

## Optical Coherence Tomography Angiography (OCT-A) in Exudative Age-related Macular Degeneration (nAMD)

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**Abstract:**

**Aim:** To determine specificity and sensitivity of OCT-A in detecting choroidal neovascular lesions (CNV) in eyes with suspected nAMD. **Setting:** Al Mashreq Eye Center, in the period between Jul-2021 to Nov-2021. **Methods:** A prospective, comparative study included 44 eyes to assess accuracy of OCT-A in the detection of nAMD compared to conventional OCT. Eyes were divided into a study group with nAMD, and a control group with dry AMD. OCT of the central macula was conducted, followed by OCT-A. **Results:** This study was performed on 25 patients with a mean age of  $69.88 \pm 8.31$  years. The mean BCVA was  $0.45 (\pm 0.31)$ , and that of SE was  $0.16 (\pm 1.52)$ . IOP had a mean of  $15.39 (\pm 3.08)$ . According to SD-OCT criteria; 24 eyes (54.5%) were diagnosed as dry AMD, and 20 eyes (45.5%) with nAMD. Cases of nAMD were subdivided into type-1 (70%), and type-2 (30%). For eyes with type 1, 8 cases (57.1%) had an associated fibrovascular PED. Using OCT-A, 28 eyes were classified as dry AMD, and 16 eyes with nAMD that were differentiated into: Type-1 (6-cases), Type-1 with PED (5-cases) and Type-2 (5-cases). There was no statistically significant difference between OCT and OCT-A regarding percentage of positive cases ( $p=0.386$ ), and their finding of type-1, type-1 with PED, and type-2 ( $p=1.000$ ). **Conclusion:** There was a statistically

significant relation in classification agreement between SD-OCT and OCT-A findings ( $p < 0.001$ ). OCT-A demonstrated a sensitivity of 70.0%, specificity of 91.7%, and accuracy of 81.8% in prediction of OCT results.

**Key Words:** OCT-A , CNV , AMD , Wet AMD

### Introduction:

Age-related macular degeneration (AMD) is one of the leading causes of visual impairment in the aging population, with an estimated incidence of 6.8% in the

population age of 40 years and older.<sup>(1)</sup> It is categorized into dry AMD with deposition of drusen between the retinal pigment epithelium (RPE) and the Bruch's

membrane followed by atrophy of the overlying RPE and outer retinal layers, and wet AMD (or neovascular AMD, nAMD) with choroidal neovascular membrane (CNV) formation that results in exudation and hemorrhage.<sup>(2)</sup> The latter category has been subject of great focus since therapeutic options exist for reversing or limiting its morbidity.<sup>(3)</sup> Fundus fluorescein angiography (FFA) remains the gold-standard test for diagnosis of nAMD. The combined use of optical coherence tomography (OCT) with color fundus photographs was shown to attain comparable sensitivity to FFA.<sup>(4)</sup> OCT angiography (OCT-A) is a non-invasive technology that provides depth-resolved images of blood flow within both the choroid and retina, that makes its value in detection deep vascular lesions, such as CNV.<sup>(5)</sup> The diagnostic accuracy of OCT-A for CNV, was found to have a positive likelihood ratio of 97%.<sup>(6)</sup> However, OCT-A has some limitations, superficial vessels may obscure the deeper layers, and artefacts are also common.<sup>(7)</sup> This has somewhat limited the sensitivity of the test in detecting CNV.<sup>(6)</sup> So, it is used as a diagnostic tool for nAMD but is not part of the standard approach.<sup>(7)</sup> Consequently, the best choice for imaging nAMD has remained a subject of debate.<sup>(6)</sup> More research is needed to determine the most appropriate test for each stage of the disease, so that the efficacy of imaging utilization is increased.

### **Aim of the Work:**

To determine the specificity and sensitivity of OCT-A in detecting CNV lesions in eyes with suspected nAMD.

### **Patients and Methods:**

#### **Study Design & Setting:**

This was a prospective, comparative, diagnostic study including 44-eyes that set out to assess the accuracy of OCT-A in the detection of nAMD compared to conventional OCT. The study was carried out at Al Mashreq Eye Center, Cairo, Egypt. The study spanned the duration of 6 months between July 2021 to November 2021.

Eyes were divided into two groups: the study group with treatment-naïve proven vascular pathology (nAMD), and a control group with dry AMD for comparison.

#### **Inclusion Criteria:**

Patients included in the study aged 50 years or older. Conventional OCT (Optovue, Angiovue Inc., Fremont, CA, United States) imaging was conducted using 6x6 mm area centered on the fovea. Eyes included were belonging to one of the following groups:

*Study Group:* Treatment-naïve eyes with OCT evidence of active nAMD (CNV) including fibrovascular/hemorrhagic PED, which is often described as subretinal hyperreflective material (SHRM) that are associated with IRF, SRF, and/or sub-RPE fluid.

*Control Group:*

Eyes with OCT evidence of dry-type AMD including drusen, drusenoid PED, and/or GA with no signs of CNV.

**Exclusion Criteria**

The following cases were excluded from the study:

- Individuals younger than 50 years of age.
- High myopia (> -6.00 D) with OCT suggestive of myopic-rather than age-related-CNV.
- Eyes previously treated by intravitreal injection of anti-VEGF or macular laser prior to first presentation.
- Ocular surgery in the prior 3 months.
- Eyes with diabetic retinopathy/maculopathy, retinal vascular disorder, e.g., retinal artery or vein occlusion, or retinal inflammatory disease.
- Significant media opacity that affected the imaging quality.

**Study Procedure:**

Individuals taking part in the study were subjected to the following:

*History Taking:* This included past medical and surgical history, past ocular history, and presenting symptom including its onset, course, and duration.

*Full Ophthalmological Examination:* This included slit-lamp examination of the anterior segment, IOP assessment,

refraction (SE), BCVA using Snellen chart (decimal system), and dilated fundus examination.

*Imaging Protocol:* We utilized the Optovue Avante (Angiovue Inc, Fremont, CA, United States) for OCT/A imaging. Line scanning OCT of the central macula was conducted, followed by radial scans centralized around the fovea. The AngioVue software was then used to capture 6x6 mm or 3x3 mm retina angio scans.

*Classification of lesions:*

- Activity on SD-OCT scanning was considered when the following was/were present: SRF/IRF, serous, hemorrhagic or fibrovascular PED, RPE tears, and disciform scarring.
- Activity on OCT-A was considered as the pattern I criteria that was reported previously<sup>(8)</sup> and included the presence of at least 3 of the following: shape (well-defined lacy-wheel or sea-fan pattern), branching (numerous tiny capillaries), anastomoses and loops, morphology of vessel termini (peripheral arcade rather than “dead tree”), and perilesional hypointense halo. The CNV lesion was considered inactive (pattern II) if it displayed less than three of the aforementioned criteria.

**Statistical Analysis:**

Data were collected and encoded into the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard

deviations and ranges. Also, qualitative variables were presented as number and percentages. The comparison between groups with qualitative data was done by using *Chi-square test*. The agreement between two methods was assessed using *Kappa-agreement with 95% confidence interval (CI)*.

Receiver operating characteristic curve (ROC) was used in the qualitative mode to assess the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of OCT-A in prediction of OCT results.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following:  $P > 0.05$ : non-significant,  $P < 0.05$ : Significant, and  $P < 0.01$ : Highly significant.

#### **Ethical consideration:**

We confirm that the participants' data were not used for any other purpose outside this study. All participants signed an informed consent in simple language before their inclusion in the study. The study was approved by Faculty of Medicine-Helwan University Research Ethics Committee on 28 April 2021 by serial: 28-2021.

#### **Results:**

This study included 25 patients (44 eyes): 16 patients (64%) were females, and 9 patients (36%) were males. Their ages ranged from 51 to 86 years, with a mean of  $69.88 \pm 8.31$  years. Clinical presentation: The best-

corrected visual acuity (BCVA) ranged from 0.05 to 1.00 with a mean (SD) of  $0.45 (\pm 0.31)$ , and spherical equivalent (SE) ranged from (-3.25) to (+2.25) with a mean of  $0.16 (\pm 1.52)$ . Intra-ocular pressure (IOP) ranged from 10-24 mmHg with a mean of  $15.39 (\pm 3.08)$ .

Nine eyes (20.5%) had previous cataract surgery. According to SD-OCT criteria of activity; 24 eyes (54.5%) were diagnosed as dry AMD with no evidence of exudation, and 20 eyes (45.5%) with nAMD showing at least one criteria of activity (Fig. 1).

The most common macular findings encountered on SD-OCT (in descending order) were drusen that represented the most common sign, manifested in 61.4% of studied eye, followed by Pigment epithelium detachment (PEDs) 29.5%, Neurosensory Detachment (SRF) 27.3%, Geographic atrophy (GA) 13.6%, and Cystoid Macular Edema (IRF) 6.8%. Cases with positive CNV activity on SD-OCT ( $n = 20$ ), were subdivided into 14 eyes (70%) as type-1 CNV, and 6 eyes (30%) as type-2 CNV. For eyes with type-1 CNV (14 eyes), 8 (57.1%) had an associated fibrovascular PED, while 6 (42.9%) did not have an associated PED (Fig. 2). Using OCT-A, 28 eyes were classified as negative, while 16 eyes were classified as positive (pattern I). The positive eyes were differentiated into 3 sub-groups: Type-1 CNV, Type-1 CNV with PED and Type-2 CNV (table-1, Fig.3). There was no statistically significant difference between OCT and OCT-A

regarding percentage of positive cases ( $p=0.386$ , kappa agreement: 0.627, and 95% CI:0.398-0.856).

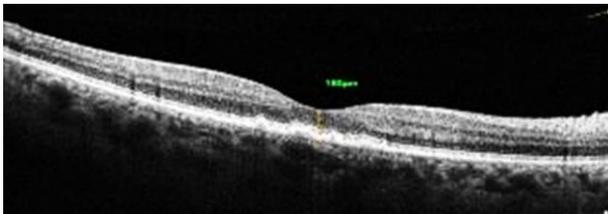
regarding their finding of type-1 CNV, type-1 with PED, and type-2 CNV ( $p=1.000$ , 0.890 and 0.664, respectively) (table 2). There was a statistically significant relation ( $p < 0.001$ ) in classification agreement between SD-OCT and OCT-A findings (table 2). OCT-A demonstrated a sensitivity of 70.0%, specificity of 91.7%, and accuracy of 81.8% in prediction of OCT results (PPV: 87.5, NPV: 78.6).

Two eyes were described by SD-OCT to have a dry AMD, where OCT-A showed vascular lesions within the choriocapillaris zone. In one case (Figure 4)

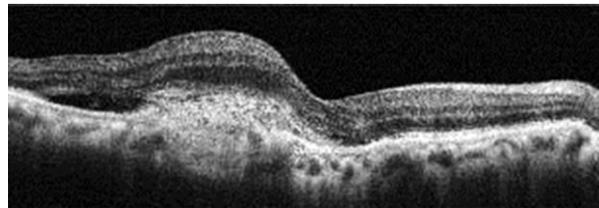
OCT showed foveal drusen with no signs of exudation while the OCT-A (of the same

Furthermore, there was no statistically significant difference between both methods

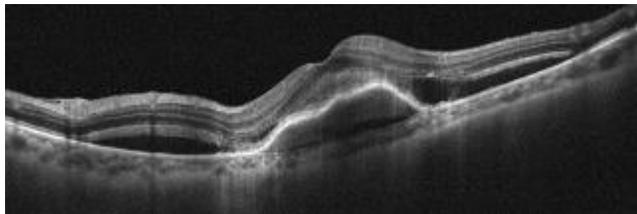
eye) showed a central branching sea-fan shaped vascular lesion with inter-capillary anastomosis and peripheral arcade within the choriocapillaris zone. This eye showed foveal subretinal exudation on SD-OCT scans after 4 months of follow up. Six cases proved to have active CNV by SD-OCT, however such cases showed no vascular lesion on OCT-A: 5 cases with type-1 CNV, and 1 case with type-2 CNV. Follow up imaging after intravitreal injection of anti-VEGF showed regressed CNV activity on SD-OCT images with appearance of traces of vascular lesion within the choriocapillaris zone at the site of the resolved PED.



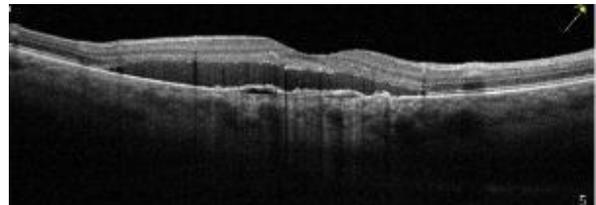
**Fig. (1):** A. Dry AMD with drusen



**B.** Active nAMD (type-2) with SHRM, fibrovascular PED, and SRF.



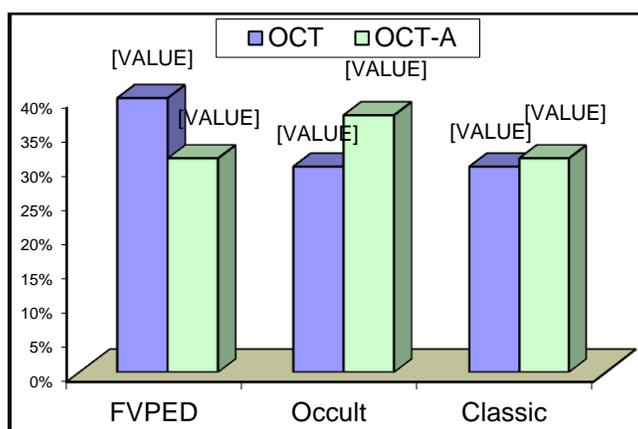
**Fig. (2):** A. Type-1 CNV (SD-OCT) with fibrovascular PED and SRF.



**B.** Type-1 CNV (SD-OCT) without PED and only SRF.

**Table (1):** SD-OCT and OCT-A classification of AMD types.

	OCT		OCT-A		Kappa agreement 95% CI	P-value
	No.	%	No.	%		
<b>Negative</b>	24	54.5%	28	63.6%	0.627 (0.398 to 0.856)	0.386
<b>Positive</b>	20	45.5%	16	36.4%		
<b>Type-1</b>	6	30.0%	6	37.5%	1.000 (1.000 – 1.000)	1.000
<b>Type-1 with PED</b>	8	40.0%	5	31.2%	1.000 (1.000 – 1.000)	0.890
<b>Type-2</b>	6	30.0%	5	31.2%	1.000 (1.000 – 1.000)	0.664



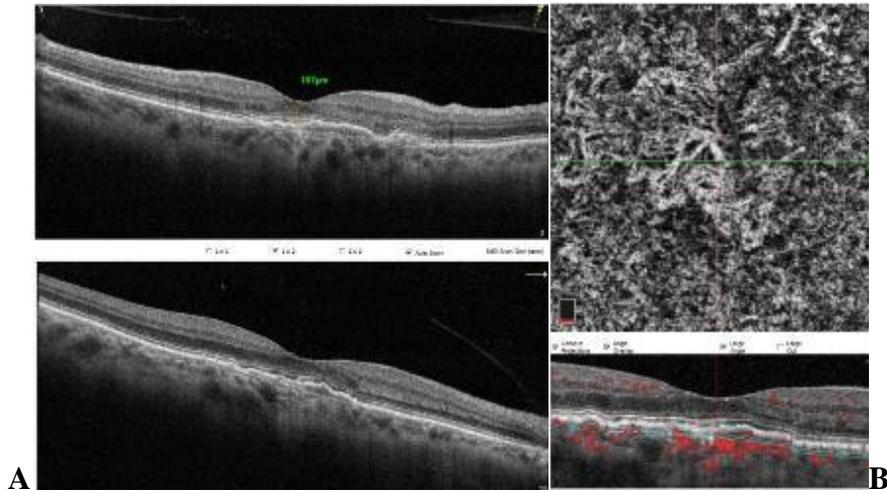
**Fig. (3):** CNV types according to SD-OCT and OCT-A.

(Occult=Type-1, FVPED=Type-1 with PED, Classic=Type-2)

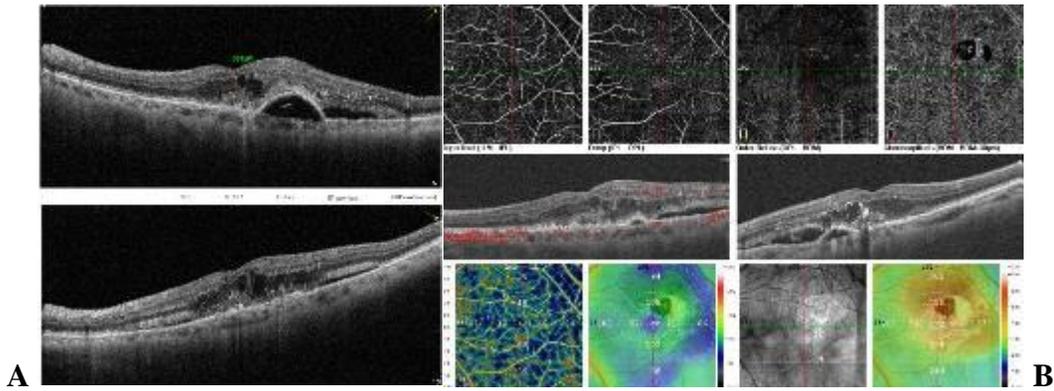
**Table (2):** Agreement significance between SD-OCT and OCT-A.

AMD types	OCT findings				Test value	P-value	
	Negative		Positive				
	No.	%	No.	%			
<b>OCT-A findings</b>	Negative	22 (TN)	91.7%	6 (FN)	30.0%	17.927*	<b>&lt;0.001</b>
	Positive	2 (FP)	8.3%	14 (TP)	70.0%		

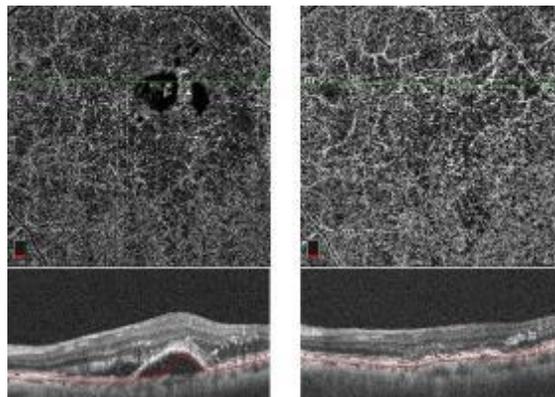
TN (True Negative), TP (True Positive), FP (False Positive), FN (False Negative), PPV, NPV (positive and negative predictive values)



**Fig. (4):** (A) OCT with no signs of CNV activity. (B) OCT-A (same eye) showing a sub-foveal type-1 CNV within the choriocapillaris zone.

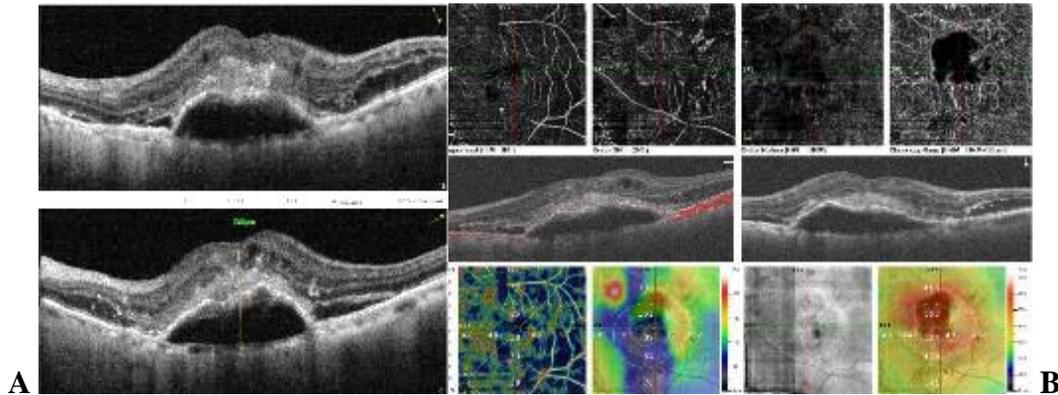


**Fig. (5):** (A) OCT showing type-1 CNV with overlying serous PED, subretinal fluid and intra-retinal edema. (B) OCT-A (same eye) showing no evidence of vascular lesion within the choriocapillaris layer.



**Fig. (6):** Comparison between pre and post Anti-VEGF injection OCT-A imaging for the same eye showing traces of vascular lesion within the choriocapillaris zone after resolution of PED.

### **Type-2 CNV:**



**Fig. (7):** (A) OCT showing subretinal CNV with underlying serous PED, adjacent subretinal fluid and intra-retinal edema. (B) OCT-A (same eye) showing a vascular lesion of very low intensity within the deep retinal layers level not following the Pattern I criteria of activity.

### **Discussion:**

The current study included 44 eyes with AMD, it was found that OCT-A showed high specificity and sensitivity in the detection of vascular lesions in cases of nAMD. There was a strong agreement between the results of SD-OCT and OCT-A in diagnosing CNV activity. However, its utility was limited by several factors including shadowing, segmentation artifacts, weak vascular flow, and PED.

A similar prospective study was conducted on 80 eyes (73 patients) with exudative AMD to compare the detection capacity of OCT-A to that of traditional multimodal imaging, including FFA, ICGA, and OCT. In 59 eyes (73.7%), the lesion was defined as Pattern I, with 90% correspondence between OCT-A findings of inactivity and multimodal imaging. The authors concluded that OCT-A constitutes a useful, non-invasive tool for monitoring of CNV activity.<sup>(8)</sup>

In another case control study that examined quantitative variables of CNV on OCT-A, including CNV area and flow index, and found strong positive correlation with FFA.<sup>(9)</sup> On the other hand, other coworkers examined the detection capacity of OCT-A using qualitative variables in angiographically-proven nAMD cases, and found a sensitivity of 94%.<sup>(10)</sup> However, in both studies the CNV type and rate of fibrovascular PED were not reported. A later study found the sensitivity and specificity of OCT-A in detection of CNV associated with nAMD to be 50% and 91%, respectively.<sup>(11)</sup> The sample size was, however, small and the classification criteria for CNV activity were not clearly defined; it is likely that the lack of discrimination between active and inactive disease resulted in the highly reported false-positive rates and that the lesion was evolving but not angiographically active at the time of imaging. This highlights the importance of studies with well-defined

criteria of activity and with adequate sample sizes when examining the detection ability of OCT-A.

The sensitivity of OCT-A in detection of angiographically-proven CNV lesions associated with nAMD was reported in another study.<sup>(12)</sup> Masked observers were asked to assess OCT-A scans of eyes with dry AMD, nAMD, and healthy subjects. The overall sensitivity was found to be 81%. Most of the false negative instances were attributable to the presence of subretinal hemorrhage which masked the underlying signal, and with the exclusion of cases with subretinal hemorrhage, sensitivity increased to 94%. Furthermore, the addition of cross-sectional OCTA along with en face OCTA improved the sensitivity to 100%. In our study, there were no cases with significant subretinal hemorrhage that could have resulted in false negative signals.

A retrospective comparative study was carried out to examine the sensitivity and specificity of each imaging modality separately in detection of CNV through masked graders.<sup>(13)</sup> They found the sensitivity and specificity of FFA to be 74.5% and 82.3%, respectively, while those of OCT-A were 85.6% and 81.5%, respectively. The highest sensitivity was detected by combining FFA and SD-OCT and was found to be 92.7%. From the previous data, traditional angiography does not necessarily maintain its “gold-standard” status and may be surpassed by OCT-A, and that combining modalities has the best diagnostic accuracy.<sup>(14)</sup> In fact, when it comes to monitoring disease activity and prediction of occurrence in the fellow eye,

SD-OCT was found to be the most superior diagnostic tool.<sup>(15)</sup> This is the reason why we elected to refer to SD-OCT as our reference diagnostic tool when assessing OCT-A utility. This also explains why recent deep-learning approaches are utilizing SD-OCT and OCT-A to define and utilize biomarkers for CNV.<sup>(16)</sup>

In a comparative study, eyes were classified according to the presence fibrovascular PED when comparing OCT-A with traditional multimodal imaging. Patients with pigment epithelial detachment with subretinal/intraretinal fluid (PED+F) were compared to patients with PED without subretinal/intraretinal fluid (PED-F). In the PED+F group, all studied eyes demonstrated CNV on multimodal imaging, while only 90% demonstrated CNV on OCT-A.<sup>(17)</sup> The presence of PED was relevant in our study, since it resulted in lowering of signal intensity and masking of the underlying CNV; this may explain the relatively high false negative rate (6 cases) and relatively low sensitivity (70%) of OCT-A in our sample when compared to previous studies.

The strengths of our study include the relatively large sample size, the accurate definition of activity criteria, the classification of CNV into types and according to the presence or absence of PED. The limitations include the cross-sectional nature of the work, with lack of follow up to define accuracy measures in disease monitoring. Furthermore, our reference imaging was SD-OCT rather than multimodal imaging due to setting limitations. Other limitations include ones inherent to OCT-A, mainly artefacts and

operator dependency. Future, large, well-controlled studies would further corroborate our findings.

### Conclusion:

There was a statistically significant relation in classification agreement between SD-OCT and OCT-A findings ( $p < 0.001$ ). OCT-A demonstrated a sensitivity of 70.0%, specificity of 91.7%, and accuracy of 81.8% in prediction of OCT results.

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