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Optical coherence tomography characteristics in hydroxychloroquine retinopathy and the correlations with visual deterioration in Taiwanese

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Abstract:

PURPOSE: This study aimed to investigate optical coherence tomography (OCT) characteristics in hydroxychloroquine (HCQ) retinopathy and their correlation with visual acuity among Taiwanese patients.

MATERIALS AND METHODS: We retrospectively recruited patients undergoing long-term HCQ treatment who had received examinations of best-corrected visual acuity and OCT scans. We observed disruptions in the ellipsoid zone (EZ) and retinal pigment epithelium (RPE) across different retinal regions. Principal component analysis (PCA) was employed to identify the most significant factors associated with visual deterioration.

RESULTS: Among the 120 eyes included in the study, HCQ retinopathy was present in 42 eyes (35.0%). In patients with mild-to-moderate retinopathy, the pericentral pattern was predominant (75.0%), whereas no parafoveal pattern was observed. Serial examinations revealed that lesions typically progressed from pericentral to parafoveal and foveal regions. EZ disruption was observed in all affected cases, most frequently at the pericentral region (100%), followed by the perifoveal (87.4%), parafoveal (72.1%), and foveal (43.2%) regions. RPE disruption was noted in 59.5% of cases, with the highest prevalence at the pericentral (53.2%) and perifoveal (52.3%) regions, followed by the parafoveal (33.3%) and foveal (28.8%) regions. PCA identified RPE disruption at the fovea and parafoveal regions as the most strongly correlated factors for visual deterioration.

CONCLUSIONS: In Taiwanese patients, HCQ retinopathy predominantly manifests with pericentral lesions, while isolated parafoveal lesions are rare as an initial presentation. RPE disruption, rather than EZ disruption, appears to be the primary determinant for visual deterioration in this population.

Keywords:

Ellipsoid zone, hydroxychloroquine retinopathy, optical coherence tomography, retinal pigment epithelium, visual acuity

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Introduction

Hydroxychloroquine (HCQ) is widely used to treat systemic lupus erythematosus, rheumatoid arthritis, and other systemic autoimmune or inflammatory conditions. With excessive daily doses and an extended duration of use,[1,2] long-term usage of HCQ can progressively induce retinal toxicity and cause severe and irreversible vision loss. Early recognition of HCQ retinopathy can prevent further progression of retinopathy after the discontinuation of treatment. In addition, in the late stage of HCQ retinopathy, the preservation of visual acuity is associated with the integrity of the fovea.[3] To minimize visual loss, fundus imaging is an important technique for facilitating the detection of retinal toxicity in its early stage.

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Optical coherence tomography (OCT), color fundus photography, and fundus autofluorescence are commonly used techniques in fundus imaging. Among the three imaging techniques, spectral domain OCT (SD-OCT) is highly specific and adequately sensitive, allowing for the recognition of retinal toxicity and subtle structural changes. Abnormalities of SD-OCT in HCQ retinopathy included (1) Early abnormalities of ellipsoid zone (EZ) band attenuation and/or loss of a continuous interdigitation zone (IZ) band described by Garrity *et al*.,[4] (2) Late abnormalities of parafoveal loss of the EZ and IZ bands with foveal conservation, which was described as the "flying saucer sign,"[5] and (3) Advanced toxicity of retinal pigment epithelium (RPE) defects. For Asian patients, a distinct retinopathy pattern might manifest as a pericentral pattern of damage in the EZ band and RPE.[6,7] Thus, the use of SD-OCT for early detection is recommended according to the 2016 American Academy of Ophthalmology guidelines.[8] Even if the fovea is spared in early HCQ retinopathy, patients may still have blurred vision. However, correlations between OCT changes and visual acuity in long-term HCQ users are still not clear. It is also not clear whether the degree of EZ disruption and RPE disruption contributes to visual loss similarly. The purpose of this study was to investigate the correlations between OCT characteristics and visual acuity in patients with HCQ retinopathy and to evaluate the impacts of EZ and RPE lesions on vision.

Materials and Methods

Patient selection

This retrospective study included patients who received long-term HCQ treatment at National Taiwan University Hospital (NTUH) between January 2006 and August 2022 and who had undergone best-corrected visual acuity (BCVA) and SD-OCT (Optovue Avanti RTVue XR OCT, Optovue, Inc., Fremont, CA, USA) examinations between January 2014 and August 2022. Patients with any of the following characteristics were excluded: treatment with HCQ for <1 continuous year, a maximum gap in therapy of more than 1 year, no available ophthalmic examinations before cessation of HCQ treatment, retinopathy or visual acuity loss secondary to other causes (e.g., age-related macular degeneration, diabetic retinopathy, cataract, and trauma), history of any ophthalmic surgery except cataract surgery, and a BCVA <20/400. Finally, 120 eyes of 67 patients were enrolled [Figure 1]. Fourteen patients had only one eye enrolled because of retinopathy or visual acuity loss secondary to other causes in the fellow eyes. The research was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the NTUH (No. 202109060RIND). The requirement for informed consent was waived due to the retrospective design of this study.

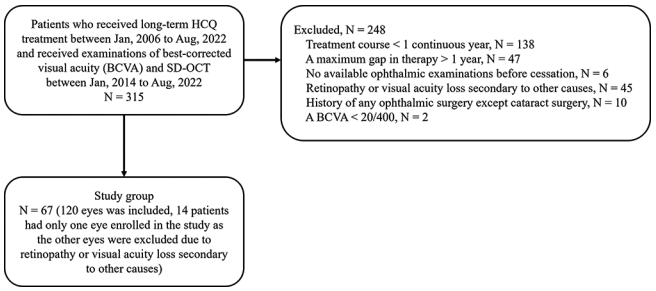

Figure 1: Flowchart for patient selection

Ophthalmic examinations

All eligible patients received regular ophthalmic examinations, including BCVA and SD-OCT measurements. For each patient, all available SD-OCT and BCVA data were collected during different visits. At each visit, the SD-OCT data were paired with the nearest BCVA measurement in both eyes, which were measured on the same day or within 2 weeks. BCVA measurements were performed using a Landolt C chart.

For SD-OCT, the images of both vertical and horizontal sections of 10-mm B-scan OCT were used for analysis. Each image was divided into four regions: the fovea, which is the central 1.5 mm-diameter area; the parafovea, which is the area between concentric circles with diameters of 1.5 mm and 2.5 mm centered on the fovea; the perifovea, which is the area between concentric circles with diameters of 2.5 mm and 5.5 mm centered on the fovea; and the pericentral region, which is the area outside the 5.5 mm-diameter circle centered on the fovea. Each region was then examined carefully for the integrity of the EZ band and RPE. The region was annotated as abnormal if any disruption within the region was noted, and the abnormalities of the EZ and RPE were annotated separately [Figure 2].

Sequential SD-OCT examinations were analyzed to classify eyes with HCQ retinopathy into three patterns: parafoveal (where disruption of photoreceptor or RPE first appeared at the parafoveal area), pericentral (where disruption of photoreceptor or RPE first appeared at the pericentral area), or mixed (where disruption of photoreceptor or RPE in both the parafoveal and pericentral areas appeared at the first presentation). Furthermore, the severity of HCQ retinopathy was delineated into three stages: early (patchy disruption of photoreceptor), moderate (partial [>180°] ring-like photoreceptor disruption around fovea), and severe (combined disruption of photoreceptor and RPE).

Statistical analysis

Frequency and descriptive statistics were obtained from demographic and history data on HCQ treatment. The data are expressed as the mean ± standard

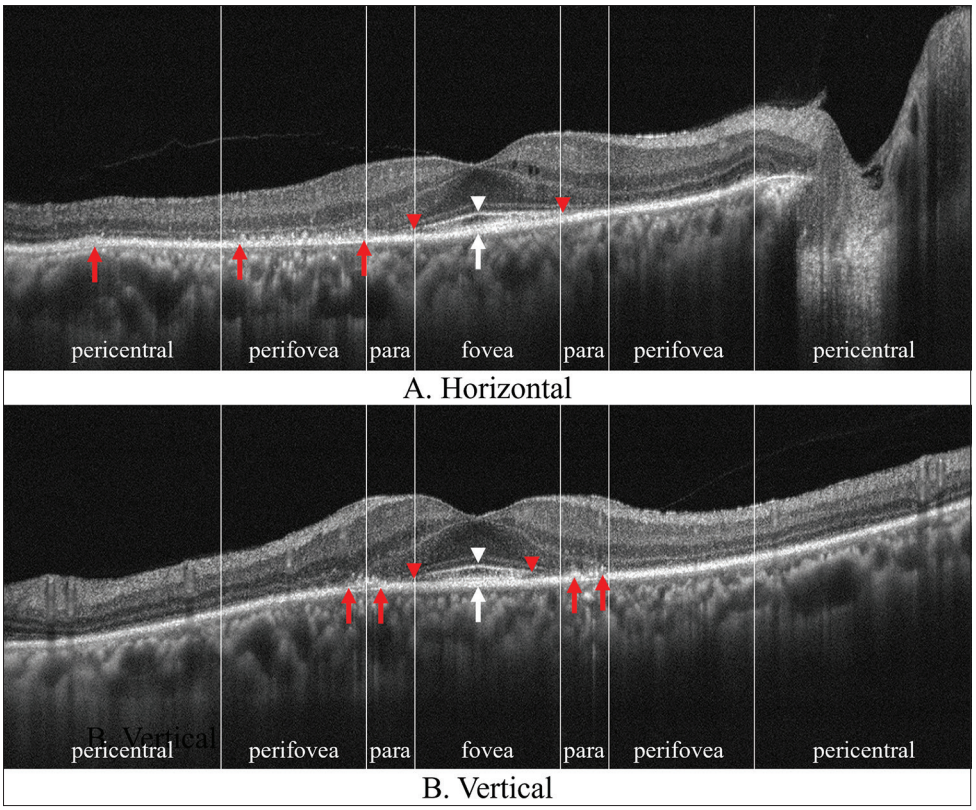

Figure 2: Definition for different regions measured in 10-mm B-scan optical coherence tomography and an example of a case with advanced hydroxychloroquine retinopathy. The fovea, parafovea, perifovea, and pericentral region of the macula were divided by white straight line and defined as follows: the fovea is the central 1.5 mm-diameter area; the parafovea is the area between concentric circles with diameters of 1.5 mm and 2.5 mm centered on the fovea; the perifovea is the area between concentric circles with diameters of 2.5 mm and 5.5 mm centered on the fovea; and the pericentral region is the area outside the 5.5-mm diameter circle centered on the fovea. Continuity of the ellipsoid zone (EZ) band (white arrowheads) and retinal pigment epithelium (RPE) (white arrows) was the reference of abnormality. In (A) Horizontal section of spectral domain-optical coherence tomography (SD-OCT), attenuation and loss of continuity of the EZ band (red arrowheads) were presented on the parafovea, perifovea, and pericentral region, In (B) Vertical section of SD-OCT, they were presented on all regions. Thus, the annotation would be abnormal on all four regions of the EZ band. (A) RPE defect on the perifovea and the pericentral region, whereas (B) Disruptions presented on the parafovea and the perifovea region. Therefore, the annotation would be abnormal on the parafovea, perifovea, and pericentral region

deviation unless otherwise specified. The BCVA was further converted to the logarithm of the minimum angle of resolution (logMAR) for analyses. Mann–Whitney *U* test was used to compare BCVA between early-moderate and severe group. Pearson's correlation coefficient tests were used to evaluate the correlations among the degree of EZ/RPE disruption in different regions (fovea, parafovea, perifovea, and pericentral regions). Simple linear regression analysis was performed to evaluate the associations between the logMAR of BCVA and EZ or RPE disruption in different regions as well as demographic data and HCQ treatment history. Multivariate linear mixed models were used to eliminate the collinearity among different examinations of the same eyes and bilateral eyes of the same patients. Forward selection was subsequently performed to reveal the factors most significantly associated with vision.

To address the collinearity among the abnormal findings at different regions, principal component analysis (PCA) was applied for three models: EZ only (four regions), RPE only (four regions), and both EZ and RPE (eight regions). The number of principal components was set to two, and simple and multivariate linear regression analyses with forward selection were used to evaluate the factors associated with BCVA. All the statistical analyses were performed with SPSS 29.0 (IBM Corp. Released 2022. IBM SPSS Statistics for Windows, Version 29.0). P <0.05 was considered to indicate statistical significance (Armonk, NY, USA: IBM Corp.).

Results

This study included a total of 363 BCVA and OCT examinations from 120 eyes of 67 patients (7 males and 60 females). The detailed demographic and history data of HCQ treatment, as observed during the most recent consultation, are delineated in Table 1. The average patient age was 59.8 ± 14.0 years. The mean cumulative dose of HCQ was 821.6 ± 630.3 g on average, whereas the mean medication duration was 6.4 ± 4.4 years. The mean daily dose to real body

weight was 5.9 ± 2.5 mg/kg. The mean logMAR of BCVA was 0.27 ± 0.32.

Patterns and severity for hydroxychloroquine retinopathy

Among the 120 enrolled eyes of the 67 enrolled patients, HCQ retinopathy identified with OCT was noted in 42 eyes (35.0%) of 25 individuals (37.3%). Of these 25 patients, 17 had bilateral lesions, 5 had only one eye enrolled for studying, and the other 3 had unilateral lesion with early change of HCQ retinopathy. Of the 42 lesioned eyes, the specific regions that exhibited disruption at the final observation are presented in Figure 3. The distribution for the HCQ retinopathy patterns was as follows: pericentral in 14 eyes (33.3%) and mixed pattern in 28 eyes (66.7%). Concerning the severity of retinopathy, 11 (26.2%), 5 (11.9%), and 26 (61.9%) eyes showed early, moderate, and severe retinopathy, respectively. Within the subgroup of eyes exhibiting early or moderate retinopathy, the observed patterns were pericentral in 14 eyes (87.5%) and mixed in 2 eyes (12.5%). Notably, in early HCQ retinopathy, all cases demonstrated a pericentral pattern. Table 2 shows the summary for the retinopathy patterns and severity.

Sequential changes of optical coherence tomography characteristics in hydroxychloroquine retinopathy

Among the 363 serial OCT examinations from the 120 eyes, HCQ retinopathy presented in 111 of them (30.6%), as shown in Table 3. All 111 examinations showed abnormalities in the EZ band. The pericentral region had the greatest proportion of abnormalities (98.2%), followed by the perifoveal region (87.4%), the parafoveal region (72.1%), and the fovea (43.2%). On the other hand, 66 OCT examinations (59.5%) also revealed RPE defects. RPE abnormalities also appeared most frequently in the pericentral region (53.2%) and the perifoveal region (52.3%), followed by the parafoveal region (33.3%) and the fovea (28.8%). In EZ band of all patients, no defects were present at the fovea or the parafoveal region before appearing at the perifoveal or pericentral regions. Furthermore, a pattern of defect progression toward the central fovea was observed in serial examinations.

Table 1: Characteristics of included 120 eyes from 67 patients in the latest visit

Characteristics	Mean±SD or *n* (%)
Age (years)	59±14.0
Sex (female)	64 (89.6)
Height (cm)	156.1±6.2
Weight (kg)	56.8±11.7
BMI (kg/m^2)	23.2±4.5
Cumulative doses (g)	821.6±630.3
Medication duration (years)	6.4±4.4
Daily dose/body weight (mg/kg)	5.9±2.5
LogMAR of BCVA	0.27±0.32

BMI=Body mass index, BCVA=Best-corrected visual acuity, SD=Standard deviation

Table 2: Patterns of hydroxychloroquine retinopathy for different severities

	Pattern of HCQ retinopathy, case number (%)		
	Parafoveal	Pericentral	Mixed
Total (*n*=42)	0	14 (33.3)	28 (66.7)
Early retinopathy (*n*=11)	0	11 (100)	0
Moderate retinopathy (*n*=5)	0	3 (60)	2 (40)
Severe retinopathy (*n*=26)	0	0	26 (100)

HCQ=Hydroxychloroquine

Correlating factors for visual acuity in hydroxychloroquine retinopathy

Table 4 presents the correlations between the logMAR of BCVA and demographic data, history of HCQ treatment, and OCT characteristics. Age, cumulative dose, and

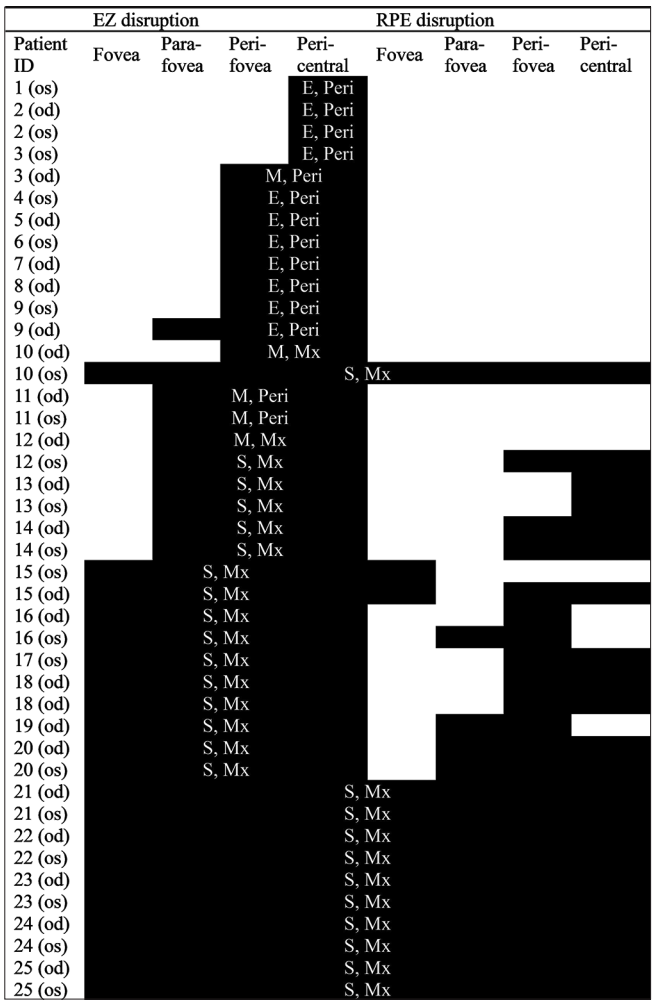

Figure 3: Distribution of disrupted optical coherence tomography regions for each eye in the last visit. EZ band: Ellipsoid zone band (inner/outer segment line), RPE: Retinal pigment epithelium, E: Early, M: Moderate, S: Severe, Peri: Pericentral pattern, Mx: Mixed pattern. The patterns were classified based on the sequential changes

medication duration were also significantly correlated with BCVA ($P < 0.001$, 0.015, and <0.001, respectively) but daily dose per body weight was not ($P = 0.406$). Among the OCT characteristics, disruption of the EZ band or RPE at different regions was all significantly correlated with BCVA ($P < 0.001$ for all), and RPE disruption at the fovea had the strongest correlation.

Because the lesions in all regions of the EZ band and RPE were correlated to one another, multivariate linear regression with forward selection method was used to select the most correlated characteristics for BCVA. Cumulative doses were excluded for the multivariate models due to its strong collinearity with medication duration. Three different models were used to enroll different regions in OCT [Table 5]: EZ band only (fovea, parafovea, perifovea, and pericentral), RPE only (fovea, parafovea, perifovea, and pericentral), and both EZ band and RPE (fovea, parafovea, perifoveal, and pericentral for both). In all three multivariate linear regression models, fovea was associated with visual deterioration (EZ band only: $\beta = 0.408$, $P < 0.001$; RPE only: $\beta = 0.305$, $P < 0.001$; and EZ band and RPE combined: $\beta = 0.305$, $P < 0.001$). For the two models containing RPE, the fovea and parafovea of RPE were selected. Age was also significantly associated with BCVA in all three models (EZ band only: $\beta = 0.308$, $P < 0.001$; RPE only: $\beta = 0.420$, $P < 0.001$; and EZ band and RPE combined: $\beta = 0.420$, $P < 0.001$). Notably, the goodness of fit of the model with RPE only was the same as that with both the EZ band and RPE ($R^2 = 0.352$ for both), because the same parameters were selected for both models (age, fovea, and parafovea for RPE). The model with only the EZ band had the lowest performance level, with an R^2 of 0.250.

Principal component analysis for visual acuity in hydroxychloroquine retinopathy

To consider the contribution of all regions in OCT for visual deterioration in HCQ retinopathy, with prevention of collinearity at the same time, PCA was implemented for three models: EZ band only (four regions), RPE only (four regions), and both EZ band and RPE (eight regions). Forward selection methods then were performed in the multivariate linear regression models with age, cumulative dose, and the 1st and 2nd principal components from the three comparison groups [Table 6]. The model with two principal components of RPE had the highest goodness of fit, with an R^2 of 0.351, whereas the model with two principal components of both EZ band and RPE had a lower R^2 of 0.335. The model with two principal components of the EZ had the lowest performance, with an R^2 of 0.248. Table 7 shows the rotated loading regarding the 1st and 2nd principal components of different models. For the best-fitted model (RPE only), the fovea and parafoveal regions of RPE contributed most in the first principal component. Therefore, another variable that equaled the sum of the original foveal and parafoveal data was created for multivariate regression analysis along with

Table 3: Distribution of the diseased regions in eyes with hydroxychloroquine retinopathy

Regions	*n* (%)
EZ band	111 (100)
Fovea	52 (43.2)
Parafovea	80 (72.1)
Perifovea	97 (87.4)
Pericentral	109 (98.2)
RPE	66 (59.5)
Fovea	32 (28.8)
Parafovea	37 (33.3)
Perifovea	58 (52.3)
Pericentral	59 (53.2)

EZ=Ellipsoid zone, RPE=Retinal pigment epithelium

Table 4: Correlating factors for visual acuity in hydroxychloroquine retinopathy using simple linear regression analysis

Variables	Coefficient (95% CI)	*P*
Age (years)	0.006 (0.004–0.008)	<0.001
Sex (male as the reference)	0.008 (−0.086–0.102)	0.865
Cumulative doses (g)	<0.001 (0.000–0.000)	0.015
Medication duration (years)	0.010 (0.004–0.016)	<0.001
Daily dose/body weight (g/kg)	−0.005 (−0.016–0.006)	0.406
EZ band		
Fovea	0.295 (0.223–0.366)	<0.001
Parafovea	0.178 (0.117–0.238)	<0.001
Perifovea	0.181 (0.125–0.237)	<0.001
Pericentral	0.148 (0.093–0.203)	<0.001
RPE		
Fovea	0.377 (0.294–0.461)	<0.001
Parafovea	0.341 (0.262–0.420)	<0.001
Perifovea	0.259 (0.193–0.326)	<0.001
Pericentral	0.256 (0.190–0.322)	<0.001

RPE=Retinal pigment epithelium, EZ=Ellipsoid zone, CI=Confidence interval

Table 5: Correlating factors for visual acuity in hydroxychloroquine retinopathy using multivariate linear regression analysis with forward selection

Models Selected variables	Coefficient (95% CI)	*P*
EZ band only (R^2=0.250)		
Age (year)	0.006 (0.005–0.008)	<0.001
Fovea (EZ)	0.305 (0.238–0.373)	<0.001
RPE only (R^2=0.352)		
Age (year)	0.008 (0.007–0.010)	<0.001
Fovea (RPE)	0.273 (0.127–0.419)	<0.001
Parafovea (RPE)	0.208 (0.071–0.345)	0.003
Both the EZ band and RPE (R^2=0.352)		
Age (year)	0.008 (0.007–0.010)	<0.001
Fovea (RPE)	0.273 (0.127–0.419)	<0.001
Parafovea (RPE)	0.208 (0.071–0.345)	0.003

RPE=Retinal pigment epithelium, EZ=Ellipsoid zone, CI=Confidence interval

Table 6: Correlating factors for visual acuity in hydroxychloroquine retinopathy using principal component analysis

Models Variables	Univariable analysis	
	Coefficient (95% CI)	*P*
PCA for EZ band only (R^2=0.248)		
Age (year)	0.006 (0.004–0.008)	<0.001
1st component of 4 regions in the EZ band	0.039 (0.016–0.062)	<0.001
2nd component of 4 regions in the EZ band	0.096 (0.073–0.119)	<0.001
PCA for RPE only (R^2=0.351)		
Age (year)	0.008 (0.007–0.010)	<0.001
1st component of 4 regions in RPE	0.059 (0.038–0.081)	<0.001
2nd component of 4 regions in RPE	0.121 (0.099–0.143)	<0.001
PCA for both EZ band and RPE (R^2=0.335)		
Age (year)	0.008 (0.006–0.010)	<0.001
1st component of 8 regions in the EZ band and RPE	0.127 (0.105–0.149)	<0.001
2nd component of 8 regions in the EZ band and RPE	0.031 (0.009–0.052)	<0.001
Sum of fovea and parafovea in RPE (R^2=0.354)		
Age (year)	0.008 (0.007–0.010)	<0.001
Sum of fovea and parafovea	0.242 (0.203–0.281)	<0.001

RPE=Retinal pigment epithelium, EZ=Ellipsoid zone, CI=Confidence interval, PCA=Principal component analysis

Table 7: Principal component loadings for different models

Variables	EZ				RPE			
	Fovea	Parafovea	Perifovea	Pericentral	Fovea	Parafovea	Perifovea	Pericentral
EZ band only								
1st component	0.935	0.544	0.366	0.280				
2nd component	0.337	0.776	0.901	0.921				
RPE only								
1st component					0.898	0.852	0.441	0.365
2nd component					0.361	0.447	0.858	0.897
EZ + RPE								
1st component	0.818	0.447	0.301	0.240	0.905	0.896	0.708	0.616
2nd component	0.444	0.841	0.913	0.907	0.228	0.289	0.603	0.652

RPE=Retinal pigment epithelium, EZ=Ellipsoid zone

other demographic data. It is found that this model had the highest goodness of fit with an R^2 of 0.354 [Table 7]. The equation for the model is as follows:

Predicted logMAR of BCVA = 0.242 × (original fovea score in RPE + original parafovea score in RPE) + 0.008 × Age − 0.329.

Discussion

In this study, we found that the majority of patients (66.7%) exhibited a mixed pattern of HCQ retinopathy, characterized by lesions in both the parafoveal and pericentral areas. The pericentral pattern was noted in 33.3% of cases, whereas no patient displayed the parafoveal pattern in our cohort. This can be attributed to the high incidence of severe HCQ retinopathy (61.9%) among our patients, all of whom exhibited the mixed type due to extensive macular involvement.

On examining patients with early-to-moderate HCQ retinopathy, the pericentral pattern predominated (87.5%), with no eye showing the parafoveal pattern. Notably, in early HCQ retinopathy, all cases demonstrated a pericentral pattern. This suggests that pericentral lesions typically manifest first in Taiwanese and then progress centrally toward the parafoveal and foveal regions. In fact, all patients with HCQ retinopathy exhibited pericentral lesions in the EZ band regardless of severity in this study. Conversely, the occurrence of the classic parafoveal lesions commonly seen in Caucasians was rare in our Taiwanese study group,[9] which is consistent with previous reports of HCQ retinopathy in Asians.[6,7] Furthermore, our findings indicated that the damage initially appeared in the EZ band and subsequently progressed to the RPE, which was also consistent with previous studies.[3,10-13]

The primary objective of this study was to assess the relationship between OCT characteristics and visual acuity in HCQ retinopathy. We found that disruptions in all regions of the EZ and RPE were all associated with poorer visual acuity, which is not surprising given previous research findings. Several studies[3,14,15]

have demonstrated the correlations between abnormal findings in these regions and visual outcomes in HCQ retinopathy. Marmor and Hu[3] concluded that the integrity of outer segment structures in the fovea predicted the retention of visual acuity. An OCT-based staging system proposed by Allahdina *et al*.[14] revealed a worse baseline and follow-up visual acuity with disruption involving the fovea in the EZ band. Sallam *et al*.[15] discovered that changes in central macular thickness, before clinically evident HCQ retinopathy, were associated with a decrease of visual acuity. To further investigate the key factors contributing to visual deterioration, we employed two different analytical approaches, multiple regression analysis with forward selection and PCA, to address the collinearity among different regions within the EZ and RPE. Both methods consistently indicated that RPE disruption provided a superior goodness of fit for explaining visual acuity deterioration compared to EZ disruption. In multiple regression analysis using forward selection, only RPE disruptions in the foveal and parafoveal regions were selected into the model, while EZ regions were not.

As for PCA, the model containing eight regions of the EZ band and RPE even had poorer predictability for visual acuity than the model containing four regions of RPE only. The principal components of the model containing RPE only showed that both the foveal and parafoveal regions of RPE were most significantly correlated with visual deterioration, whereas the perifoveal and pericentral regions of RPE were also correlated with less significance. These mean that disruption of RPE rather than EZ was the key factor for visual deterioration in HCQ retinopathy. We then chose age and the sum of fovea and parafovea of RPE for regression analysis, and it resulted in the model with the highest R^2. According to the model, RPE disruption at either the fovea or parafovea would increase the logMAR of BCVA by 0.242.

Previous studies[3,16-20] have indicated that retinopathy progression may continue for years following cessation of HCQ medication, and the severity of retinopathy at cessation would serve as a prognostic factor for progression magnitude. If HCQ treatment is discontinued early in the course of retinopathy, progression of the condition may be prevented or limited. Several studies have demonstrated potential for functional and/or structural improvement using advanced imaging and examinations.[14,20,21] Our study revealed that HCQ retinopathy in Taiwanese patients usually initiates in pericentral areas, so the diagnosis might potentially be delayed due to a mild initial impact on vision. However, encroachment into the central fovea or parafoveal regions would lead to irreversible visual deterioration. Thus, we advocate for the use of sensitive imaging techniques as recommended in guidelines[8] to screen for HCQ retinopathy and prevent vision loss. Timely cessation or reduction of HCQ intake, as long as the lesions are confined to pericentral or perifoveal areas, may halt disease progression and preserve vision.

A major limitation of this study is that some patients already presented with severe HCQ retinopathy involving multiple areas at the initial examination, making it uncertain which area developed disruption first. Nevertheless, our observations revealed that many cases exhibited lesions solely in pericentral areas, while only a few involved parafoveal areas alone. In addition, both eyes of the same patient may share similarities compared to the eyes of different patients, prompting us to use a linear mixed model to mitigate potential bias stemming from the hierarchical and repeated data structure. Our findings demonstrated that even after accounting for differences between and within subjects, disruption of the RPE at the fovea emerged as a critical predictor of visual acuity loss. Another limitation stems from the potential selection bias inherent in the retrospective design of our study. Approximately 30% of eligible eyes were excluded, and 12% of eyes exhibited other retinal comorbidities such as epiretinal membrane formation, as noted in a separate study.[22] Finally, in this study, we happened to enroll no cases of HCQ retinopathy with the parafoveal pattern. A longer, more consistent follow-up period with comprehensive OCT imaging and BCVA records could provide a more precise assessment of visual acuity outcomes and risk analysis. Despite these limitations, we believe that bias did not significantly influence our conclusions.

Conclusions

Our study revealed that in HCQ retinopathy, the majority of patients initially developed lesions in the pericentral areas, which subsequently progressed toward the central parafoveal and foveal regions. Damage to the central (foveal and parafoveal) regions of the RPE was the most significant determinant of visual deterioration in HCQ retinopathy. To prevent irreversible vision loss, regular follow-up screening for HCQ retinopathy using sensitive imaging techniques such as OCT, as recommended in guidelines for HCQ users, is essential.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Nil.

Conflicts of interest

Prof. Yi-Ting Hsieh, an an editorial board member at, *Taiwan Journal of Ophthalmology* had no role in the peer

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