagnosis. Without ICGA confirmation in all cases, a degree of diagnostic misclassification cannot be completely excluded. Additionally, we did not account uniformly for systemic risk factors known to be associated with CSCR such as corticosteroid use, psychological stress, *Helicobacter pylori* infection, obstructive sleep apnea or endogenous and exogenous androgen exposure which may differ between gender and act as residual confounders. These factors should be considered when interpreting the observed gender-related differences. Despite these constraints, this remains one of the largest longitudinal studies examining CSCR clinical course over time in men and women matched for age.

In conclusion, significant gender-related differences exist in the baseline characteristics, disease course, and visual outcomes of CSCR. Men tend to present with more complex anatomical alterations and experience higher rates of persistent SRF (Figure 2), while women show better visual outcomes and more favorable structural evolution. Baseline PROS irregularities, complex disease subtype, presence of CNV, male gender, and poorer BRVA strongly predict persistent fluid, whereas visual recovery is limited by greater CMT, poorer baseline vision, HRD in the choroidal stroma, and persistent disease course. These findings refine the understanding of gender-specific disease behavior and may help guide personalized management strategies. Nonetheless, future prospective studies with balanced treatment analysis are needed to validate these observations.

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