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Association between subretinal fluid duration in central serous chorioretinopathy and chorioretinal structure in unaffected fellow eyes

Takafumi Suzuki[1,2]✉, Chisato Otaki[1], Hideo Tate[1] & Yoshiki Ueta[1]

This study investigated the association between the duration of subretinal fluid (SRF) persistence in affected eyes and baseline chorioretinal structure in unaffected fellow eyes among patients with unilaterally naïve central serous chorioretinopathy (CSC). This retrospective case series comprised 25 healthy control patients and 46 patients with unilaterally naïve CSC, defined as first-episode and untreated within 1 month from symptom onset, who were categorized into prolonged (> 3 months) and nonprolonged (≤ 3 months) groups according to SRF duration in affected eyes from the first visit. Central retinal thickness, outer nuclear layer thickness, central choroidal thickness (CCT), luminal area (LA), stromal area (SA), total choroidal area (TCA), and choroidal vascularity index (CVI) were measured in unaffected fellow eyes at the first visit, and the duration of SRF persistence in affected eyes was recorded. As a result, CCT, SA and TCA were significantly greater, and CVI was significantly lower in the unaffected fellow eyes compared to the healthy control eyes (all $p < 0.05$). The optimal model for predicting SRF persistence > 3 months in affected eyes involved CVI ($p = 0.015$) in fellow eyes. Baseline choroidal thickening, mainly in the choroidal stroma of unaffected fellow eyes, was shown to correlate with SRF persistence in the affected eyes in unilateral naïve CSC. This information may be valuable for the identifying cases with a heightened risk of prolonged SRF persistence and for the timely initiation of treatment.

Keywords Central serous chorioretinopathy, Choroidal thickness, Choroidal vascularity index, Fellow eye, Optical coherence tomography, Subretinal fluid

Central serous chorioretinopathy (CSC) predominantly occurs in middle-aged male patients, leading to the accumulation of subretinal fluid (SRF) with diverse symptoms, including metamorphopsia and central scotoma[1,2]. The underlying etiology of CSC involves elevated permeability and congestion of the choroidal vessels[3–6]. CSC often resolves on its own via the fluid absorption[7]. Continuous SRF accumulation generally results in irreversible damage to the retinal pigment epithelium (RPE) and neuroretina, triggering permanent vision loss[8–11].

Currently, the threshold of SRF persistence or therapeutic approach for nonresolving CSC is controversial. Studies employing enhanced depth imaging optical coherence tomography (EDI-OCT) have reported an increase in central choroidal thickness (CCT) in eyes with CSC compared with that in normal eyes[12–15]. Additionally, the luminal-to-total choroidal ratio or choroidal vascularity index (CVI) was higher in eyes with CSC than in normal eyes[16,17].

Decreased optical coherence tomography angiography (OCTA) signals have been reported in the SRF area in CSC, often attributed to shadowing artifacts caused by SRF[18]. Previous reports investigating CVI in CSC eyes[16], indicated that one of the OCT findings with SRF exhibited mild shadowing artifacts. Therefore, we hypothesized that SRF in CSC eyes can lead to inaccurate analysis of the choroidal structures in both OCTA and OCT. In patients with CSC, unaffected fellow eyes have been shown to exhibit greater CCT and higher CVI than the healthy control eyes[15,19,20], indicating that choroidal structural changes occur in both eyes of patients with unilateral CSC. We hypothesized that by investigating the choroidal structure of unaffected fellow eyes with OCT, unaffected by SRF artifacts, we could predict the disease status of the affected eyes, particularly the duration of SRF persistence.

To our knowledge, no prior study has examined the association between the choroidal structure of unaffected fellow eyes and SRF duration in affected eyes with unilateral naïve (first-episode and untreated) CSC during the

[1]Department of Ophthalmology, Shinseikai Toyama Hospital, Imizu, Japan. [2]Department of Ophthalmology, The University of Tokyo Hospital, 7-3-1 Hongō, Bunkyō-ku, Tokyo 113-8655, Japan. ✉email: etoile1914100@gmail.com

acute phase. Our primary aim was to examine the association between baseline OCT observation during the acute phase, including CCT, luminal area (LA), stromal area (SA), total choroidal area (TCA) and CVI in the unaffected fellow eyes, and SRF persistence in affected eyes in patients with unilateral naïve CSC. We believe that this study's findings are expected in the identification of cases with an increased likelihood of prolonged SRF persistence using baseline OCT observation, enabling timely intervention.

Materials/subjects and methods

Our study adhered to the principles outlined in the Declaration of Helsinki, and Institutional Review Board approval was obtained (Shinseikai Toyama Hospital; approval number: 231031-1). This study involved a retrospective analysis using an opt-out consent process. Due to the retrospective nature of the study, Institutional Review Board of Shinseikai Toyama Hospital waived the need of obtaining informed consent.

We conducted a comprehensive review of patient records obtained from the database at Shinseikai Toyama Hospital, spanning from December 2010 to September 2023. The clinical diagnosis of unilateral naïve CSC was established based on symptoms: decreased visual acuity; distorted vision, micropsia, dyschromatopsia, or central scotoma; and the presence of SRF identified through fundus examination and EDI-OCT (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany). All patients underwent a comprehensive ophthalmic examination of both eyes during the first visit, including a keratometry reading using an ophthalmokeratometer (Topcon KR-8100 A, Tokyo, Japan or Nidek ARK-1, Gamagori, Japan); best-corrected visual acuity (BCVA) measurement using a Landolt decimal acuity chart, which was converted into the logarithm of the minimal angle of resolution; intraocular pressure measurement using noncontact tonometry (Nidek NT-530, Gamagori, Japan); slit-lamp examination; and OCT examination with a horizontal scan covering the fovea. The duration of symptoms was also recorded. In all cases, the onset of symptoms was determined based on patients' complaints. Additionally, the presence of RPE damage due to chronic SRF accumulation was assessed in both affected and unaffected eyes using fundus autofluorescence (FAF) with a confocal scanning laser ophthalmoscope (Heidelberg Retina Angiograph 2 system; Heidelberg Engineering). In several cases, patients were administered oral kallidinogenase at a dosage of 150 mg/day for at most 3 months from the initial consultation based on the discretion of the examining physicians.

The exclusion criteria were as follows: first visit > 1 month after symptom onset; inadequate follow-up or loss of follow-up in both eyes; a previous CSC episode in either eye; FAF showing chronic or bilateral CSC; a history or clinical signs of intraocular diseases other than CSC; local therapy including intravitreous injection of anti-vascular endothelial growth factor agents, photodynamic therapy, or photocoagulation within 3 months of the first visit; inability to define symptom onset; or steroid use. The monitoring plan for this observational study involved monthly clinical evaluations for > 3 months or until SRF was resolved.

The assessment of the central retinal thickness (CRT) was conducted by a skilled orthoptist (CO) who was blinded to the demographic information of the patient. The axial distance was measured from the inner aspect of the internal limited membrane at the fovea to the inner aspect of RPE using EDI-OCT scans. A retinal expert (TS) also evaluated CRT and serve as an adjudicator when CO encountered difficulties or exhibited uncertainty in the assessment. CCT was assessed similarly, with measurement of the axial distance from the outer aspect of the RPE to the outer choroid/scleral interface. Likewise, the outer nuclear layer (ONL) thickness at the fovea was assessed (Fig. 1A).

Binarized images were obtained using the Niblack method with ImageJ software (U.S. National Institute of Health, Bethesda, MD, USA), as previously described[16]. In brief, an image of one horizontal scan passing through the fovea was selected and converted into eight bits; the Niblack auto-local threshold was applied to binarize the images and separate the choroidal luminal and stromal areas. Thereafter, the total subfoveal 1500-μm-wide choroidal area (TCA), the area of dark pixels (LA) and area of light pixels (SA) were calculated. To determine the vascularity status of the choroid, CVI was calculated by dividing the LA by the TCA. (Fig. 1B).

We classified all 46 unaffected fellow eyes of the 46 patients into two groups based on the duration of the persisting SRF in the affected eyes, which exceeded 3 months from the initial visit, as per previous studies[21–23]. The nonprolonged group comprised patients whose SRF resolved within 3 months, while the prolonged group

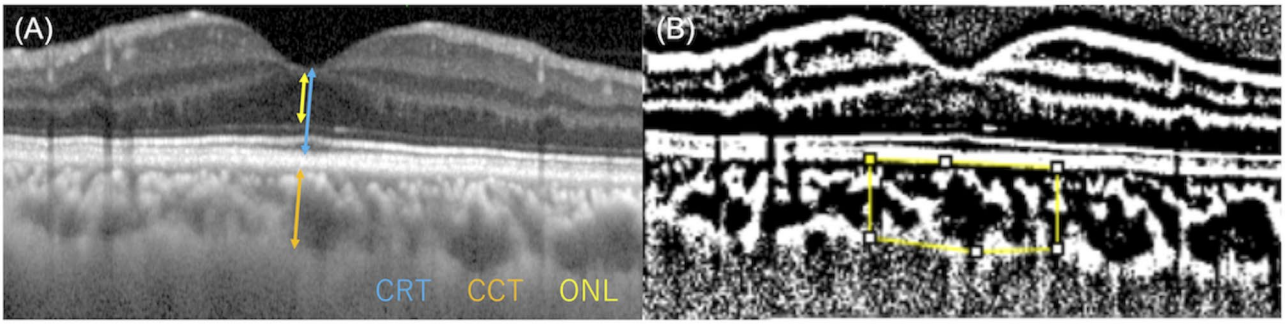

Fig. 1. Representative case of the current study. The OCT image at the initial visit (**A**) shows CRT, CCT, and ONL; the binarized image at the initial visit (**B**) shows CVI, calculated as luminal pixels/total choroidal pixels in the total choroidal area with a width of 1500 μm. *OCT* optical coherence tomography, *CRT* central retinal thickness, *CCT* central choroidal thickness, *ONL* outer nuclear layer, *CVI* choroidal vascularity index.

included those with SRF duration exceeding 3 months from the first visit. In addition, we included 25 healthy control eyes of 25 patients that were age- and spherical equivalent (SE)-matched. We compared age, sex, time from onset to the first visit, oral kallidinogenase use, and SE, BCVA, CRT, ONL, CCT, LA, SA, TCA, and CVI measurements at the first visit among the two fellow-eye groups and the control group. Multivariate analysis was also performed to identify factors including age, sex, SE, CRT, ONL, CCT, and CVI in the unaffected fellow eyes, associated with an SRF resolution in > 3 months in the affected eyes. In addition, receiver operating characteristics (ROC) curve analysis was performed to determine the sensitivity and specificity of the explanatory factor for the SRF duration in the affected eyes.

Statistical analysis

Continuous variables are represented as the mean ± standard deviation. The disparities in sex and oral kallidinogenase administration, along with age, time from onset to the initial visit, SE, BCVA, CRT, ONL, CCT, LA, SA, TCA, and CVI among the nonprolonged, prolonged, and the control groups were calculated via the Fisher's exact test with Bonferroni Holm correction and Tukey's multiple comparison test, respectively.

To identify the best explanatory variables for SRF persistence exceeding 3 months in the affected eyes, a multivariate logistic regression analysis using model selection with the modified Akaike information criterion index (AICc) was conducted. The optimal model for SRF persistence exceeding 3 months in the affected eyes was determined from 2^7 patterns from the parameters including age, sex, SE, CRT, ONL, CCT, and CVI in the unaffected fellow eyes.

Statistical significance was defined at $p < 0.05$. Statistical analyses were conducted using R version 4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria). ROC curve analysis was performed using JMP® 18 (JMP Statistical Discovery LLC, Cary, NC, USA).

Results

Subjects

Characteristics of patients at the first visit are summarized in Table 1. The nonprolonged group comprised 28 eyes of 28 men and seven eyes of seven women, the prolonged group comprised nine eyes of nine men and two eyes of two women, and the control group comprised twelve eyes of twelve men and thirteen eyes of thirteen women. Age ($p = 0.987$ (between nonprolonged and prolonged groups), $p = 0.051$ (between nonprolonged and control groups) and $p = 0.154$ (between prolonged and control groups)), time from onset to the first visit ($p = 0.064$), and oral kallidinogenase use ($p = 1.000$) did not have significant differences between the groups. Sex had significant differences between nonprolonged and control groups ($p = 0.040$) but not between prolonged and control groups ($p = 0.154$) or between nonprolonged and prolonged groups ($p = 1.000$). In 19 of the 46 affected eyes investigated, FAF assessments were performed within 1 month of the initial visit. Remarkably, the 19 eyes exhibited uniform decrease in autofluorescence, diffusely speckled hyper-FAF, or no observable changes in the regions affected by SRF persistence. These phenomena, known as "blocked FAF"[24] and "mottled FAF pattern"[25], respectively, are typically indicative of early disease stages. The average duration of symptoms associated with these phenomena

Variables	Nonprolonged group	Prolonged group	Control group
Number of eyes	35	11	25
Age (years)	46.4 ± 8.9	45.8 ± 7.8	53.24 ± 13.7
Male/Female	28/7*	9/2	12/13*
Time from onset to initial visit (days)	10.5 ± 8.5	17.0 ± 10.4	–
Oral kallidinogenase use	17	6	–
Spherical equivalent (diopter)	− 1.35 ± 1.66	− 1.10 ± 1.97	− 1.30 ± 1.70
BCVA (LogMAR)	− 0.12 ± 0.07	− 0.14 ± 0.05	− 0.12 ± 0.08
CRT (μm)	189.2 ± 20.5	184.1 ± 9.73	183.4 ± 19.9
ONL (μm)	101.0 ± 14.4	93.8 ± 10.3	95.4 ± 17.1
CCT (μm)	294.4 ± 106.8*	362.5 ± 90.8**	213.5 ± 69.6*,**
LA (μm^2)	281,670 ± 89,860	316,063 ± 61,753	244,306 ± 79,528
SA (μm^2)	145,783 ± 58,248*	183,101 ± 42,042**	99,049 ± 18,340*,**
TCA (μm^2)	427,454 ± 146,485*	499,164 ± 101,235**	337,674 ± 104,960*,**
CVI (%)	66.6 ± 3.3*	63.5 ± 2.3**	72.3 ± 5.1*,**
SRF duration (days)	54.1 ± 26.0*	143.3 ± 14.0*, †	–

Table 1. Characteristics of patients and unaffected fellow eyes at the first visit. *, ** Significant difference between two groups ($p < 0.05$). † SRF duration of the affected eyes in the prolonged group was recorded only in six cases without topical treatments including intravitreous injection of anti-vascular endothelial growth factor agents, photodynamic therapy, or photocoagulation, because the other 5 cases received the treatment 3 months after the initial visit. *BCVA* best-corrected visual acuity, *CCT* central choroidal thickness, *CRT* central retinal thickness, *CVI* choroidal vascular index, *LA* luminal area, *LogMAR* Converted to the logarithm of the minimal angle of resolution, *ONL* outer nuclear layer thickness, *SA* stromal area, *SRF* subretinal fluid, *SRF* duration, time from initial visit to SRF resolution, *TCA* total choroidal area.

was documented to be under 1 month[25], which corresponds with our study's inclusion criteria, emphasizing on eyes with an onset-to-first visit interval of up to a month. Hence, the objective judgment of the onset by FAF was considered in line with that of onset according to the patient's complaints. In 19 of the 46 unaffected eyes that were investigated, FAF assessments were obtained within 1 month of the first visit. Among all 19 eyes, no observable changes were detected.

Comparison of fellow eyes in the nonprolonged group, fellow eyes in the prolonged group, and control eyes

There was no significant difference between values for SE ($p = 0.911$ (between nonprolonged and prolonged groups), $p = 0.993$ (between nonprolonged and control groups) and $p = 0.947$ (between prolonged and control groups)), BCVA ($p = 0.608$ (between nonprolonged and prolonged groups), $p = 0.934$ (between nonprolonged and control groups) and $p = 0.789$ (between prolonged and control groups)), CRT ($p = 0.725$ (between nonprolonged and prolonged groups), $p = 0.484$ (between nonprolonged and control groups) and $p = 0.994$ (between prolonged and control groups)), and ONL ($p = 0.365$ (between nonprolonged and prolonged groups), $p = 0.349$ (between nonprolonged and control groups) and $p = 0.953$ (between prolonged and control groups)) among the three groups at the first visit. CCT in the nonprolonged (294.4 ± 106.8 µm) and prolonged groups (362.5 ± 90.8 µm) were significantly greater than that in the control group (213.5 ± 69.6 µm; $p = 0.005$ and $p = 0.0001$ respectively). Similarly, SA in the nonprolonged (145783 ± 58248 µm) and prolonged groups (183101 ± 42042 µm) were significantly greater than that in the control group (99049 ± 18340 µm; $p = 0.0008$ and $p < 0.0001$ respectively), as well as TCA in the nonprolonged (427454 ± 146485 µm) and prolonged groups (499164 ± 101235 µm) than that in the control group (337674 ± 104960 µm; $p = 0.027$ and $p = 0.0028$ respectively). However, LA were not significantly different among the three groups ($p = 0.469$ (between nonprolonged and prolonged groups), $p = 0.215$ between (nonprolnged and control groups), and $p = 0.055$ (between prolonged and control groups)). CVI in the nonprolonged (66.6 ± 3.3%) and prolonged groups (63.5 ± 2.3%) were significantly lower than that in the control group (72.3 ± 5.1%; $p < 0.0001$ both). CCT, SA, TCA, or CVI were not significantly different between nonprolonged and prolonged groups ($p = 0.102$, $p = 0.059$, $p = 0.251$, and $p = 0.070$ respectively). The duration of SRF persistence in the nonprolonged group was 54.1 ± 26.0 days, while that for the six cases undergoing no therapy in the prolonged group was 143.3 ± 14.0 days ($p = 0.0001$) (Table 1).

Optimal model for predicting the duration of SRF persistence > 3 months in the affected eyes using data from the unaffected fellow eyes and ROC curve analysis

Following the model selection, the optimal model for predicting the duration of SRF persistence exceeding 3 months in the affected eyes included CVI ($p = 0.015$) for the unaffected fellow eyes (AICc = 46.004) (Table 2). ROC curve analysis was performed and area under the curve was 0.753 (Fig. 2).

Discussion

In the current study, we observed that the baseline CCT, SA, and TCA, but not LA in the unaffected fellow eyes were significantly greater than in the control eyes and that the baseline CVI in the unaffected fellow eyes was significantly lower than in the control eyes. The baseline CVI of unaffected fellow eyes was closely associated with SRF persistence for > 3 months in the affected eyes.

Previous reports have suggested that CVI in the affected eyes is significantly higher than that in healthy control eyes[16]. Additionally, CCT in the affected eyes is significantly greater than that in healthy control eyes[15]. CCT and CVI are also greater and higher, respectively, in unaffected fellow eyes of patients with CSC than in healthy control eyes[15,19,20]. Notably, indocyanine green angiography (IA) also demonstrated choroidal vascular hyperpermeability in both affected and unaffected fellow eyes, even in patients with unilateral CSC[15], underscoring the bilateral characteristics of these choroidal alterations, including choroidal thickening primarily in the luminal area and hyperpermeability in both eyes.

Variables	Coefficient	SE	*p*-value
Age	N.S.	–	–
Sex	N.S.	–	–
Spherical equivalent	N.S.	–	–
CRT	N.S.	–	–
ONL	N.S.	–	–
CCT	N.S.	–	–
CVI	− 0.40	0.17	0.015*

Table 2. Optimal model for predicting the duration of SRF persistence for > 3 months in the affected eyes using data from the unaffected fellow eyes. Multivariate logistic regression analysis with AICc model selection for predicting the association between SRF duration longer than 3 months and age, sex, spherical equivalent, CRT, CCT, CVI, and ONL. The optimal model included CVI (AICc = 46.004). *AICc* Modified Akaike information criterion, *CCT* central choroidal thickness, *CRT* central retinal thickness, *CVI* choroidal vascular index, *N.S.* not selected, *ONL* outer nuclear layer thickness, *SE* standard error, *SRF* subretinal fluid.

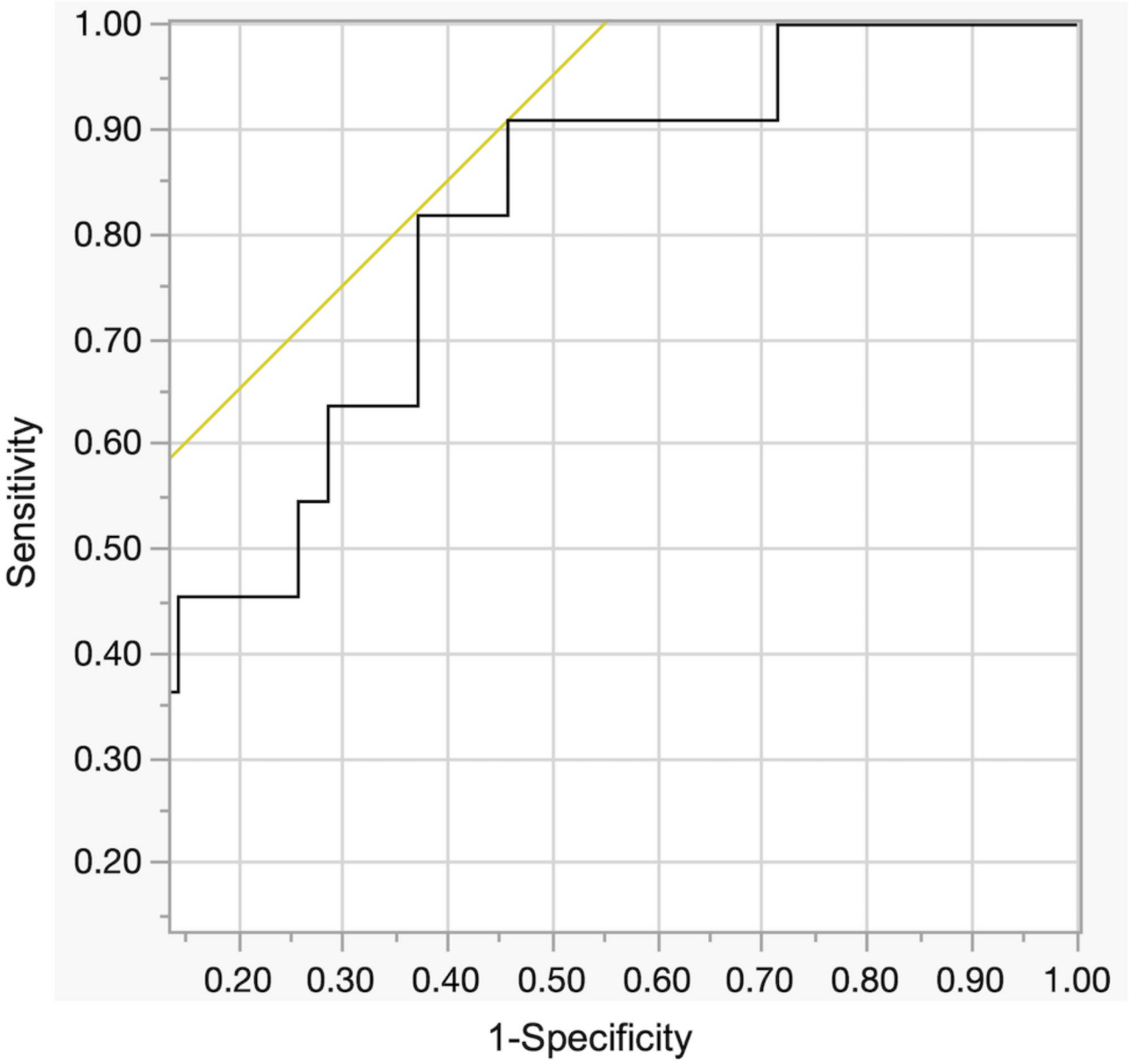

Fig. 2. ROC curve of baseline CVI in unaffected fellow eyes for predicting prolonged SRF persistence in affected eyes. ROC curve analysis was performed for predicting SRF duration exceeding 3 months in 46 affected eyes from baseline CVI in 46 unaffected fellow eyes. Area under the ROC curve was 0.753; *ROC* receiver operating characteristics, *CVI* choroidal vascularity index, *SRF* subretinal fluid.

In contrast, our study showed that choroidal thickening, primarily in the stromal area unlike the previous report[20], is characteristic of the fellow eyes in first-episode and treatment-naïve CSC cases within 1 month of onset, and it can also predict SRF persistence in affected eyes. The mechanism is considered as follows.

All living organisms regulate fluid balance to sustain homeostasis. Water constitutes the predominant substance in the body, accounting for approximately 50–60% of total body weight. Total body water is categorized into intracellular and extracellular fluid (ECF), comprising approximately 55–75% and 25–45% of the body's fluid composition, respectively[26]. ECF is further divided into intravascular plasma volume (25%) and extravascular interstitial space (75%), and the fluid balance between these compartments is maintained by hydrostatic and oncotic pressure, as described by Starling. The other two important factors in fluid balance are vessel wall permeability and the lymphatic system[27]. When the intravascular volume fluctuates, fluid shifts between the interstitial and intravascular compartments to preserve the overall intravascular volume, thereby maintaining the circulatory dynamics of the human body[28]. As mentioned earlier, there is a threefold difference in volume between the intravascular and interstitial volumes, and the interstitium serves as a regulator of intravascular pressure. In other words, changes in the interstitial volume transpire more readily than those in the intravascular volume. Aligning with this concept, the choroidal interstitial volume is more easily altered than

the choroidal intravascular volume and serves as a regulator to maintain choroidal intravascular pressure. In both eyes of unilateral CSC in acute phase, a fluid shift from the choroidal vessels to the interstitium can result in predominant choroidal interstitial thickening rather than choroidal vessel dilation as in our study. In addition, we believe that the choroidal thickening, primarily in the choroidal stroma in the unaffected fellow eyes can reflect the intensity of leakage from the choroidal vessels in acute phase and SRF persistence in the affected eyes.

The difference in the location of choroidal thickening, occurring primarily in the stromal area in our study versus the vascular area in previous reports, is most likely attributable to differences in the inclusion criteria. A previous study[16] on CVI included affected eyes with a time duration from onset to initial visit that was, on average, 47.2 days longer than that in our study. Another study[17] on CVI in affected eyes focused exclusively on chronic CSC cases, while a separate report[20] on CVI in unaffected fellow eyes included both acute and chronic CSC cases. Diffuse leakage from the choriocapillaris into the choroidal stroma, as observed on IA, is a characteristic feature of the acute stage of CSC[24,29,30]. It has also been suggested that in acute CSC, choroidal thickness gradually decreases over time as the condition self-resolves, eventually matching the choroidal thickness of the fellow eye[19]. Furthermore, choroidal vascular dilation without extravasation may be indicative of the recovery phase of acute CSC[15]. Based on these considerations, we speculated that in the acute phase of CSC, fluid initially leaks from the choroidal vessels into the stroma, leading to choroidal thickening primarily within the stromal compartment in both affected and unaffected fellow eyes. During the resolution process, fluid is thought to move from the choroidal stroma back into the choroidal vessels in both affected and fellow eyes. Our study may have captured this transition at an earlier stage, whereas most previous reports observed it at a later stage.

A previous study[17] demonstrated a reduction in the choroidal stromal area in chronic CSC eyes. Chronic venous capillary pressure may induce the extravasation of proinflammatory and prothrombotic proteins and mediators into the choroidal stroma, leading to stromal atrophy as a result of chronic low-grade inflammation. This process may also account for the larger CVI reported in previous studies compared to our findings.

This study had some limitations. The study design was retrospective, observational, and a small case series study with less than ten times the number of variables to perform multivariate logistic regression analysis, and the criterion for the initial episode primarily depended on patients' initial subjective symptoms, including distorted vision and central dark spots, which may not be always accurate. Furthermore, the study encompassed an Asian population, which typically demonstrates a higher prevalence of myopia; this may have impacted the study outcomes. In our study, SE, which did not differ significantly among the three groups, was measured instead of axial length due to the retrospective study design. It should serve as a substitute for axial length, as the included cases were relatively young, phakic, and free of other intraocular diseases aside from CSC. Additionally, this study did not take into account the results of fluorescein angiography (FA) and IA because these tests are rarely conducted in patients with CSC at their initial visit. The oral intake of kallidinogenase for at most 3 months might have affected choroidal blood flow[31]. Lastly, the short follow-up period may have led to the potential oversight of later recurrences of SRF in the nonprolonged group; therefore, a nonprolonged case may not necessarily signify absence of chronicity.

To conclude, our findings suggested that baseline choroidal thickening, mainly in the choroidal stroma of unaffected fellow eyes, correlates with SRF persistence in unilateral naïve CSC. This information can be valuable for identifying cases with an elevated risk of prolonged SRF persistence and for timely treatment initiation. Future research should take into account prospective examination of factors influencing the clinical visual prognosis of CSC, including FA/IA assessments, in a larger cohort.

Data availability

The datasets used and analyzed in the current study are available from the corresponding author upon reasonable request.

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Author contributions
TS was involved in the study design, data collection, analysis of results, and manuscript drafting. CO and HT participated in data collection. YU reviewed and edited the manuscript. All the authors have read and approved the final manuscript.

Declarations

Competing interests
The authors declare no competing interests.

Additional information
Correspondence and requests for materials should be addressed to T.S.

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