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Optical coherence tomography angiography evaluation of retinal and optic disc microvascular morphological characteristics in retinal vein occlusion

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ABSTRACT

Background: To evaluate microvascular morphological characteristics of the retina and optic disc (OD) in retinal vein occlusion (RVO) patients using optical coherence tomography angiography (OCTA), compare the results to age- and gender-matched healthy subjects, and determine correlations between OCTA parameters and best-corrected visual acuity (BCVA) and age.

Methods: In this retrospective study, right eyes of 53 RVO patients and 51 healthy subjects were compared regarding BCVA, as well as superficial and deep capillary plexus (SCP and DCP) vessel densities (VDs), foveal avascular zone (FAZ) parameters, outer retinal and choriocapillaris flow areas, OD whole and peripapillary VDs, and retinal nerve fiber layer thickness (RNFLT). Retinal vein occlusion patients were further divided into subgroups based on therapy and risk factors, and OCTA parameters were compared.

Results: Retinal vein occlusion rate or OCTA parameters did not differ significantly by gender ($p > 0.05$). Retinal vein occlusion patients had significantly decreased BCVA, whole, parafoveal and perifoveal SCP and DCP VDs, as well as VDs 300 μm area around FAZ (FD-300) than healthy subjects ($p < 0.001$). Their choriocapillaris flow area, RNFLT, whole and peripapillary VDs were also affected. However, FAZ area did not differ significantly between groups. Superior RNFLT ($p = 0.016$) and whole peripapillary VD ($p < 0.001$) differed significantly between laser photocoagulation-treated and non-treated patients. The remaining OCTA parameters revealed no significant differences

Conclusions: The RVO and its therapeutic alternatives may affect both OD and retinal VDs. Given its numerous benefits, it seems that OCTA will be used more frequently in clinics for RVO diagnosis, monitoring, and therapeutic response evaluation.

1. Introduction

Retinal vein occlusion (RVO) is the second leading cause of vision loss among retinal vascular diseases, after diabetic retinopathy (DR.) [1]. The degree of occlusion of a retinal venous drainage determines whether a condition is classified as central, hemispheric, or branched RVO (BRVO). The clinical characteristics and prognosis of central and hemispheric RVO are further classified as ischemic and non-ischemic [2]. Branched RVO is more common than central RVO (CRVO), occurring at a rate of approximately 0.4% globally, whereas the latter occurs at a rate of approximately 0.08% [3].

The pathogenesis of RVO is multifactorial; however, three mechanisms, known as the Virchow triad, have been documented. These mechanisms include vein compression at the arterio-venous junction, vessel wall degeneration, and hematological factor abnormalities. Moreover, several risk factors have been linked to an increased RVO rate, including hypertension (HT), hyperlipidemia (HL), diabetes mellitus (DM), coronary artery disease, advanced age, smoking, high body mass index (BMI), systemic vasculitides, hematological neoplasms, hypercoagulopathy disorders, as well as medications (oral contraceptives, diuretics, and hypotensive drugs) [4].

The vast majority of RVO patients present with varying degrees of painless visual impairment caused by macular edema (ME) or ischemia. A thorough examination of the patient's medical history and clinical findings can greatly aid in the diagnosis of RVO. Fundoscopy typically reveals retinal vein enlargement, retinal hemorrhages, soft exudates resembling discarded cotton, as well as optic disc (OD) edema and ME [5]. Retinal hemorrhages in the four fundal quadrants distinguish

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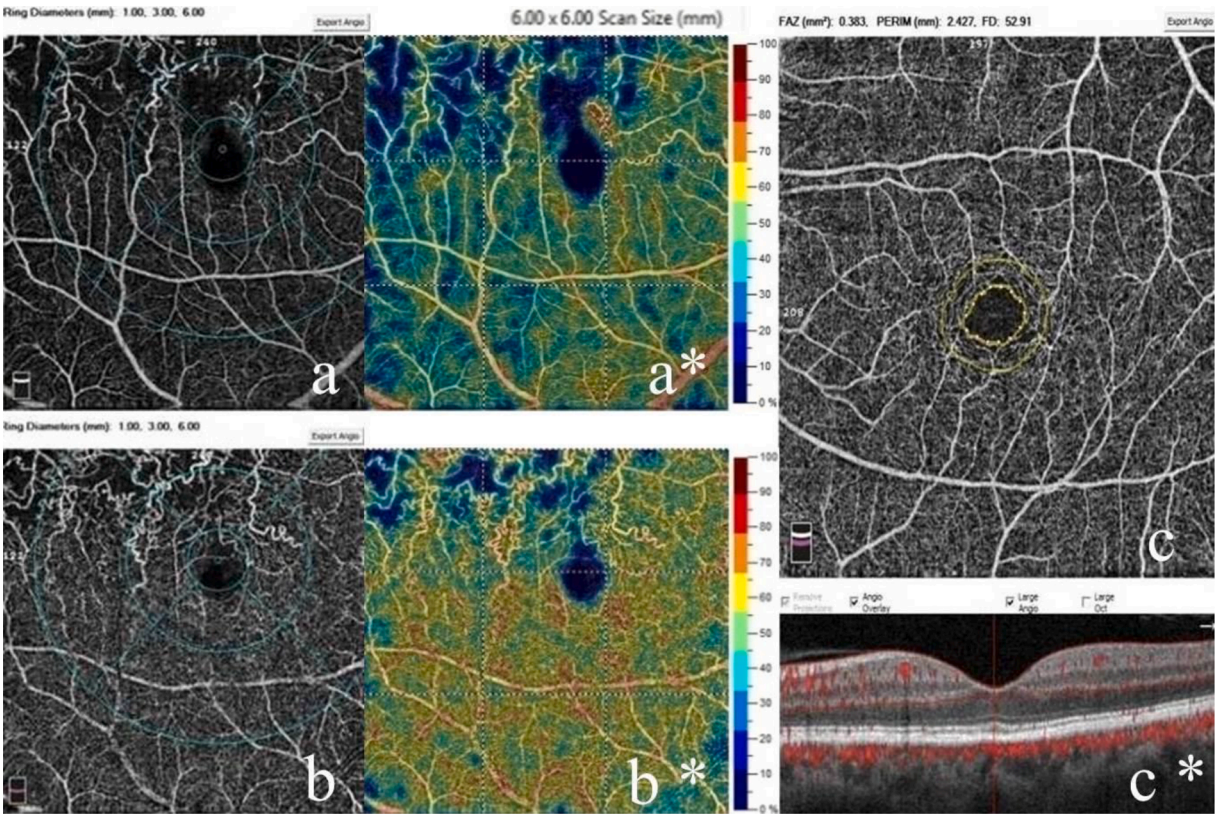

Fig. 1. The 6 × 6 mm optical coherence tomography angiograms (a, a*, b, b*) of the right eye of a branched retinal vein occlusion patient displaying the quantification of vessel densities in whole, foveal, parafoveal, and perifoveal superficial (a, a*) and deep (b, b*) capillary plexus. The upper and, more specifically, the upper-left portion of the angiograms reveal areas of vascular occlusion. Warm color in a* and b* sections indicate areas with increased micro-vessel density. (c) An en face slab of a healthy subject's left eye demonstrating quantification of foveal avascular zone parameters such as foveal avascular zone area and perimeter, as well as vessel densities 300 μm area around foveal avascular zone. The image below (c*) shows a cross-section through the macula center with normal foveal anatomical ultrastructure. Scan quality for both images: 9/10.

CRVO. However, in BRVO, these hemorrhages are restricted to the area drained by the occluded branched retinal vein, whereas in hemispheric RVO, they are only visible in the superior or inferior hemisphere.

Additional therapeutic tests, including optical coherence tomography (OCT), fundus fluorescein angiography (FFA) and OCT angiography (OCTA), are commonly used to determine therapy and improve patient follow-up reliability. Optical coherence tomography angiography is a novel non-invasive, sequential B-scanning modality that allows for evaluation of the retinal microvascular network without using intravenous dye. Instead, it generates images by tracking erythrocyte movement within the vessel, yielding high-resolution 3D angiograms of the retinal and choroidal vascular networks. In contrast to FFA, which only assesses the superficial capillary plexus (SCP), OCTA assesses multiple vascular plexuses [6].

Optical coherence tomography angiography has a limited field of view and is insensitive to leakage. Its progress, on the other hand, has the potential to boost our comprehension of ocular physiology and pathophysiology, particularly in the context of microvascular morphological changes such as in RVO. This could be especially beneficial in the future clinical diagnosis and monitoring of this patient population. The current study was therefore designed to evaluate microvascular morphological characteristics of the retina and OD in RVO patients using OCTA, and compare the results to age- and -gender matched healthy subjects. The correlations between OCTA parameters and best-corrected visual acuity (BCVA) and age were also determined.

2. Materials and methods

2.1. Study design

This single-center retrospective study, which took place between 15 January and 15 June 2021, included 53 RVO patients who were followed-up at the Afyonkarahisar Health Sciences University Faculty of Medicine Department of Ophthalmology Retina Unit. The control group consisted of 51 healthy subjects who visited the out-patient ophthalmology clinic for routine ophthalmological control. Retinal vein occlusion was diagnosed using data from medical records, including clinical exam findings, OCT, and FFA imaging. This study followed the Helsinki Declaration and was approved by the Afyonkarahisar Health Sciences University Clinical Research Ethics Committee under Approval number: 2011-KAEK-2. Each participant signed a written informed consent form before participation.

2.2. Inclusion and exclusion criteria

The study included patients with RVO who had no prior ocular surgery other than uncomplicated cataract surgery and no corneal and/or lens opacity that would interfere with posterior segment imaging procedures. Patients with ME caused by non-RVO ocular pathologies were excluded from the study, as were those with uveitis, diabetic retinopathy, age-related macular degeneration, uncontrolled glaucoma, high refractive error, dense cataract, and corneal problems other than dry eye. Out-patient clinic participants with no systemic diseases (HT, DM, thyroid gland disease, rheumatic diseases) and/or obvious ocular pathology other than dry eye and simple refractive error were included

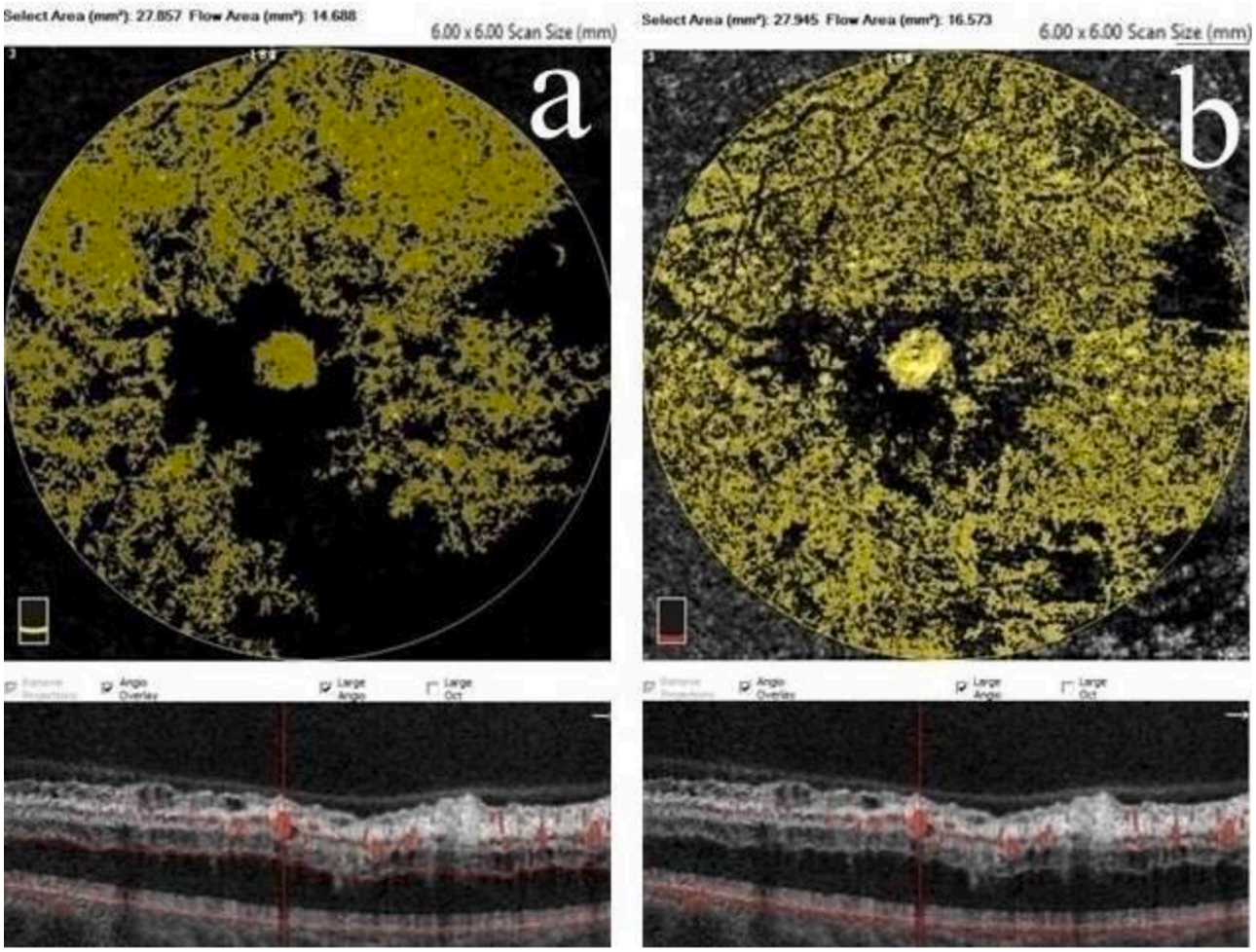

Fig. 2. The 6 × 6 mm optical coherence tomography angiography en face slab of a right eye of a patient with a central retinal vein occlusion showing quantification of capillary flow areas at the levels of (a) outer retina and (b) choriocapillaris. Below is a cross-section through the macula center that depicts distorted anatomical ultrastructure of the fovea as well as increased retinal thickness. Scan quality for both images: 8/10.

in the control group.

2.3. Patient classification

Based on the location of the occlusion, RVO patients were classified as having CRVO or BRVO. These patients were further subdivided depending on the presence or absence of: (a) comorbidities such as HT, DM, and HL, (b) ME detected by spectral domain OCT (Spectralis HRA OCT, Heidelberg Engineering, Heidelberg, Germany), (c) intravitreal therapy such as anti-vascular endothelial growth factors (VEGF) or dexamethasone implant, and (d) laser photocoagulation (LPC) therapy (sectorial and panretinal LPC for ischemic BRVO and CRVO, respectively). In addition, patients were divided into two groups based on their comorbidities: (a) RVO+HT and (b) RVO+HT+DM. Due to the small number of comorbid HL patients, hyperlipidemia was not considered for grouping. Also, the presence or absence of ischemia in FFA was not considered in the study.

2.4. Ophthalmological examination

Data from medical charts were retrieved and recorded, including demographic data such as age and gender, followed by a comprehensive ophthalmological exam that included measuring BCVA using the Early Treatment of Diabetic Retinopathy Study (ETDRS) and Snellen charts and converting it to logarithm of the Minimum Angle of Resolution (logMAR), as well as intraocular pressure (IOP) using Goldmann applanation tonometry (Goldmann; Haag-Streit AG, Köniz, Switzerland). The anterior and posterior slit-lamp biomicroscopy with a 90 diopter (D) lens was performed before and after artificial mydriasis with tropicamide 1% and phenylephrine 10%.

2.5. Optical coherence tomography angiography acquisition

All OCTA (AngioVue Avanti RTVue-XR, OptoVue, Fremont, CA) recording procedures were performed by the same technician using the same device. During the procedure, the 'Auto Adjust' mode was used to fine-tune axial length, refraction correction, and image polarization. The device's eye tracking system and projection artifact removal system (PAR) were used to reduce artifacts. Images with scan quality (SQ) indicator values <5 were not evaluated. The OCTA angio retina mode was used on a 6 × 6 mm macula, and angio disc mode was used on a 4.5 × 4.5 mm OD. The SCP and deep capillary plexus (DCP) vessel densities (VDs) in foveal, parafoveal, and perifoveal regions were quantified by selecting the 'density' function in the angio retina mode. Foveal avascular zone (FAZ) parameters, including FAZ area, FAZ perimeter (PERIM), and VDs 300 μm area around FAZ (FD-300), were measured using the device's FAZ function (Fig. 1 (a and a*), (b and b*), and (c and c*)). The maximum circular area that could be captured by the fovea-centered image section with a radius of 2.98 mm was manually created in the outer retinal and choriocapillaris layers. Flow areas quantified automatically by the device software were then recorded as the outer retinal and choriocapillaris flow areas (Fig. 2(a) and (b)). The

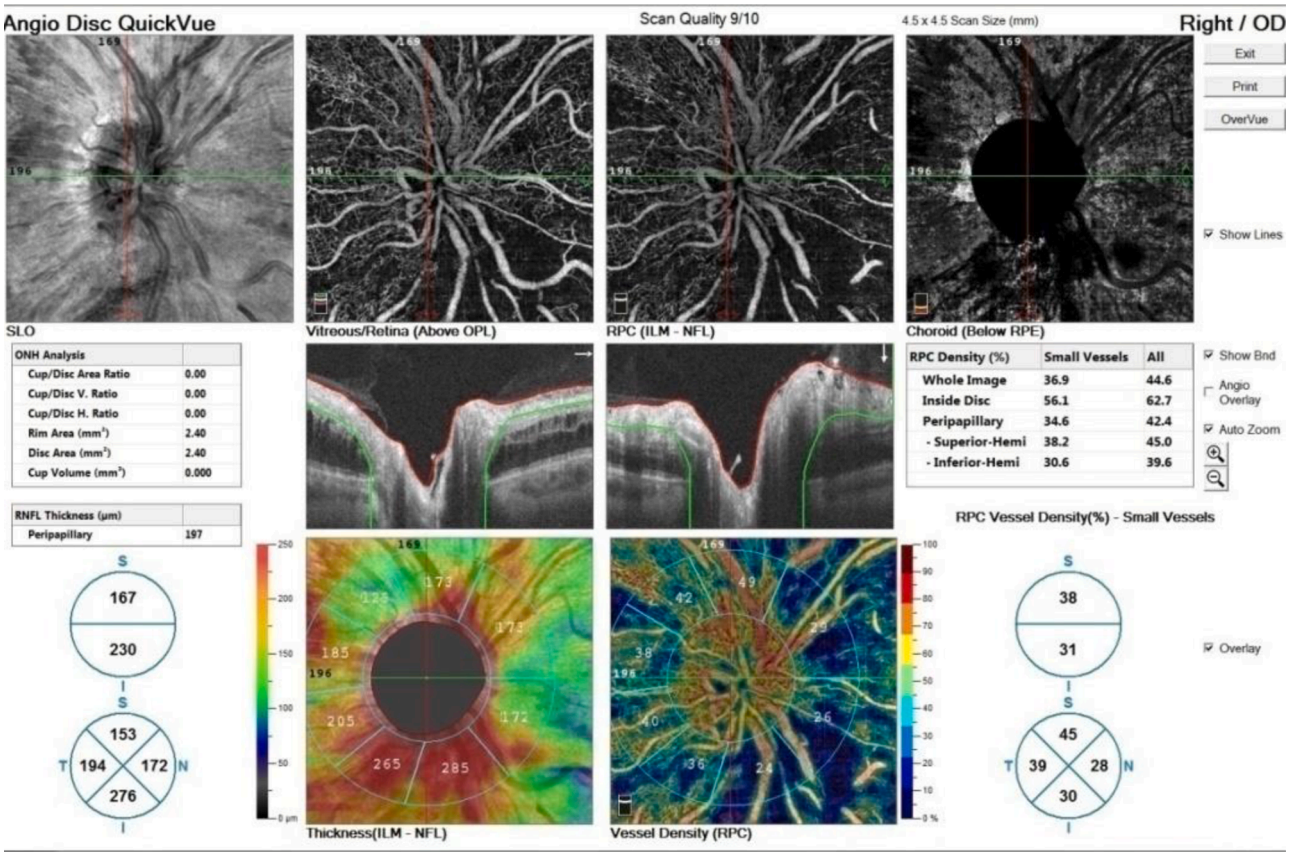

Fig. 3. The 4.5 × 4.5 mm Angio Disc Quick View demonstrating quantification of retinal nerve fiber layer thickness, and optic disc vessel density in a central retinal vein occlusion patient. The angio disc function was used to quantify optic disc vessel density in whole peripapillary region and in quadrants, whereas retinal nerve fiber layer thickness was measured in peripapillary region and in quadrants.

angio disc function was used to quantify OD VDs, including whole peripapillary, as well as superior, temporal, nasal, and inferior quadrant VDs. The retinal nerve fiber layer thickness (RNFLT) was determined in the peripapillary region, as well as in superior, temporal, nasal, and inferior quadrants (Fig. 3).

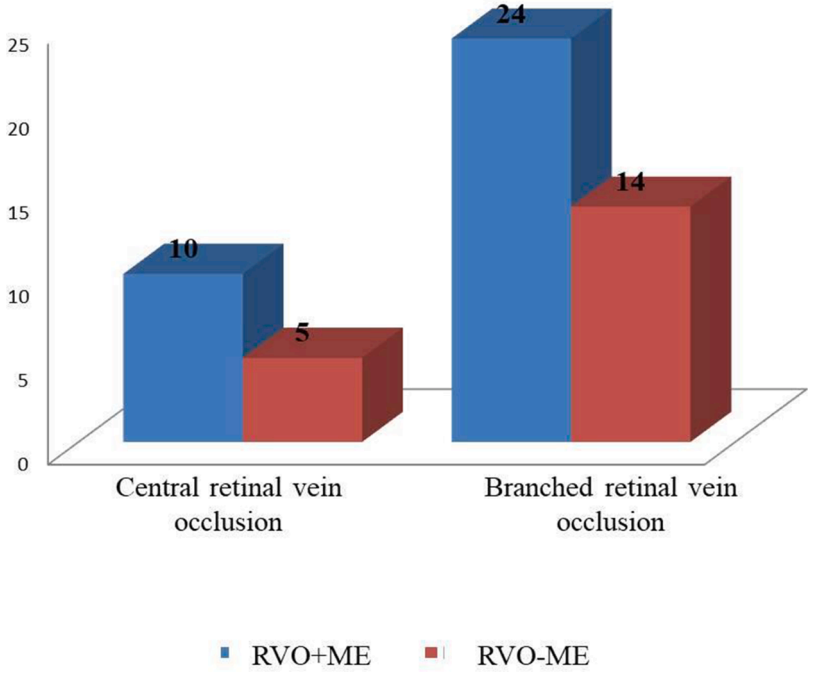

Fig. 4. A graphical distribution of macular edema in central and branched retinal vein occlusion patients.

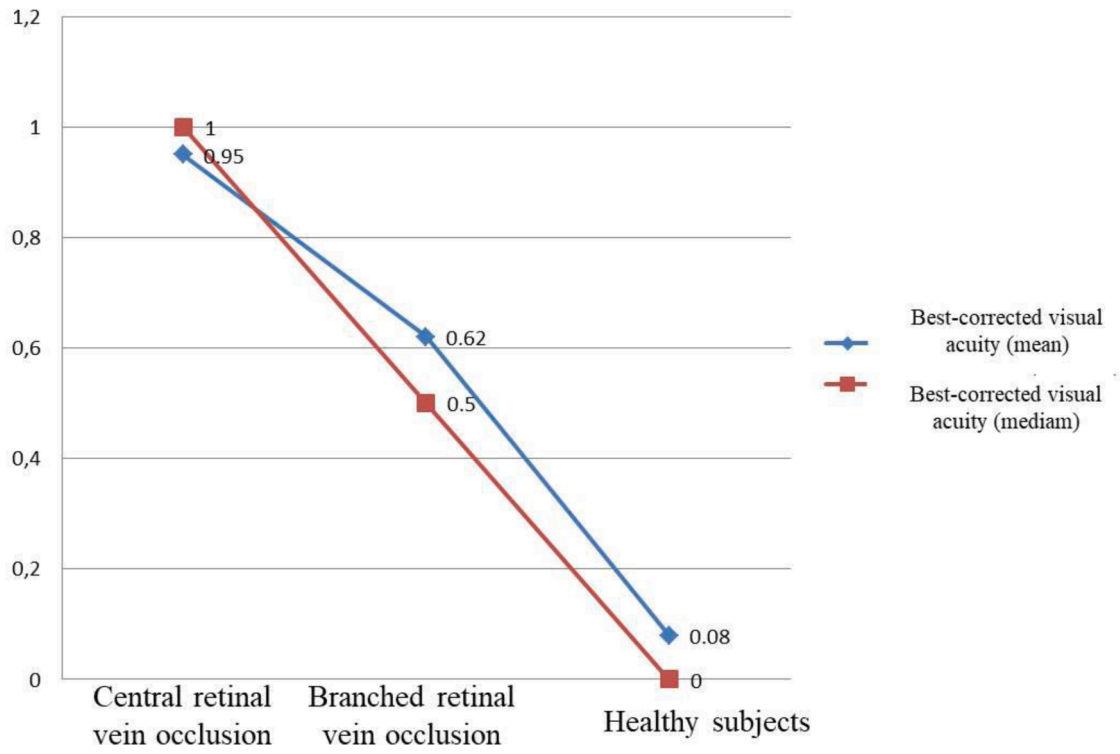

Fig. 5. A graphic depicting the mean and median logMAR best-corrected visual acuities in central and branched retinal vein occlusion patients, as well as healthy subjects.

2.6. Data analysis

Statistical analysis was carried out using a statistical package (SPSS Inc., version 23.0, Chicago, IL, USA). The Skewness and Kurtosis coefficients, the Kolmogorov Smirnov test, and the Histogram were used to test the normality assumptions of continuous variables. Continuous variables were described using mean and standard deviation values, while categorical variables were described using frequency and percentage. The Mann-Whitney test was used to compare two groups' abnormally distributed continuous variables, whereas the independent samples *t*-test was used to compare normally distributed continuous variables. Three inter-group comparisons were performed using one-way ANOVA with Games-Howell or Tukey post hoc tests for normally distributed data and Mann-Whitney U test with Bonferroni correction and Kruskal-Wallis test for abnormally distributed data. The correlations between continuous variables were investigated using Spearman's (Spearman's rho) correlation analysis. The level of statistical significance was set at $p < 0.05$.

3. Results

3.1. Demographics

There were 53 (51%) RVO patients (15 CRVO and 38 BRVO) and 51 (49%) healthy subjects among the total 104 study participants. The overall mean age was 60.1 ± 9.50 years (range: 33–80 years), with CRVO and BRVO patients, as well as healthy subjects having mean ages of 58.6 ± 10, 61.84±9.34, and 60.04 ± 9.51 years, respectively. The female-to-male ratios in CRVO and BRVO patients were 9:6 and 16:22, respectively, while the ratio in healthy subjects was 25:26. Gender differences did not result in significant differences in any of the OCTA parameters ($p > 0.05$). The majority of RVO patients had macular edema (ME) (RVO+ME), as did 66.7% of CRVO and 63.3% of BRVO patients (Fig. 4)

3.2. Comorbidities

Twenty-five (47.1%) patients had RVO+HT, 8 (15.09%) had RVO+HT+DM, and 1 (1.89%) had HT+DM+HL. As the number of comorbidities increased, it is likely that the associated microvascular morphological changes would worsen. So, the objective in this context was to see if there was a significant difference regarding OCTA parameters among the three groups. However, due to the fact that there was only one patient with three comorbidities, statistical analysis was restricted to the first two groups. Consequently, while most parameters decreased in RVO+HT+DM group more than RVO+HT, only perifoveal SCP VD was significant ($p = 0.017$); changes in other parameters were not significant ($p > 0.05$).

3.3. Best-corrected visual acuity

While CRVO and BRVO patients had mean logMAR BCVAs of 0.95 (min = 0.2–max = 2.0) and 0.62 (min = 0.1–max = 1.6), respectively, healthy subjects had a mean logMAR BCVA of 0.08 (min = 0–max = 0.4) ($p < 0.001$) (Fig. 5).

3.4. Optical coherence tomography angiography comparative analysis

3.4.1. Superficial and deep capillary plexus vessel densities

Compared to healthy subjects, CRVO and BRVO patients had significantly lower SCP and DCP VDs in whole, parafoveal, and perifoveal regions ($p < 0.001$) (Table 1).

3.4.2. Foveal avascular zone parameters

When FAZ parameters of CRVO and BRVO patients were compared to those of healthy subjects, FD-300 ($p < 0.001$), but not FAZ area ($p = 0.554$) or PERIM ($p = 0.522$), was significantly lower in the former subgroups (Table 2).

Table 1
A comparative analysis of microvascular densities among CRVO and BRVO patients versus healthy subjects.

Parameters (%)		Study groups	Mean±SD (min-max).	*P* value
SCP VD	Whole	CRVO	45.82 ± 6.46 (37.50–60.50)	<0.001
		BRVO	45.71 ± 4.25 (34.20–54.00)	
		Healthy subjects	50.65 ± 3.46 (43.40–56.90)	
	Foveal	CRVO	26.95 ± 11.94 (8.60–50.00)	0.115
		BRVO	22.53 ± 9.52 (5.40–48.50)	
		Healthy subjects	20.78 ± 6.94 (5.80–36.70)	
	Parafoveal	CRVO	43.75 ± 7.06 (32.40–54.20)	<0.001
		BRVO	46.35 ± 5.56 (34.60–57.80)	
		Healthy subjects	53.10 ± 4.09 (43.50–60.90)	
	Perifoveal	CRVO	47.07 ± 6.80 (40.40–65.90)	<0.001
		BRVO	46.56 ± 4.35 (33.90–55.80)	
		Healthy subjects	51.33 ± 3.50 (44.30–58.20)	
DCP VD	Whole	CRVO	45.91 ± 7.90 (37.60–68.10)	<0.001
		BRVO	46.64 ± 5.53 (36.30–56.20)	
		Healthy subjects	52.35 ± 6.18 (38.00–64.30)	
	Foveal	CRVO	39.41 ± 13.90 (20.40–72.60)	0.448
		BRVO	36.00 ± 10.36 (13.80–56.90)	
		Healthy subjects	36.27 ± 6.15 (22.90–49.50)	
	Parafoveal	CRVO	48.05 ± 7.95 (34.80–71.50)	<0.001
		BRVO	47.74 ± 6.23 (33.70–55.80)	
		Healthy subjects	55.14 ± 4.76 (38.50–63.70)	
	Perifoveal	CRVO	46.44 ± 8.93 (34.70–70.50)	<0.001
		BRVO	48.47 ± 5.82 (35.90–58.80)	
		Healthy subjects	53.70 ± 6.57(38.40–66.80)	

VD=Vessel density, CRVO=Central retinal vein occlusion, BRVO=Branched retinal vein occlusion, SCP=Superficial capillary plexus, DCP=Deep capillary plexus, SD=Standard deviation.

Table 2
A comparative analysis of FAZ parameters among CRVO and BRVO patients versus healthy subjects.

Parameters	Study groups	Mean±SD (min-max).	*P* value
FAZ area (mm^2)	CRVO	0.26 ± 0.13 (0.06–0.47)	0.554
	BRVO	0.29 ± 0.14 (0.03–0.77)	
	Healthy subjects	0.30 ± 0.10 (0.09–0.57)	
PERIM (mm)	CRVO	2.08 ± 0.53 (1.05–2.85)	0.522
	BRVO	2.22 ± 0.56 (1.24–4.29)	
	Healthy subjects	2.13 ± 0.38 (1.16–3.01)	
FD-300 (%)	CRVO	45.38 ± 8.71 (32.39–69.38)	<0.001
	BRVO	47.73 ± 5.52 (30.16–57.51)	
	Healthy subjects	53.66 ± 4.76 (39.15–62.22)	

FAZ=Foveal avascular zone, CRVO=Central retinal vein occlusion, BRVO=-Branched retinal vein occlusion, SD=Standard deviation, PERIM=FAZ perimeter, FD-300=Vessel densities 300 μm area around FAZ.

Table 3
A comparative analysis of flow areas among CRVO and BRVO patients versus healthy subjects.

Parameters		Study groups	Mean±SD (min-max).	*P* value
Flow areas	Outer retina	CRVO	8.60 ± 3.42 (3.44–14.69)	0.908
		BRVO	8.64 ± 3.35 (4.27–20.20)	
		Healthy subjects	8.29 ± 2.06 (5.19–14.49)	
	Choriocapillaris	CRVO	17.92 ± 1.20 (15.78–19.98)	0.001
		BRVO	18.64 ± 1.18 (14.24–20.48)	
		Healthy subjects	19.10 ± 1.08 (15.22–20.62)	

CRVO=Central retinal vein occlusion, BRVO=Branched retinal vein occlusion, SD=Standard deviation.

3.4.3. Capillary flow areas

There were significant differences among groups in the choriocapillaris ($p = 0.001$), but not in the outer retina ($p = 0.908$), with CRVO patients having significantly lower flow areas than healthy subjects (Table 3).

3.4.4. Optic disc parameters

Superior RNFLT ($p < 0.007$) differed significantly among groups, with BRVO patients exhibiting the lowest values. Temporal ($p < 0.001$) and nasal quadrant RNFLTs ($p = 0.009$) differed significantly among groups, with healthy subjects having the lowest values. Despite having the highest peripapillary ($p = 0.084$) and inferior ($p = 0.204$) quadrant RNFLTs in CRVO patients relative to BRVO patients and healthy subjects, the difference was not statistically significant.

Retinal vein occlusion patients, especially CRVO followed by BRVO patients, had significantly lower peripapillary VD in whole region ($p < 0.001$), as well as in all quadrants ($p < 0.05$) with the exception of the nasal quadrant ($p = 0.473$) (Table 4).

3.5. Intragroup analysis of retinal vein occlusion patients

3.5.1. Anti-vascular endothelial growth factors-treated versus non-treated

There were 48 intravitreal anti-VEGF treated and 5 non-treated RVO patients in total (Fig. 6). Despite treatment in 93.3% of CRVO and 89.5% of BRVO patients, OCTA parameters did not differ significantly between the two groups ($p > 0.05$) (Table 5).

3.5.2. Corticosteroid-treated versus non-treated

There were 35 intravitreal corticosteroid-treated and 18 non-treated RVO patients in total (Fig. 6). Despite treatment (intravitreal triamcinolone and/or dexamethasone implant) in 73.3% of CRVO and 63.2% of BRVO patients, the OCTA parameters did not differ significantly between the two groups ($p > 0.05$) (Table 6).

3.5.3. Laser photocoagulation-treated versus non-treated

53.3% of CRVO and 31.6% of BRVO patients received LPC therapy (Fig. 6). Only superior RNFLT ($p = 0.016$) and whole peripapillary VD ($p < 0.001$) differed significantly between LPC-treated and non-treated RVO patients. The remaining OCTA parameters revealed no statistically significant differences (Table 7).

3.6. Correlation analysis among BCVA, age, and other OCTA parameters

There was a significant positive correlation between age and logMAR BCVA ($r = 0.275$, $p = 0.005$). However, the age correlated significantly negatively with the following OCTA parameters: (a) SCP VD in whole ($r = -0.314$, $p < 0.001$), parafoveal ($r = -0.269$, $p = 0.006$), and

Table 4
A comparative analysis of the OD OCTA parameters among CRVO and BRVO patients versus healthy subjects.

Parameters		Study groups	Mean±SD (Min-max).	*P* value
RNFLT (μm)	Peripapillary	CRVO	127.07 ± 37.72 (56–197)	0.084
		BRVO	107.74 ± 15.89 (70–154)	
		Healthy subjects	110.31 ± 11.31 (80–135)	
	Superior	CRVO	126.47 ± 37.96 (38–180)	<0.007
		BRVO	114.63 ± 30.01 (64–182)	
		Healthy subjects	132.47 ± 17.01 (102–186)	
	Temporal	CRVO	101.73 ± 34.36 (74–194)	<0.001
		BRVO	75.05 ± 18.21 (49–162)	
		Healthy subjects	73.33 ± 11.35 (42–109)	
	Nasal	CRVO	124.33 ± 35.15 (72–185)	0.009
		BRVO	104.16 ± 13.08 (75–129)	
		Healthy subjects	99.20 ± 13.98 (66–133)	
	Inferior	CRVO	155.13 ± 62.32 (39–276)	0.204
		BRVO	137.79 ± 23.50 (70–186)	
		Healthy subjects	137.59 ± 15.87 (97–179)	
Peripapillary VD (%)	Whole	CRVO	44.93 ± 5.11 (35.80–52.70)	<0.001
		BRVO	46.20 ± 3.83 (28.50–51.70)	
		Healthy subjects	48.74 ± 2.62 (41.60–54.70)	
	Superior	CRVO	44.93 ± 6.10 (35–55)	<0.001
		BRVO	46.34 ± 7.61 (23–60)	
		Healthy subjects	51.75 ± 4.09 (43–62)	
	Temporal	CRVO	49 ± 5.87 (39–56)	0.012
		BRVO	50.82 ± 4.50 (29–56)	
		Healthy subjects	53.02 ± 3.39 (43–61)	
	Nasal	CRVO	44.07 ± 8.10 (28–54)	0.473
		BRVO	47.37 ± 3.37 (41–54)	
		Healthy subjects	47.75 ± 3.88 (36.−55)	
	Inferior	CRVO	47.13 ± 8.04 (30–57)	0.006
		BRVO	50.68 ± 5.87 (25–62)	
		Healthy subjects	52.59 ± 4.17 (39–60)	

OD=Optic disc, OCTA=Optical coherence tomography angiography, RNFLT=Retinal nerve fiber layer thickness, VD=Vessel density, CRVO=Central retinal vein occlusion, BRVO=Branched retinal vein occlusion, SD=Standard deviation,.

perifoveal ($r = -0.278$, $p = 0.004$); (b) DCP VD in whole ($r = -0.333$, $p = 0.001$), parafoveal ($r = -0.202$, $p = 0.040$), and perifoveal ($r = -0.351$, $p = 0.001$); and (c) whole peripapillary VD ($r = -0.223$, $p = 0.023$). Also, logMAR BCVA correlated significantly negatively with the following OCTA parameters: (a) SCP VD in whole region ($r = -0.540$, $p < 0.001$), parafoveal ($r = -0.589$, $p = 0.006$), and perifoveal ($r = -0.536$, $p < 0.001$); (b) DCP VD in whole ($r = -0.571$, $p < 0.001$), parafoveal ($r = -0.606$, $p < 0.001$), and perifoveal ($r = -0.539$, $p < 0.001$); (c) FD-300 ($r = -0.537$, $p < 0.001$); and (d) whole peripapillary VD ($r = -0.402$, $p < 0.001$) (Fig. 7).

4. Discussion

The current study investigated microvascular morphological characteristics of the retina and OD in RVO patients, as well as the correlations between OCTA parameters and BCVA, and age. Retinal vein occlusion, one of the most common causes of sudden painless unilateral vision loss [7], can also lead to complications such as ME, impaired macular perfusion, vitreoretinal hemorrhages, neovascularization, vitreomacular interface pathologies, and retinal detachment [8]. The location of occlusion in BRVO, the degree of occlusion, and the efficiency of collateral circulation may all influence visual prognosis [9]. Mean BCVA less than 0.3 logMAR has previously been reported in 63.64% of RVO patients [10], which is consistent with the current study, in which the mean BCVA was 0.95 and 0.62 logMAR in CRVO and BRVO patients, respectively. Compared to healthy subjects, RVO patients were associated with significantly lower BCVA.

Total RVO, CRVO, and BRVO prevalence rates have been reported to be 5.2/1000, 0.8/1000, and 4.42/1000 people, respectively, with BRVO being five times more common than CRVO [11]. As in prior studies, BRVO patients made up 66% of RVO patients in the current study, while CRVO patients made up 34%. The difference in sample size and characteristics could explain why the current study had a higher rate of CRVO than prior studies.

The risk of RVO increases with age [11]. In the current study, patients with CRVO and BRVO, as well as health subjects had mean ages of 58.60 ± 10, 61.84 ± 9.34, and 60.04 ± 9.51 years, respectively. Arteriosclerosis, as well as age-related increased systemic and ocular risk factors, could explain the increased RVO rate with age. While RVO is more common in older patients, it can also be seen in younger patients under the age of 45. Moreover, the current study included 25 females and 28 males with RVO, and there was no gender-related significant difference in RVO rate, which is consistent with prior epidemiological studies [11,10].

Systemic HT has been reported in 34.7% of CRVO and 48.2% of BRVO patients. Besides, DM has been revealed in 20.2% of CRVO and 9.9% of BRVO patients [12]. In the current study, comorbid HT was found in 71.4% and 68.4% of CRVO and BRVO patients, respectively, as was DM in 33.3% and 26.3% of CRVO and BRVO patients, and HL in 13.3% and 15.8% of CRVO and BRVO patients, respectively. These findings, which are consistent with prior research, lend support to the association between RVO and comorbid systemic risk factors, including DM, HL, and, in particular, systemic HT [13]. Unlike Lee et al. [12]., there was no significant difference in the rates of these systemic comorbidities between the two RVO subgroups in the current study. Besides, systemic comorbidities were not present in 15.09% of RVO patients. Other RVO risk factors, such as smoking and atherosclerosis, were assumed to exist in these patients though not considered in the study.

Therapeutic approaches, including intravitreal injections, LPC, and surgery may all be used in treating BRVO and CRVO. Laser photocoagulation has been reported as a standard treatment option for patients suffering from neovascularization [14]. Corticosteroid therapy, such as intravitreal triamcinolone (IVTA) and intravitreal Ozurdex implants, has also been demonstrated to be effective in RVO patients [15]. Moreover, intravitreal anti-VEGFs, including ranibizumab, aflibercept, and bevacizumab, which have recently become the standard therapy for RVO, target the ME pathogenesis [16]. In the current study, LPC-treated patients made up 53.3% of CRVO and 31.6% of BRVO patients. Anti-VEGF-treated patients made up 93.3% of CRVO and 89.5% of BRVO patients. And, 73.3% of CRVO as well as 63.2% of BRVO patients were treated with intravitreal corticosteroids.

By defining the retinal microvascular morphological details in SCP

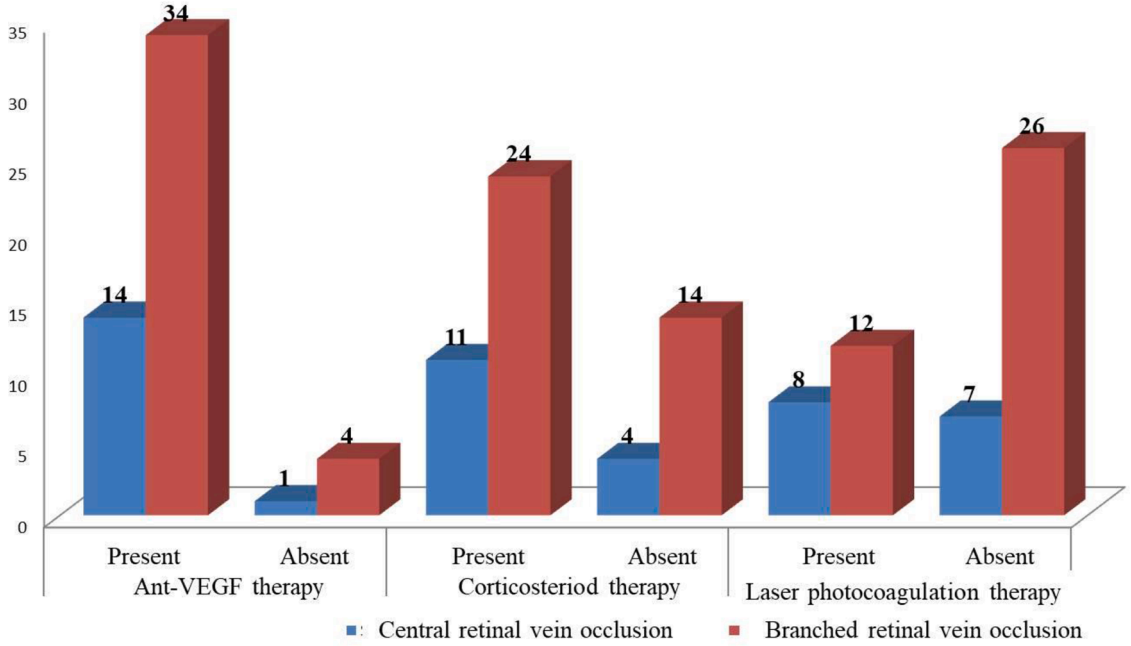

Fig. 6. A graphic demonstrating the intravitreal anti-vascular endothelial growth factors and corticosteroid, as well as laser photocoagulation therapies used in central and branched retinal vein occlusion patients.

and DCP, OCTA aids in the diagnosis of retinal microvascular diseases, including RVO [17]. Moussa et al. [18]., found 111 eyes with reduced SCP VD in ≥1 quadrant and 33 with normal SCP VD, as well as 142 with reduced DCP VD in ≥1 quadrant and two with normal DCP VD. Kang et al. [19]., reported significantly lower parafoveal SCP and DCP VDs in RVO affected eyes compared to contralateral eyes and healthy subjects. Similarly, Deng et al. [20] found that whole and parafoveal SCP and DCP VDs were lower in CRVO patients than in healthy subjects. The current study revealed corresponding results in which VDs decreased significantly in both SCP and DCP.

Another OCTA study reported that since foveal VDs vary so much in healthy subjects, corresponding VDs in RVO patients may not always be affected [21]. Kang et al. [19]., found no significant difference in foveal SCP and DCP VDs between patients' affected and contralateral unaffected eyes, and health subjects. As FAZ area covers the majority of the fovea, ischemic changes may not have a significant effect on foveal VD [19]. Deng et al. [20]., also found no difference in foveal SCP and DCP VDs between CRVO patients and healthy subjects. Likewise, no significant difference was observed in the current study between patients with CRVO and BRVO, as well as health subjects in foveal SCP and DCP VDS.

Foveal avascular zone dimension varies among healthy individuals [22]; however, studies show that FAZ area is enlarged in RVO eyes, particularly in DCP, relative to contralateral eyes and healthy subjects [22,23]. Further, different SCP FAZ findings have been reported in various studies. Rispoli et al. [24]., and Casselholmde Salles et al. [22]., reported increased ischemic area in SCP, whereas Suzuki et al. [23]., observed no significant changes. Parodi et al. [25]., found that patients with macular BRVO had a larger FAZ area and PERIM than healthy controls. Adhi et al. [26]., calculated FAZ using unsegmented OCTA images to minimize ME-induced artifacts segmentation errors, and revealed that RVO eyes had a larger FAZ area than contralateral eyes and healthy subjects. Suzuki et al. [23]., proposed that eyes with fewer intravitreal anti-VEGF injections had a larger FAZ area in both plexuses than eyes with more frequent injections, and that FAZ size could be related to intraocular VEGF levels. Foveal avascular zone area and PERIM did not differ between health subjects and CRVO patients, according to Deng et al. [20]; however, FD-300 ($p = 0.0002$) was significantly lower in the latter group. In the current study, similar to Deng et al., no significant difference was found between patients with CRVO and BRVO, as well as healthy subjects, in terms of FAZ area and PERIM; however, CRVO and BRVO patients had significantly lower FD-300 than healthy subjects. This is thought to be due to variations in FAZ dimensions in healthy subjects, differences in the number of intravitreal anti-VEGF injections, or the current study's inability to evaluate FAZ area separately in SCP and DCP.

The choriocapillaris flow area has been found to be significantly lower in CRVO patients than in healthy subjects. Further, intravitreal anti-VEGF therapy has been linked to decreased ME and increased capillary flow area. This condition led to the hypothesis that fluid accumulation due to ME could cause an attenuated OCT signal with the shadowing effect, resulting in an overestimation of the degree of decreased vascular perfusion in choriocapillaris [20]. Corresponding results were observed in the current study, where choriocapillaris flow area within a circular area with a radius of 2.98 mm revealed significantly lower values in CRVO patients compared to healthy subjects.

The RNFL damage in RVO has been studied extensively. This damage may be caused by glaucoma and systemic vascular diseases such as HT, DM, or RVO itself [27]. Kim et al. [27]., reported that in RVO patients, the RNFLT was significantly higher in the first month due to edema caused by occlusion in the affected eye than in the unaffected eye, and significantly lower 6 and 12 months later due to RNFL atrophy. Shin et al. [28]., found significantly lower mean RNFLT in the contralateral eyes of unilateral RVO patients relative to healthy subjects. Unlike prior studies, there was no significant difference in peripapillary RNFLT between RVO patients and healthy subjects in the current study. This could be attributed to the study's inclusion of both acute and chronic RVO patients, as well as the varying rates of associated systemic vascular diseases. In addition, the superior quadrant RNFLT analysis revealed that BRVO patients had significantly lower thickness than healthy subjects, which appears to be due to occlusion location in BRVO patients; however, this relationship could not be established since the occluded regions involved in BRVO patients were not specified.

Another finding by Shin et al. [28]., revealed decreased inferior and temporal quadrant RNFLTs in the contralateral eyes of RVO patients compared to healthy subjects. However, the analysis of age-related RNFLT change revealed that axons in the inferior quadrant were more

Table 5
The OCTA parameters between intravitreal anti-VEGF-treated versus non-treated RVO patients.

Parameters		Anti-VEGF therapy	Mean±SD (min-max)	*P* value
SCP VD (%)	Whole	Treated	45.45 ± 4.97 (34.20–60.50)	0.180
		Non-treated	48.56 ± 3.54 (44.80–54.00)	
	Foveal	Treated	23.27 ± 10.13 (5.40–48.50)	0.330
		Non-treated	28.68 ± 12.34 (19.70–50.00)	
	Parafoveal	Treated	45.28 ± 6.24 (32.40–57.80)	0.223
		Non-treated	48.74 ± 2.63 (45.70–51.50)	
	Perifoveal	Treated	46.45 ± 5.17 (33.90–65.90)	0.273
		Non-treated	49.10 ± 3.94 (45.50–55.80)	
DCP VD (%)	Whole	Treated	46.85 ± 6.11 (37.00–68.10)	0.133
		Non-treated	42.44 ± 6.51 (36.30–49.80)	
	Foveal	Treated	36.97 ± 11.85 (13.80–72.60)	0.993
		Non-treated	36.92 ± 7.10 (29.10–47.50)	
	Parafoveal	Treated	47.99 ± 6.85 (33.70–71.50)	0.465
		Non-treated	46.26 ± 4.94 (41.70–52.50)	
	Perifoveal	Treated	48.41 ± 6.62 (34.70–70.50)	0.089
		Non-treated	42.96 ± 7.40 (35.90–51.80)	
FAZ parameters	FAZ area (mm^2)	Treated	0.29 ± 0.14 (0.03–0.77)	0.124
		Non-treated	0.20 ± 0.12 (0.06–0.37)	
	PERIM (mm)	Treated	2.22 ± 0.55 (1.24–4.29)	0.075
		Non-treated	1.76 ± 0.46 (1.05–2.29)	
	FD-300 (%)	Treated	46.96 ± 6.75 (30.16–69.38)	0.729
		Non-treated	48.05 ± 5.08 (39.70–53.54)	
Peripapillary VD (%)	Whole	Treated	45.63 ± 4.37 (28.50–52.70)	0.195
		Non-treated	47.84 ± 1.39 (45.60–49.30)	
RNFLT (μm)	Peripapillary	Treated	112 ± 26.22 (56–197)	0.229
		Non-treated	116 ± 14.47 (101–141)	

OCTA=Optical coherence tomography angiography, VD=Vessel density, RVO=Retinal vein occlusion, SCP=Superficial capillary plexus, DCP=Deep capillary plexus, SD=Standard deviation, RNFLT=Retinal nerve fiber layer thickness, FAZ=Foveal avascular zone, PERIM=FAZ perimeter, FD-300=Vessel densities 300 μm area around FAZ.

Table 6
The OCTA parameters between intravitreal corticosteroid-treated versus non-treated RVO patients.

Parameters		Steroid therapy	Mean±SD (min-max).	*P* value
SCP VD (%)	Whole	Treated	45.94 ± 5.12 (34.20–60.50)	0.690
		Non-treated	45.36 ± 4.58 (38.70–54.00)	
	Foveal	Treated	23.08 ± 9.36 (5.40–43.50)	0.707
		Non-treated	25.16 ± 12.21 (10.20–50)	
	Parafoveal	Treated	45.88 ± 6.48 (32.40–57.80)	0.639
		Non-treated	45.09 ± 5.30 (34.60–52.50)	
	Perifoveal	Treated	46.90 ± 5.51 (33.90–65.90)	0.690
		Non-treated	46.31 ± 4.31 (38.60–55.80)	
DCP VD (%)	Whole	Treated	47.11 ± 6.19 (37.00–68.10)	0.279
		Non-treated	45.13 ± 6.25 (36.30–56.20)	
	Foveal	Treated	37.77 ± 12.17 (13.80–72.60)	0.481
		Non-treated	35.40 ± 10.00 (22.10–55.40)	
	Parafoveal	Treated	48.65 ± 7.13 (34.10–71.50)	0.132
		Non-treated	46.23 ± 5.54 (33.70–55.80)	
	Perifoveal	Treated	48.67 ± 6.65 (37.10–70.50)	0.251
		Non-treated	46.39 ± 7.05 (34.70–57.30)	
FAZ parameters	FAZ area (mm^2)	Treated	0.29 ± .0.15 (0.03–0.77)	0.851
		Non-treated	0.27 ± 0.12 (0.06–0.46)	
	PERIM (mm)	Treated	2.23 ± 0.57 (1.42–4.29)	0.423
		Non-treated	2.10 ± 0.53 (1.05–3.04)	
	FD-300 (%)	Treated	47.21 ± 7.61 (30.16–69.38)	0.819
		Non-treated	46.77 ± 4.06 (39.70–54.21)	
Peripapillary VD (%)	Whole	Treated	45.29 ± 4.50 (28.50–52.30)	0.130
		Non-treated	46.89 ± 3.50 (36.90–52.70)	
RNFLT (μm)	Peripapillary	Treated	110.57 ± 24.27 (56–183)	0.579
		Non-treated	118.33 ± 27.16 (81–197)	

OCTA=Optical coherence tomography angiography, VD=Vessel density, RVO=Retinal vein occlusion, SCP=Superficial capillary plexus, DCP=Deep capillary plexus, SD=Standard deviation, FAZ=Foveal avascular zone, PERIM=FAZ perimeter, FD-300=Vessel densities 300 μm area around FAZ, RNFLT=Retinal nerve fiber layer thickness.

resistant to age-related RNFLT loss, with no age-related significant change in this region [29]. Likewise, the current study found no significant difference in inferior quadrant RNFLT between RVO patients and healthy subjects. This could imply that the inferior quadrant is more resistant to changes, as observed in RVO, where aging and systemic vascular diseases, the prevalence of which rises with age, are significant risk factors.

Interestingly, in the current study, increased RNFLT was found in all quadrants of CRVO patients compared to BRVO patients and healthy subjects, with temporal and nasal quadrant RNFLT being the most pronounced. This could indicate that CRVO-induced edema in OD and adjacent retinal tissue has not yet resolved, or that OD edema may cause long-term changes in OD microstructure. Another study [30] appears to support this hypothesis, stating that edema in the OD and adjacent retinal tissue could affect OCT measurements, with significantly higher RNFLT in groups with OD edema than in healthy subjects. Since CRVO patients in the current study were not divided into acute and chronic groups, it is difficult to interpret the changes seen in CRVO patients.

Compared to healthy subjects, the contralateral eyes of RVO patients have been revealed to have lower peripapillary VD. Vascular dysfunction and ganglion cell damage could both contribute to VD reduction [28]. Similarly, compared to healthy subjects, RVO patients had

Table 7
The OCTA parameters between LPC-treated versus non-treated RVO patients.

Parameters		LPC therapy	Mean±SD (min-max).	*P* value
SCP VD (%)	Whole	Treated	45.14 ± 5.43 (37.50–60.50)	0.493
		Non-treated	46.11 ± 4.61 (34.20–54)	
	Foveal	Treated	25.08 ± 9.69 (8.60–43.50)	0.364
		Non-treated	22.99 ± 10.78 (5.40–50)	
	Parafoveal	Treated	43.95 ± 6.69 (32.40–57.80)	0.093
		Non-treated	46.62 ± 5.52 (34.60–54.20)	
	Perifoveal	Treated	46.19 ± 5.81 (39.10–65.90)	0.572
		Non-treated	47.01 ± 4.68 (33.90–55.80)	
DCP VD (%)	Whole	Treated	45.61 ± 7.20 (37–68.10)	0.457
		Non-treated	46.94 ± 5.60 (36.30–57.20)	
	Foveal	Treated	40.09 ± 12.50 (21.30–72.60)	0.122
		Non-treated	35.07 ± 10.49 (13.80–56.70)	
	Parafoveal	Treated	46.72 ± 8.34 (34.10–71.50)	0.121
		Non-treated	48.49 ± 5.47 (33.70–55.80)	
	Perifoveal	Treated	46.92 ± 7.82 (37.10–70.50)	0.421
		Non-treated	48.49 ± 6.18 (34.70–58.80)	
FAZ parameters	FAZ area (mm^2)	Treated	0.27 ± 0.11 (0.03–0.48)	0.934
		Non-treated	0.29 ± 0.15 (0.06–0.77)	
	PERIM (mm)	Treated	2,19 ± ,40 (1.42–2.88)	0.946
		Non-treated	2.18 ± 0.64 (1.05–4.29)	
	FD-3OO (%)	Treated	45.53 ± 9.15 (30.16–69.38)	0.189
		Non-treated	47.99 ± 4.28 (39.70–57.51)	
Peripapillary VD (%)	Whole	Treated	43.97 ± 2.91 (35.80–49.50)	0.001
		Non-treated	46.97 ± 4.52 (28.50–52.70)	
RNFLT (μm)	Peripapillary	Treated	109.35 ± 25.14 (56–183)	0.383
		Non-treated	115.55 ± 25.50 (70–197)	

OCTA=Optical coherence tomography angiography, RVO=Retinal vein occlusion, VD=Vessel density, LPC=Laser photocoagulation, SCP=Superficial capillary plexus, DCP=Deep capillary plexus, SD=Standard deviation, RNFLT=Retinal nerve fiber layer thickness, FAZ=Foveal avascular zone, PERIM=FAZ perimeter, FD-300=Vessel densities 300 μm area around the FAZ.

significantly decreased whole and peripapillary VDs, as well as superior, temporal, and inferior quadrant peripapillary VDs. Shin et al. [28]., also found that the nasal quadrant is less affected in the outer ring, possibly due to the nasal region having larger vessels than the temporal region. This appears to be consistent with the current study, which found no significant difference in nasal quadrant peripapillary VDs between RVO patients and healthy subjects, and, as previously stated, there was significantly decreased VDs in all quadrants except the nasal quadrant.

In terms of the relationship between anti-VEGF therapy and OD VDs, the current study found lower OD VDs in anti-VEGF-treated patients compared to non-treated patients, though the difference was not statistically significant. Indeed, the lack of investigation into how long before the measurement time anti-VEGF therapy was administered and how many doses were administered complicates interpretation of the study. Nonetheless, these findings suggest that anti-VEGF therapy may change the OD microvascular morphological structure; however, more precise results require prospective and multicenter studies.

Laser photocoagulation has been associated with narrowing of arterial and vein diameters [31]. This vasoconstrictive effect has been presumed to be an auto-regulation mechanism that occurs with an increase in oxygen in the inner retina due to more oxygen diffusing from the choroidal microvascular system towards the damaged outer retina [32]. The analysis of OD VDs in relation to LPC in the current study also revealed that LPC-treated patients had significantly lower whole and peripapillary VDs than non-treated ones. Investigation of OD VDs in LPC-treated patients is intriguing, and these findings suggest that LPC application may affect both retinal microvascular morphological structures and OD blood flow.

Due to its direct communication with large vascular structures and lack of vascular smooth muscles, DCP has been shown to be more sensitive to hemodynamic disorders and hypoperfusion following RVO than the SCP [33]. Photoreceptor axon terminals, horizontal cells, and bipolar cells synapse at the inner nuclear layer's outer border, which is the boundary between deep inner nuclear and outer plexiform layers [34]. As a result, it is assumed that DCP, which is in charge of nutrition in this region, is essential for the nutrition and oxygen support of synaptic connections responsible for visual transmission [35]. Ischemia is more likely in inner nuclear and outer plexiform layers because they are in a lower oxygen environment than inner and outer retinas [36], and DCP hypoperfusion may cause acute nutritional deficiency in synaptic connections, resulting in decreased BCVA [37]. Best-corrected visual acuity and SCP and DCP VDs have previously been found to have a negative correlation [19,38], which is consistent with the current study's findings.

Various studies have produced conflicting results regarding the correlation between BCVA and FAZ area. According to Samara et al. [38]., and Kang et al. [19]., there is a positive correlation between the two parameters. Additionally, Casselholm de Salles et al. [22]., investigated FAZ area as a visual prognostic factor in CRVO cases, discovering that FAZ area was enlarged in both SCP and DCP, as well as a significant correlation between FAZ area and BCVA in non-ME cases. Seknazi et al. [39]., on the other hand, found no significant correlation between the two parameters, just as the current study did. These disparities among studies are thought to be due to sample differences and variations in FAZ area.

The current study also investigated the correlation between BCVA and FD-300, as well as OD VDs, and found a negative correlation between FD-300, whole and peripapillary VD, and BCVA. To our knowledge, this could be the first study to investigate the correlation between OD VDs and BCVA in RVO patients. The OD VDs have been found to be significantly decreased in non-arteritic anterior ischemic optic neuropathy patients than in healthy controls, with a negative correlation found between BCVA and whole and peripapillary VDs [40]. The analysis of BCVA, FD-300, and OD VDs revealed negative correlations between FD-300, whole and peripapillary VD, and BCVA in the current study. Given these findings, it is reasonable to conclude that microvascular dysfunctions affecting the OD microvascular morphological structure may influence visual prognosis.

Few studies have investigated the correlations between age and OCTA parameters. Age and flow density in deep retinal layer have been found to have a negative correlation [41]. Macular and peripapillary VDs have been shown to decrease with age [42]. Also, parafoveal VDs have been found to decrease with age in the Chinese population [43]. Contrarily, other research has found no correlation between age and parafoveal VDs [44], nor between age and perifoveal VDs [45]. The current study, however, found a significant negative correlation between age and SCP and DCP VDs.

The superficial FAZ area has been reported to be significantly smaller

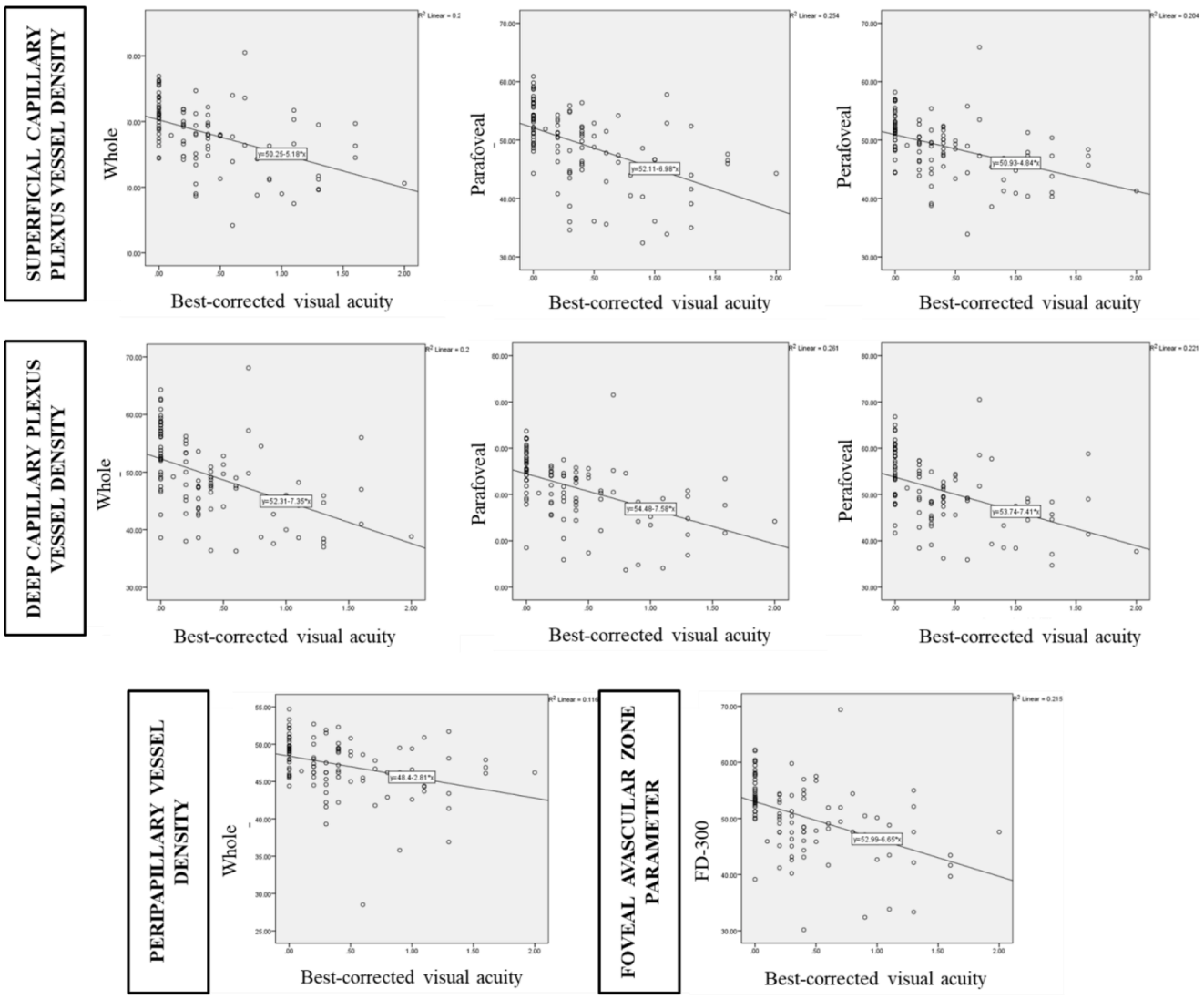

Fig. 7. Graphs illustrating the correlations between best-corrected visual acuity and optical coherence tomography angiography parameters in retinal vein occlusion patients. Best-corrected visual acuity was significantly negatively correlated with vessel densities in whole, parafoveal, and perifoveal regions of superficial (*first row*) and deep (*second row*) capillary plexus. There was also a statistically significant negative correlation with peripapillary vessel density (*third row, first graph*), and FD-300 (*third row, second graph*).

in elderly [46]. This seems to be ascribable to a decrease in perifoveal VDs in elderly patients, confirming the presence of an age-related decrease in FAZ area, which could be explained by atrophic and occlusive changes in the macular capillaries. Yet, there has been no reported significant difference in FAZ area in DCP [47]. Gadde et al. [44]., on the other hand, revealed no significant age-related change in FAZ area in both SCP and DCP. Correspondingly, no significant age-related changes in FAZ area were discovered in the current study. Unlike past studies, the analysis of age-related OD VDs revealed a significant negative correlation between age and whole and peripapillary VDs, suggesting that retinal and OD VDs could be influenced by age-related atherosclerosis or degenerative changes. Furthermore, a positive correlation between age and BCVA was found, which could be attributed to age-related ocular pathologies such as cataracts or microvascular structural alterations.

Vessel density has been reported to be significantly higher in over-60-year-old females than in males, possibly due to late microvascular aging in the former group [46]. It has also been demonstrated that parafoveal VDs decrease more rapidly in males than in females as they age [43]. While SCP VDs have been found to increase in adult females [48], the opposite was found to be true for boys versus girls [49]. On the other hand, Shahlaee et al. [50]., found no gender-related significant difference in retinal VDs. There were no gender-related significant differences in retinal and OD VDs in the current study. Presently, the cause of the contradictory gender-related findings in various studies is yet to be elucidated. The analysis of FAZ parameters by gender revealed that females had significantly larger FAZ areas in SCP and DCP than males [51]. In contrast, Samara et al. [52]., found no significant gender-related differences in FAZ area in SCP and DCP, which is consistent with the current study. Moreover, despite the fact that Khawaja et al. [53] revealed in an OCT study that females have higher RNFLT than males, other studies found no significant differences [54]. The current study also found no gender-related significant differences in RNFLT. Again, Içel et al. [55]., found no significant difference in SCP, DCP, as well as OD radial peripapillary VDs in boys and girls in an OCTA study involving healthy children. The current study also found non-gender-related significant differences in OD VDs.

There are some limitations to the current study. This includes (a) a retrospective study design, (b) a relatively small number of study participants, (c) a lack of RVO classification as acute or chronic, (d) a lack of occlusion area specification in BRVO patients, (e) a lack of evaluation of intravitreal injection and LPC therapy doses, and (f) an uncertainty of time between therapy and OCTA procedure, making interpretation of

the results difficult. Besides, the current software in the OCTA device calculates the automated FAZ value by evaluating the full-thickness retina, so it cannot be compared to studies that separately examine the FAZ parameters of SCP and DCP.

The current study differs from previous RVO studies in that it divides patients into anti-VEGF-, corticosteroid-, and LPC-treated and non-treated groups, as well as patients with comorbid systemic diseases. Aside from that, one of the current study's strengths is that many parameters were compared between different subgroups, including variables that have received little attention in the past, such as outer retinal and choriocapillaris flow areas, as well as OD VDs.

5. Conclusions

Changes in retinal VDs and OD VDs may occur as a result of RVO and associated therapeutic measures. Given the numerous advantages of OCTA, it appears that this novel non-invasive device will be used more frequently in clinical practice for diagnosis, follow-up, and therapeutic response evaluation in RVO, the second most common retinal microvascular disease. Prospective, multicenter studies with large populations are required, as are long-term results on changes in retinal and OD parameters in RVO patients, as well as the factors influencing them.

Declarations

- *Presentation declaration:* This clinical study's abstract was presented as a poster (PS-TR-12) at the Turkish Ophthalmology Society's 55th National Congress, held in Antalya, Turkey, from November 3–7, 2021.
- *Funding & conflicts of interest:* The authors declare that they have received no public or private financial support or involvement in the products, methods, or materials mentioned in this manuscript, and there is no conflict of interest to disclose.
- *Financial interest*: All authors certify that they have no association or participation with any organization or individual with any financial interest or non-financial interest in the subject matter or materials discussed in this article.
- *Ethics approval:* This study followed the Helsinki Declaration and was approved by the Afyonkarahisar Health Sciences University Clinical Research Ethics Committee under Approval number: 2011-KAEK-2.
- *Consent for publication:* The authors note that human study participants have given informed consent to the release of the images.
- *Data and Material Availability:* The manuscript contains all data. The datasets used and/or analyzed during the current study, however, are available upon reasonable request from the corresponding author.

CRediT authorship contribution statement

Neriman Efe Çalışkan: Writing – review & editing, Methodology, Writing – original draft, Visualization, Investigation, Formal analysis, Conceptualization. **Mustafa Doğan:** Conceptualization, Methodology, Formal analysis, Writing – review & editing, Project administration. **Abdullah Çalışkan:** Writing – review & editing, Writing – original draft, Visualization, Investigation. **Hamidu Hamisi Gobeka:** Conceptualization, Methodology, Formal analysis, Writing – review & editing. **İbrahim Ethem Ay:** Writing – original draft, Investigation, Formal analysis.

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