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CLINICAL INVESTIGATION

A comparative study on the choroidal vascularity index and the determination of cut-off values in the pachychoroid spectrum diseases

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Abstract

Purpose To determine the cut-off levels for choroidal thickness and choroidal vascularity index (CVI) to differentiate among pachychoroid spectrum diseases.

Study design A retrospective comparative study

Methods A total of 143 eyes were included. Of these 29 had uncomplicated pachychoroid (UCP), 29 had pachychoroid pigment epitheliopathy (PPE), 25 had pachychoroid neovasculopathy (PNV), 30 had central serous chorioretinopathy (CSC), and 30 had polypoidal choroidal vasculopathy (PCV). The choroidal areas were measured with ImageJ software. The CVI, the proportion of the luminal area to the total choroidal area, was assessed.

Results The cut-off points of central choroidal thickness were determined as 360 μm for the PPE and PCV group pair (**$p < 0.001$**), 422 μm for the PNV and CSC group pair (**$p = 0.026$**), 271 μm for the PNV and PCV group pair (**$p < 0.001$**), and 341 μm for the CSC and PCV group pair (**$p < 0.001$**). The cut-off points of CVI were 72.7 for the PPE and PCV group pair (**$p < 0.001$**), 74.7 for the PNV and CSC group pair (**$p = 0.005$**), 72.6 for the PNV and PCV group pair (**$p = 0.001$**), and 73.6 for the CSC and PCV group pair (**$p < 0.001$**).

Conclusion Pachychoroid spectrum may be composed of a combination of distinct choroidal diseases with different vascular and structural characteristics.

Keywords Choroidal vascularity index · Central serous chorioretinopathy · Pachychoroid neovasculopathy · Pachychoroid pigment epitheliopathy · Polypoidal choroidal vasculopathy

Introduction

The pachychoroid spectrum reflects a group of clinical situations that have a thickened choroid or thick choroidal vessels [1]. These entities are referred to as pachychoroid pigment epitheliopathy (PPE), central serous chorioretinopathy (CSC), pachychoroid neovasculopathy (PNV), and polypoidal choroidal vasculopathy (PCV); there are other, newly described forms of pachychoroid such as peripapillary pachychoroid syndrome and focal choroidal excavation [2–4]. There is no consensus on whether these are different diseases that have a common characteristic (a thick choroid) or stages of the same disease. If they are indeed different stages of the same disease, the predicting factor for the development of choroidal neovascularization (CNV) or the presence of recurrent subretinal fluid or pigment epithelial detachment (PED), as shown in CSC cases, remains unknown.

In the evaluation of the choroid, the conventional methods, such as B scan optical coherence tomography (OCT) or enhanced depth imaging (EDI) mode, only give an idea about the subfoveal choroidal thickness and enable us to collect patients under the same terminology, such as pachychoroid, by calculating the thickness. These measurements do not give a clue about the morphology of the choroid, that is, the ratio of the lumen and stroma to the total choroid, as well as which part in each subgroup is mostly compromised. The only study evaluating the choroidal vascularity index (CVI) in different pachychoroid

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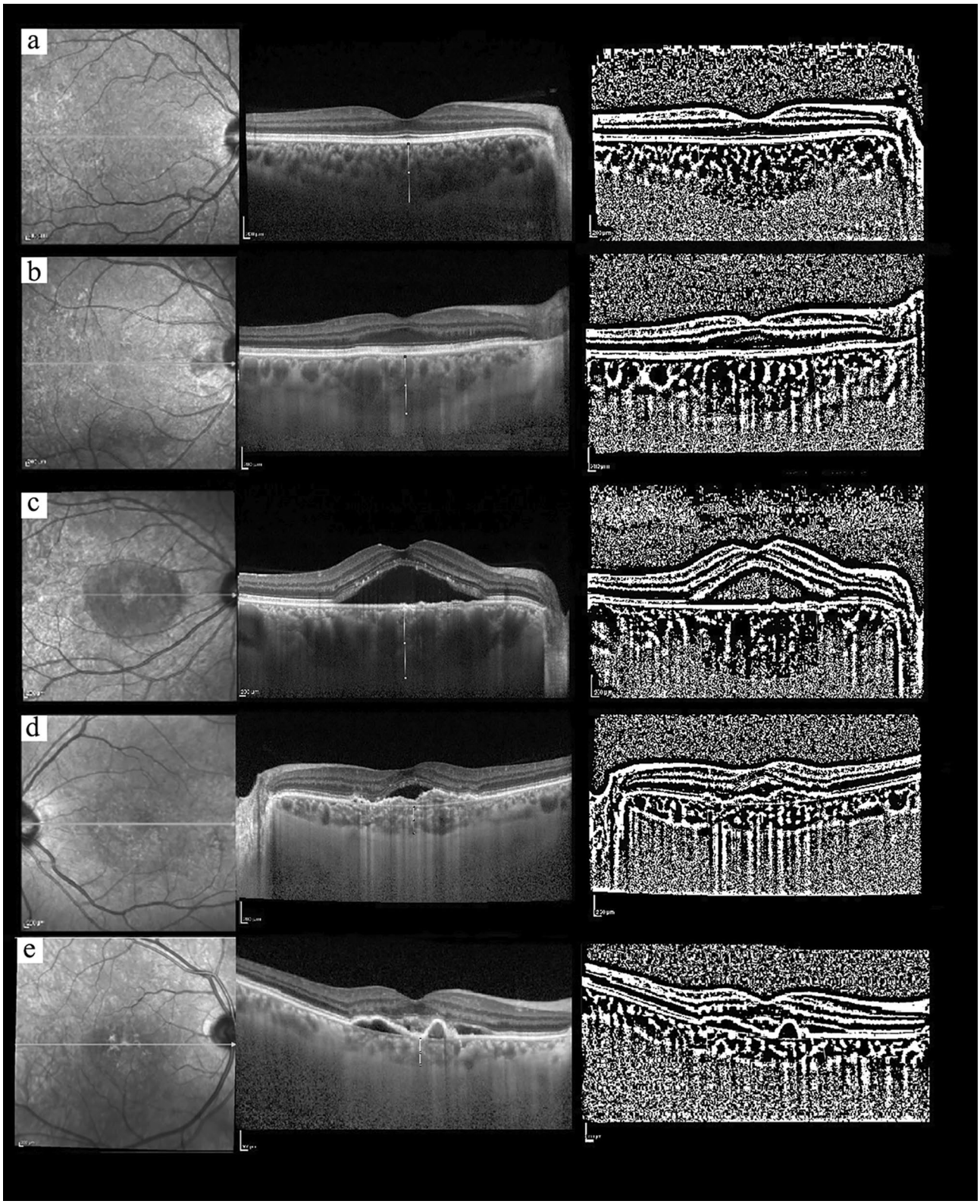

spectrum diseases (PSDs) claimed that PSDs could involve different predominant pathogenic processes, as a significantly smaller stromal area (SA) was observed in the eyes of CSC patients than in the eyes of the control, PPE, PNV, or myopic CNV patients [5]. Another recent study showed that fellow eyes of different pachychoroid groups have a diverse morphology depicted by their vascular index [6]. A study that mainly focused on the

◂**Fig. 1** EDI-OCT images of pacychoroid spectrum and converted binary images with the area of interest in the choroid demarcated with a line. a) The eye of a patient with UCP. The CCT, the choroidal area and the CVI were measured 517 µm, 1.569 mm^2, 73.34% respectively. b) The eye of a patient with PPE. The CCT, the choroidal area and the CVI were measured 525 µm, 1.657 mm^2, 74.57% respectively. c) The eye of a patient with CSC. The CCT, the choroidal area and the CVI were measured 630 µm, 1.902 mm^2, 77.26% respectively. d) The eye of a patient with PNV. The CCT, the choroidal area and the CVI were measured 242 µm, 0.717 mm^2, 70.64% respectively. e) The eye of a patient with PCV. The CCT, the choroidal area and the CVI were measured 228 µm, 0.706 mm^2, 64.96% respectively. EDI-OCT: enhanced depth imaging/ optical coherence tomography, UCP: uncomplicated pachychoroid, CCT: central choroidal thickness, CVI: choroidal vascularity index, PPE: pachychoroid pigment epitheliopathy, CSC: central serous chorioretinopathy, PNV: pachychoroid neovasculopathy, PCV: polypoidal choroidal vasculopathy

choroidal vascular characteristics of age-related macular degeneration (AMD), PCV, and CSC using swept-source OCT reported similarities in the vascular density of the large choroidal vessel layer and a diffuse pachyvessel pattern between the CSC group and the thick choroid PCV group [7]. However, the pattern of pachyvessels was focal in non-neovascular AMD, neovascular AMD, and thin choroid PCV. According to these studies, different pachychoroid diseases may indicate different predominant pathogenic processes.

We believe that performing a CVI analysis on these groups of pachychoroid can enlighten us regarding their etiopathogeneses. With our current understanding, the definitions of these groups are not yet well described. Pang and Freund described PNV as a new clinical entity characterized by increased choroidal thickness or enlarged choroidal vessels and neovasculopathy without any previous fluid from CSC [8]. However, in a real clinical setting, it is not possible to ascertain in every case that patients had CSC before they acquired CNV above a thick choroid or choroidal vessels. It does not necessarily mean that a gravitational defect in an eye diagnosed with PNV had previous CSC or vice versa. Most of the studies included eyes with CNV and considered a thick choroid as PNV regardless of patients' previous history of CSC. This is why the definition of PNV is slightly misconstrued, and we have to find a quantitative definition to understand whether these conditions are different from each other.

As far as we know, no study has yet reported quantitative data and a cut-off level using the binarization method and evaluated the CVI of eyes with different PSD. This study aimed to set a cut-off level to differentiate pachychoroid spectrum diseases rather than just placing them in the same group by considering their choroidal morphology by calculating the vascular index.

Materials and methods

Patient selection

This retrospective cross-sectional study was approved by the Institutional Review Board Committee of Ankara University (İ2-128–20). A total of 143 eyes of 143 patients diagnosed with uncomplicated pachychoroid (UCP), pachychoroid pigment epitheliopathy (PPE), pachychoroid neovasculopathy (PNV), central serous chorioretinopathy (CSC), and polypoidal choroidal vasculopathy (PCV) were included in the study. The differential diagnosis of PCV depended on the criteria defined by the EVEREST study [9]. Baseline findings of the patients before treatment were included. Patients with systemic diseases and chorioretinal and inflammatory ocular diseases that could affect clinical findings, patients with media opacities preventing adequate imaging, and patients with previous ocular surgery or laser photocoagulation were excluded from the study.

The primary outcome measures of this study were to compare the central choroidal thickness (CCT), luminal area (LA), and CVI measurements between groups and to determine the cut-off point for these parameters for each pair of diseases.

Study protocol

EDI-OCT (Spectralis®, Heidelberg Engineering Inc.) was performed on all subjects after pupillary dilatation. EDI-OCT was conducted using the technique described by Spaide et al. [10]. The device was set closer to the eye, producing an inverted mirror image of the retina, and the choroid was placed closer to the zero delay line, increasing the signal depth to visualize the choroid in detail.

The choroidal area (CA) was binarized to the LA and SA using ImageJ software (version 1.50a; National Institutes of Health) (Fig. 1). The CA was measured manually at 3000 µm wide, with margins of 1500 µm nasal and 1500 µm temporal from the foveal center horizontally and from the RPE to the chorioscleral border vertically. Binarization was performed using the Niblack auto local threshold method. The white pixels were accepted as the SA, and the dark pixels were accepted as the LA [11].

Statistical analysis

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences version 15.0). A Shapiro–Wilk test was performed to detect normality. Analysis of variance

(ANOVA) was performed to evaluate the following parametric variables: CCT, nasal choroidal thickness, temporal choroidal thickness, CA, LA, and SA. The Kruskal–Wallis test was performed to evaluate the following non-parametric variables: CVI, stromal-to-choroidal ratio, and luminal-to-stromal ratio. The Bonferroni-corrected results for ANOVA and Dunn's test results for the Kruskal–Wallis test were assessed for pairwise comparison. To determine the diagnostic cut-off point, the receiver operating characteristic (ROC) curves and the area under the curve were calculated using the Youden index. In addition, analysis of covariance (ANCOVA) test was performed in order to take into consideration the effect of age on these parameters. The data adjusted for age and corrected means were estimated with standard error and 95% confidence interval.

Results

The mean age was 47.2 ± 9.4 years in UCP group, 48.3 ± 8.8 years in PPE group, 44.9 ± 9.8 years in CSC group, 52.7 ± 9.5 years in PNV, and 66.7 ± 9.1 years in PCV group ($p < 0.001$). Pairwise comparisons revealed statistically significant differences between CSC/PCV groups ($p < 0.001$), UCP/PCV groups ($p < 0.001$), PPE/PCV groups ($p < 0.001$), and PNV/PCV groups ($p = 0.004$). The mean manifest refractive spherical equivalents were 0.14 ± 1.71 D in UCP, 0.71 ± 1.9 D in PPE, 0.20 ± 1.7 in for CSC, 0.45 ± 1.8 D in PNV, and 0.63 ± 1.2 D in PCV ($p = 0.822$).

Among the 143 eyes, 29 had UCP, 29 had PPE, 25 had PNV, 30 had CSC, and 30 had PCV. The structural OCT measurements of the groups are summarized in **Table 1**. The mean CCT thicknesses was 404.6 ± 122.5 µm in the UCP group, 471.9 ± 141.1 µm in the PPE group, 388.8 ± 139.4 µm in the PNV group, 494.3 ± 125.6 µm in the CSC group, and 230.4 ± 119.6 µm in the PCV group, and the difference between groups was statistically significant (**$p < 0.001$**). **Table 2** shows the significance for comparison of each pair. The cut-off points of the OCT measurements of the PPE and PNV groups, PPE and PCV groups, PNV and CSC groups, PNV and PCV groups, and CSC and PCV groups are outlined in **Table 3.** The cut-off points of CCT were determined as 360 µm for the PPE and PCV group pair (**$p < 0.001$**), 422 µm for the PNV and CSC group pair (**$p = 0.026$**), 271 µm for the PNV and PCV group pair (**$p < 0.001$**), and 341 µm for the CSC and PCV group pair (**$p < 0.001$**). The ROC curves are given in **Fig. 2.**

The mean luminal area determined by the binarization of the EDI-OCT images was the highest in the PPE and CSC groups. The measured values of the mean LA were 0.885 ± 0.31 mm^2 in the UCP group, 1.021 ± 0.40 mm^2 in the PPE group, 0.848 ± 0.33 mm^2 in the PNV group, 1.090 ± 0.37 mm^2 in the CSC group, and 0.540 ± 0.22 mm^2 in the PCV group, and the difference between groups was statistically significant (**$p < 0.001$**). The cut-off points of LA were determined as 0.834 mm^2 for the PPE and PNV group pair ($p = 0.058$), 0.834 mm^2 for the PPE and PCV group pair (**$p < 0.001$**), 0.794 mm^2 for the PNV and CSC group pair (**$p = 0.036$**), 0.728 mm^2 for the PNV and PCV group pair (**$p = 0.001$**), and 0.796 mm^2 for the CSC and PCV group pair (**$p < 0.001$**).

The mean CVIs were 74.4 ± 3.2 in the UCP group, 75.1 ± 3.4 in the PPE group, 73.5 ± 3.0 in the PNV group, 75.8 ± 1.5 in the CSC group, and 71.3 ± 4.4 in the PCV group, and the difference between groups was statistically significant (**$p < 0.001$**). The mean CVI was the lowest in the PCV group, and the pairwise comparisons of the PCV group with the other groups except PNV were significant. Likewise, the pairwise comparison of CVI in PNV and CSC was significant. The cut-off points of CVI were determined as 72.7 for the PPE and PCV group pair (**$p < 0.001$**), 74.7 for the PNV and CSC group pair (**$p = 0.005$**), 72.6 for the PNV

Table 1 Mean values of measurements for uncomplicated pachychoroid (UCP), pachychoroid pigment epitheliopathy (PPE), pachycoroid neovasculopathy (PNV), central serous chorioretinopathy (CSC), and polypoidal choroidal vasculopathy (PCV) groups (Mean ± Standard deviation)

Variables	UCP n = 29	PPE n = 29	PNV n = 25	CSC n = 30	PCV n = 30	p values
Central choroidal thickness (µm)	404.6 ± 122.5	471.9 ± 141.1	388.8 ± 139.4	494.3 ± 125.6	230.4 ± 119.6	**< 0.001**[a]
Nasal choroidal thickness (µm)	340.4 ± 97.8	407.9 ± 138.8	329.0 ± 132.6	443.8 ± 113.9	266.6 ± 102.4	**< 0.001**[a]
Temporal choroidal thickness (µm)	361.6 ± 114.7	392.1 ± 129.5	347.7 ± 131.4	406.1 ± 107.1	237.1 ± 91.9	**< 0.001**[a]
Choroidal area (mm^2)	1.185 ± 0.41	1.358 ± 0.46	1.149 ± 0.43	1.437 ± 0.49	0.758 ± 0.31	**< 0.001**[a]
Luminal area (mm^2)	0.885 ± 0.31	1.021 ± 0.40	0.848 ± 0.33	1.090 ± 0.37	0.540 ± 0.22	**< 0.001**[a]
Stromal area (mm^2)	0.300 ± 0.10	0.337 ± 0.13	0.301 ± 0.11	0.347 ± 0.11	0.218 ± 0.08	**< 0.001**[a]
CVI (%)	74.4 ± 3.2	75.1 ± 3.4	73.5 ± 3.0	75.8 ± 1.5	71.3 ± 4.4	**< 0.001**[b]
S/C ratios (%)	25.6 ± 3.2	24.9 ± 3.4	26.5 ± 3.0	24.2 ± 1.5	28.7 ± 4.4	**< 0.001**[b]
L/S ratios	3.0 ± 0.5	3.0 ± 0.7	2.8 ± 0.4	3.1 ± 0.2	2.5 ± 0.6	**< 0.001**[b]

[a,b]: Indicates the test used. ANOVA or Kruskal–Wallis, respectively

Table 2 P values for pairwise comparisons*

Variables	UCP vs PPE	UCP vs CSC	UCP vs PNV	UCP vs PCV	PPE vs PNV	PPE vs CSC	PPE vs PCV	PNV vs CSC	PNV vs PCV	CSC vs PCV
Central choroidal thickness (µm)	0.500	0.088	1.000	**< 0.001**	0.202	1.000	**< 0.001**	**0.031**	**< 0.001**	**< 0.001**
Nasal choroidal thickness (µm)	0.306	**0.010**	1.000	0.175	0.153	1.000	**< 0.001**	**0.004**	0.523	**< 0.001**
Temporal choroidal thickness (µm)	1.000	1.000	1.000	**0.005**	1.000	1.000	**< 0.001**	0.633	**0.005**	**< 0.001**
Choroidal area (mm^2)	0.505	0.240	1.000	**0.002**	0.288	1.000	**< 0.001**	0.133	**0.012**	**< 0.001**
Luminal area (mm^2)	1.000	0.205	1.000	**0.001**	0.592	1.000	**< 0.001**	0.087	**0.010**	**< 0.001**
Stromal area (mm^2)	1.000	1.000	1.000	0.062	1.000	1.000	**0.001**	1.000	0.078	**< 0.001**
CVI (%)	1.000	0.744	1.000	**0.034**	0.319	1.000	**0.001**	**0.037**	1.000	**< 0.001**
S/C ratios (%)	1.000	0.744	1.000	**0.034**	0.319	1.000	**0.001**	**0.037**	1.000	**< 0.001**
L/S ratios	1.000	0.744	1.000	**0.034**	0.319	1.000	**0.001**	**0.037**	1.000	**< 0.001**

UCP: uncomplicated pachychoroid, PPE: pachychoroid pigment epitheliopathy, PNV: pachycoroid neovasculopathy, CSC: central serous chorioretinopathy, PCV: polypoidal choroidal vasculopathy

*: Bonferroni corrected results for ANOVA and Dunn's test results for Kruskal–Wallis Test

and PCV group pair (**p = 0.001**), and 73.6 for the CSC and PCV group pair (**p < 0.001**).

ANCOVA test was performed in order to take into consideration the effect of age on choroidal parameters. The data adjusted for age and corrected means were estimated with standard error (**Table 4**). According to the results of ANCOVA analysis, the effect of age was statistically significant as a covariate for central (p < 0.001), nasal (p < 0.001), and temporal (p = 0.008) choroidal thicknesses, total CA (p = 0.009) and LA (p = 0.005) measurements. However, for the proportional parameters (CVI, S/C%, L/S) and SA, the results of ANCOVA test did not detect significant effect of age as a covariate on these parameters (p = 0.126, p = 0.126, p = 0.102, p = 0.065, respectively). P values for pairwise comparisons of parameters for which age is a statistically significant covariate are shown in **Table 5**. The estimated mean CCTs of PCV vs PPE (p = 0.001) and CSC vs PCV (p = 0.001) groups were significantly different. Regarding binarized measurements, estimated mean CAs of PCV vs PPE (p = 0.011) and CSC vs PCV (p = 0.029) groups were significant. Also for LA, estimated means of PCV vs PPE (p = 0.007) and CSC vs PCV (p = 0.016) groups were significant.

Discussion

This study was the first to compare the morphological and structural differences in the all PSDs, with the ImageJ binarization method and to determine the cut-off values of CCT and CVI to differentiate these diseases. The results of our study demonstrate that CCT and CVI had the lowest measurements in the PCV group and that the highest measurements were detected in the CSC group. Based on the results of our study, UCP, PPE, and CSC could be speculated to comprise progressive stages of the same pathology. As the abnormality in the choroid progresses, UCP could turn into PPE with the disruption of RPE by the pachyvessels underneath. Then, the CSC could develop with the emergence of subretinal fluid once the RPE is affected to an extend that it is unable to compensate for. However, compared with the other entities the increase in the vascular component was not prominent in the PCV and PNV groups.

An abnormality in the choroidal vascular status is a suspect factor in the etiopathogenesis of PSDs. The advent of the EDI mode enabled the measurement of the choroidal thickness and the visualization of the vascular and stromal compartments in two dimensions. This enabled the identification of the increased central choroidal thickness, making it possible to identify these diseases as pachychoroid; the dilatation of the choroidal vessels was assumed to be a causative factor for this increase [12, 13]. Further studies used the largest choroidal vessel diameter as a quantitative

Table 3 Receiver operating characteristic based cut-points+

Variables	PPE vs PNV[1]	PPE vs PCV[1]	PPE vs CSC[2]	PNV vs CSC[2]	PNV vs PCV[3]	CSC vs PCV[2]
Central choroidal thickness (μm)	446 p = 0.110 (AUC:0.631)	360 **p < 0.001** (AUC:0.897)	380 p = 0.635 (AUC:0.536)	422 **p = 0.026** (AUC:0.680)	271 **p < 0.001** (AUC:0.828)	341 **p < 0.001** (AUC:0.930)
Choroidal area (mm^2)	1.101 p = 0.085 (AUC:0.641)	1.107 **p < 0.001** (AUC:0.870)	1.970 p = 0.882 (AUC:0.511)	1.082 **p = 0.048** (AUC:0.659)	1.155 **p = 0.001** (AUC:0.765)	1.088 **p < 0.001** (AUC:0.892)
Luminal area (mm^2)	0.834 p = 0.058 (AUC:0.655)	0.834 **p < 0.001** (AUC:0.881)	1.052 p = 0.840 (AUC:0.515)	0.794 **p = 0.036** (AUC:0.670)	0.728 **p = 0.001** (AUC:0.783)	0.796 **p < 0.001** (AUC:0.899)
Stromal area (mm^2)	0.293 p = 0.198 (AUC:0.606)	0.314 **p < 0.001** (AUC:0.808)	0.375 p = 1.000 (AUC:0.500)	0.292 p = 0.156 (AUC:0.614)	0.322 **p = 0.023** (AUC:0.688)	0.312 **p < 0.001** (AUC:0.823)
CVI (%)	74.8 p = 0.057 (AUC:0.656)	72.7 **p < 0.001** (AUC:0.832)	74.2 p = 0.474 (AUC:0.555)	74.7 **p = 0.005** (AUC:0.728)	72.6 **p = 0.001** (AUC:0.765)	73.6 **p < 0.001** (AUC:0.885)
S/C ratios (%)*	25.2 p = 0.057 (AUC:0.656)	27.3 **p < 0.001** (AUC:0.832)	25.8 p = 0.474 (AUC:0.555)	25.3 **p = 0.005** (AUC:0.728)	27.4 **p = 0.001** (AUC:0.765)	26.4 **p < 0.001** (AUC:0.885)

+Youden indexes

AUC: Area Under Curve, UCP: uncomplicated pachychoroid, PPE: pachychoroid pigment epitheliopathy, PNV: pachycoroid neovasculopathy, CSC: central serous chorioretinopathy, PCV: polypoidal choroidal vasculopathy

[1] Values higher than cut-off indicate PPE except S/C ratio

[2] Values higher than cut-off indicate CSC except S/C ratio

[3] Values higher than cut-off indicate PNV except S/C ratio,

Bold values indicate statistically significant p values

*S/C ratios were inversely proportional with other choroidal measurements

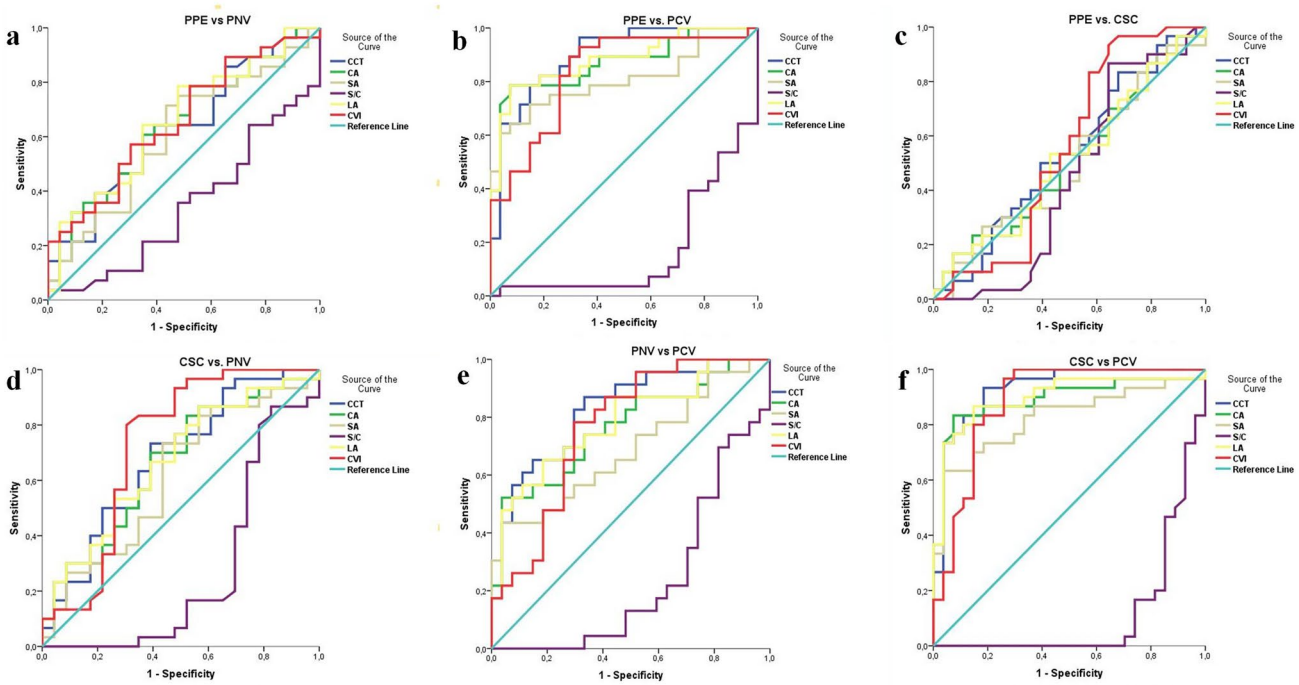

Fig. 2 Receiver operating characteristic curves of all group pairs

Table 4 Age adjusted mean values and standard errors (SE) of measurements for uncomplicated pachychoroid (UCP), pachychoroid pigment epitheliopathy (PPE), pachycoroid neovasculopathy (PNV), central serous chorioretinopathy (CSC), and polypoidal choroidal vasculopathy (PCV) groups

Variables	UCP n = 29		PPE n = 29		PNV n = 25		CSC n = 30		PCV n = 30		p* value
	Mean	**SE**	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**	
Central choroidal thickness (µm)	393.36	23.7	461.53	23.5	407.72	25.6	465.72	23.7	304.8	29.2	**< 0.001**
Nasal choroidal thickness (µm)	327.7	21.5	399.5	21.2	343.7	23.1	415.7	21.4	339.6	26.4	**< 0.001**
Temporal choroidal thickness (µm)	352.9	21.8	383.7	21.6	356.05	23.5	386.5	21.8	284.8	26.8	**0.008**
Choroidal area (mm^2)	1.159	0.08	1.388	0.08	1.200	0.09	1.368	0.08	0.950	0.10	**0.009**
Luminal area (mm^2)	0.863	0.06	1.041	0.06	0.891	0.07	1.033	0.06	0.692	0.08	**0.005**
Stromal area (mm^2)	0.297	0.02	0.347	0.02	0.309	0.02	0.335	0.02	0.258	0.03	0.065
CVI (%)	74.3	0.6	75.0	0.6	74.1	0.6	75.5	0.6	71.2	0.7	0.126
S/C ratios (%)	25.7	0.6	25.0	0.6	25.9	0.6	24.5	0.6	28.8	0.7	0.126
L/S ratios	2.9	0.08	3.1	0.08	2.9	0.09	3.1	0.08	2.6	0.10	0.102

*p values indicate the effect of age as a covariative on each parameter

Bolded p values indicate the statistically significance

parameter [14]. The diameter of the largest lumen was reported as significantly correlated with the total choroidal thickness in CSC and was significantly larger than in the eyes of the control group [14]. However, the diameter of a single vessel may not be representative of alterations in the entire choroidal vasculature. The novel binarization method for further analysis of these images enabled the repeatable and reproducible measurements of these spaces and provided quantitative data [15].

Recently, CVI has been serving as an index of proportionate changes in the vasculature of the choroid and defined as both a diagnostic marker and a follow-up tool in choroidal diseases [16, 17]. A high CVI depends on the increase in the number of vascular channels and\or the diameter of channels, whereas a low CVI is caused by the attenuation of choriocapillaris, which is the reduction in size of choroidal vessels and\or loss of large choroidal vessels [18]. The CVI is a more reliable tool for the quantification of choroidal vessels, whereas choroidal thickness that may be affected by various factors such as age, ocular and systemic parameters [19]. Furthermore, its noninvasive nature and high repeatability make it a reliable research tool [18]. In the present study, the CSC group had the highest CVI, followed by PPE and UCP. A high ratio of CVI in CSC was reported in the literature after the images were processed by ImageJ software. Ambiya et al. found a marginally higher CVI in steroid-induced CSC compared with idiopathic CSC [20]. Agrawal et al. reported an increased CVI in affected eyes of CSC cases compared with fellow ones [16]. A higher CVI was reported not only in diseased eyes but also in fellow eyes of CSC patients. In Agrawal et al.'s study, fellow eyes also had a higher CVI than age-matched healthy subjects. Similarly, in our previous study, we demonstrated that the CVI of the fellow eyes of CSC cases was significantly higher than that of the healthy control group [6].

The PCV group had the lowest CVI, which was statistically different from other groups except PNV, suggesting that the alteration in the choroidal vascularity was lower and more limited in this group. A study evaluating CVI in PCV divided the PCV cases into two subgroups depending on the presence of choroidal hyperpermeability. Surprisingly, CVI in PCV without choroidal hyperpermeability was reported to be even lower than in healthy eyes and CVI in PCV with choroidal hyperpermeability did not show any difference from the healthy controls [21]. Another study reported an interesting finding that PCV eyes with a high baseline CVI had significantly lower stroma but a slightly higher luminal area than eyes with a low baseline CVI [22]. The study speculated that the dilated choroidal vasculature in eyes with a high CVI could be accompanied by a compressed or atrophied choroidal stroma. Lee et al. found a lower CVI but a greater ratio of Haller's layer to CCT in eyes with PCV compared with controls [23]. Furthermore, a choroidal structural analysis comparing PCV and CNV secondary to AMD indicated no difference in CVI [24]. Gupta et al. found that after adjusting for age and hypertension, no significant difference was observed between typical AMD and PCV eyes in terms of choroidal thickness and choroidal vascular area [25]. This information supports the idea that in PCV, even if the ratio of CVI is very close to AMD, the localized enlarged Haller's vessels and compromised stroma around it causes PCV. It means it is not a diffuse disease such as that seen in CSC that is causing high ratio of CVI. At the same time, the topic of PCV and its further subclassifications remains controversial.

Previous studies have reported that the frequency of having a complication of type 1 CNV is 3%–9% in long-term

Table 5 P values for pairwise comparisons of parameters for which age was a statistically significant covariate according to the results of analysis of covariance test

Variables	UCP vs PPE	UCP vs CSC	UCP vs PNV	UCP vs PCV	PPE vs PNV	PPE vs CSC	PPE vs PCV	PNV vs CSC	PNV vs PCV	CSC vs PCV
Central choroidal thickness (µm)	0.394	0.267	1.000	0.282	1.000	1.000	**0.001**	1.000	0.081	**0.001**
Nasal choroidal thickness (µm)	0.168	**0.031**	1.000	1.000	0.790	1.000	0.937	0.251	1.000	0.424
Temporal choroidal thickness (µm)	1.000	1.000	1.000	0.657	1.000	1.000	0.070	1.000	0.450	0.079
Choroidal area (mm^2)	0.394	0.566	1.000	1.000	1.000	1.000	**0.011**	1.000	0.536	**0.029**
Luminal area (mm^2)	0.358	0.423	1.000	0.989	0.955	1.000	**0.007**	1.000	0.455	**0.016**

UCP: uncomplicated pachychoroid, PPE: pachychoroid pigment epitheliopathy, PNV: pachycoroid neovasculopathy, CSC: central serous chorioretinopathy, PCV: polypoidal choroidal vasculopathy

Bolded p values indicate the statistically significance.

CSC [26, 27]. However, in recent studies on flat irregular PED, CNV frequency has been reported to be as high as 35.6% [28]. This increase in frequency may be explained by the assumption of choroidal neovascularization secondary to CSC and PNV, the same disorder that was found following the recognition of flat irregular pigment epithelial detachment and the existence of type-1 CNV especially thanks to the help of optical coherence tomography. However, we believe that the etiopathogenesis of CSC and PNV may be distinct rather than different progressing stages of the same disease. A recent study evaluating genetic variations in CSC, PCV, and type 1 CNV reported supporting findings [29]. The authors divided the CSC group into two subtypes depending on the presence of irregular PED and analyzed 10 known major AMD-associated single-nucleotide polymorphisms. Researchers speculated that patients with irregular PED are genetically different from those without irregular PED and may have a genetic and pathophysiologic overlap with AMD patients. Therefore, we excluded any pachychoroid CNV case with a previous history of CSC attacks or imaging findings in favor of chronic CSC to create an exclusive PNV group.

Aside from sharing common choroidal findings, such as a thick choroid and dilated outer choroidal vessels, some PSDs subgroups, such as PNV and PCV, have distinct findings. If all PSDs are in the same spectrum of a disease, long-term prospective studies can be expected to show a development of one type into the other. However, a recent longitudinal prospective study conducted by Karaçorlu et al. reported that PPE eyes could develop CSC (17.4%) in the long term, but none of the eyes had developed pachychoroid CNV. The results of this study are important due to its prospective nature, and they revealed that none of the eyes developed CNV after PPE in the long term (at least three years) [30]. In accordance with Karaçorlu et al.'s study, PPE eyes have a similar CVI or choroidal morphology as the CSC eyes in our study. Moreover, the CSC cases had significantly higher CCT and CVI values than PNV. In the current literature, data about CVI alterations in PNV are limited. Lee et al. revealed a significantly higher CVI in the eyes of CSC patients than in the controls, PPE, PCN, or myopic CNV patients [5]. In examining CVI in CSC, Kim et al. divided patients into acute CSC, chronic CSC without flat irregular PED, and chronic CSC with flat irregular PED groups. Patients with CSC with flat irregular PED were further divided into flat irregular PED with CNV (vascularized PED) and flat irregular PED (non-vascularized PED) without CNV groups [31]. Eyes with CNV complicating CSC were reported to be a significantly lower choroidal vascular component than those with CSC without CNV. The authors suggested that the reduction of CVI in eyes with CNV could imply secondary choroidal changes due to CNV or an underlying choroidal ischemia. However, we believe that the low CVI ratio in this

group may be due to the acceptance of PNV eyes as CSC with flat irregular detachment and CNV.

Recently, CSC has been reported to be associated with vortex vein congestion that develops in eyes with asymmetric vortex veins [32]. In the same study, in contrast to acute CSC, chronic CSC was shown to have lower CCT values because vortex vein congestion was compensated with anastomosis across the horizontal watershed. Therefore, it can be speculated that, as the disease prolongs, pachychoroid features may become less obvious due to activated compensatory mechanisms. Similarly, Matsumoto et al. indicated that remodeling of choroidal drainage route was established through anastomosis at the watershed in PNV [33]. In this way, choroidal thickness further reduced and CNV arises from anastomotic vessels. Although all these results may be helpful in attempting to explain the lower choroidal values obtained in PNV and PCV groups, it is still controversial whether the one stage of the pachycoroid spectrum progresses to one of the other stages. These findings do not necessarily mean that these diseases develop out of an initial CSC. To expand this issue, we believe that longitudinal studies evaluating the long term follow-up of CSC cases that will focus on the issue of whether one pachychoroid disease develops into one of the others is necessary. Also we don't know whether CNV secondary to CSC and PNV cases are in same category as that discussed above. We concluded that according to our morphological study, it is still possible to think that PCV and PNV may be localized vascular disorders comprising not the whole but a limited choroidal area.

The major limitations of this study are its retrospective cross-sectional design and the relatively small sample size to estimate the cut-off values. Moreover, the CVI measurements were performed on two-dimensional EDI-OCT scans, which could not represent the entire choroid. More intensified volume scan protocols and the binarization of these volume scans are needed. Therefore, future studies should include many cases throughout a defined follow-up period. Finally, the CVI values were measured from single 2-dimensional scans and may not represent the entire choroidal vasculature.

In conclusion, the exact pathogenesis of PSDs has not yet been elucidated. The pachychoroid spectrum may be composed of a combination of distinct choroidal diseases with different vascular and structural characteristics. The different etiopathogenesis of these diseases may lead to common pachychoroid features.

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