Various configuration types of the foveal avascular zone with related factors in normal Chinese adults with or without myopia assessed by swept-source OCT angiography

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Abstract

● **AIM:** To describe the morphological characteristics of foveal avascular zone (FAZ) in normal Chinese adults with or without myopia by swept-source optical coherence tomography angiography (SS-OCTA) and analyze the possible associated factors.

● **METHODS:** Normal Chinese adults with or without myopia aged between 18 and 60y were recruited into the study. One eye in each individual was randomly selected for scanning using SS-OCTA. FAZ parameters, central retinal thickness (CRT) and central choroidal thickness (CCT) were then analyzed. Correlations between systemic and ocular variables and FAZ parameters were subsequently evaluated. The subgroup analysis based on refractive error was also carried out.

● **RESULTS:** In total, 127 eyes out of 127 normal subjects were finally included in the study (mean age 29.5±8.22y, 61 males and 66 females). The pattern of FAZ was variable: round configuration in 28 eyes (22%), quadrilateral configuration in 23 eyes (18%), pentagonal configuration in 20 eyes (16%), oval configuration in 15 eyes (12%), triangular configuration in 6 eyes (5%) and irregular configuration in 35 eyes (28%). The mean area of FAZ was 0.37±0.12 mm^2. Females had a larger FAZ (0.41±0.11 mm^2 *vs* 0.32±0.11 mm^2) compared with that of males ($P<0.01$). All myopic individuals showed smaller FAZ area and perimeter compared with that of normal individuals ($P<0.01$). There was no obvious correlation between age and FAZ. In the univariate regression analysis, both axial length (AL) and refractive error were significantly related to FAZ parameters. However, only CRT showed negative correlation with FAZ in the multivariate regression analysis.

● **CONCLUSION:** The pattern of FAZ configuration in normal Chinese adults with or without myopia is highly variable. Establishing quantitative parameters of FAZ would not only provide details of macular pathophysiology but could possibly contribute as a biomarker in disease staging.

● **KEYWORDS:** foveal avascular zone; swept-source optical coherence tomography angiography; central retinal thickness; myopia

INTRODUCTION

The foveal avascular zone (FAZ) is a ring-like vascular free zone located in the center of the macula, which is surrounded by a network of continuous capillary plexus from retina[1]. As a highly refined area of the human retina, FAZ possesses unparalleled significance for maintaining normal visual function. The FAZ area is highly sensitive to ischemia for its high oxygen demand. It is found that FAZ area increased in some disease states such as retinal vascular diseases[2-3] and glaucoma[4-5]. Moreover, the area of the FAZ is significantly correlated with visual acuity in diabetic retinopathy (DR) and retinal vein occlusion (RVO)[6]. Quantitative evaluation of FAZ can be used as a potential biomarker for macular ischemia in retinal vascular diseases[7-10]. In order to investigate the variation of FAZ in different disease states, it is necessary to first explore the morphological characteristics of normal

FAZ and the factors that may influence it. Although multiple studies have published data of FAZ parameter in normal individuals[11-13], less data was available using swept-source optical coherence tomography angiography (SS-OCTA).

SS-OCT is the latest development in optical coherence tomography (OCT) technology, which employs a swept-source light and optical detector. With a longer wavelength and faster scanning speed, SS-OCT can present fundus structures in a broad, high-resolution and non-invasive manner[14]. Building on the principles of OCT, SS-OCT has also been applied to SS-OCTA, thus enabling a non-invasive and depth-resolved imaging of the retinal and choroidal microvasculature[15]. Despite obvious advantages over traditional OCT/OCTA, the widespread of SS-OCT/OCTA remains relatively limited in clinical practice.

The present study aims to identify the morphological characteristics and potential influence factors of FAZ in normal individuals in order to provide normative data from a cohort of normal Chinese adults with or without myopia.

SUBJECTS AND METHODS

Ethical Approval This study was conducted according to the principles of the World Medical Association Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University. All participants in the study signed the informed consent prior to participation.

Subjects Normal Chinese adults with or without myopia were consecutively recruited from August to December 2021. The following inclusion criteria were adopted: age range between 18 and 60y; best-corrected visual acuity (BCVA) ≥ 1.0 and intraocular pressure (IOP) range 10-21 mm Hg; refractive error ≤ -10 D; axial length (AL) ≤ 28 mm; and slit lamp microscope and fundus examination with no abnormalities. Subjects with any kind of systemic disease (such as hypertension and diabetes mellitus), current pregnancy, any ocular disease (except for ametropia), any ocular trauma or any history of eye surgery were excluded. One eye per person was then randomly selected for examination.

General Ophthalmic Examinations All subjects underwent a comprehensive ophthalmic examination, including BCVA and refractive error assessment *via* autorefractor (CV-5000; Topcon Co, Japan), IOP measurement (CT-800; Topcon Co, Japan), slit-lamp microscope assessment of the anterior segment, fundus photography using Scanning Laser Ophthalmoscop (Daytona P200T; OPTOS, England), and AL measurement (Meditec IOL Master 500; Carl Zeiss, Germany).

SS-OCT/OCTA Imaging and Analysis The SS-OCT/OCTA system (VG200D; SVision Imaging, Ltd., China) has been previously described[16-18]. The core technology of the system contained: an SS laser with 1050 nm central wavelength and

A-scans with a scanning rate of 200 K per second. The device had a longitudinal resolution of 5 μm and transverse resolution of 13 μm with a scan depth of 3 mm. The instrument was embedded with an eye-tracking utility and had a combining follow-up mode to eliminate eye-motion artifacts. All examinations were performed by equally skilled photographers and adhered to consistent parameters. Macular structure images were performed by 'Star 18Line R32' mode to observe retina and choroid. In terms of angiography, the FAZ images were obtained by scanning mode 'Angio 3×3 521×512 R4', centered on the fovea. The A-scan density was 512 lines (horizontal) ×512 lines (vertical), which was repeated four times, and the average value was taken to improve the SNR. Then images with signal intensity ≥ 8 were included in the data analysis. The area (mm^2), perimeter (mm), circularity index (CI) and fractal dimension (FD) of FAZ were automatically analyzed using van Gogh v1.36.10 instrument software (Figure 1).

The macular area was divided into three regions: central fovea, parafovea, and perifovea according to the Early Treatment Diabetic Retinopathy Study (ETDRS) grid. Average central retinal thickness (CRT) and central choroidal thickness (CCT) in the central fovea were then analyzed. Choroidal vascularity index (CVI) and choroidal vessel volume (CVV) of central fovea were obtained from the research function of the instrument software.

Statistical Analysis Statistic software SPSS (version 25.0; IBM, Chicago, USA) was used for data analysis. All continuous variables were expressed as mean±standard deviation, and classification variables were expressed as frequency (%). Comparisons of factors between groups were performed using one-way ANOVA for variables with normal distributions, while Kruskal-Wallis test was adopted for variables with skewed distributions. Univariate and multivariate regression analyses were then performed in order to determine factors related to FAZ. The regression analysis of the FAZ values included: age, gender, refractive error, AL, IOP, CRT, CCT, CVI, and CVV. For all of the analyses, $P < 0.05$ was considered to be statistically significant.

RESULTS

General Characteristics This observational, cross-sectional study enrolled a total of 127 normal volunteers, including 61 males (48%) and 66 females (52%), in which 127 eyes were examined. The mean age was noted to be 29.5±8.22y (18-58y). Meanwhile, the mean area and perimeter of FAZ was found to be 0.37±0.12 mm^2 and 2.42±0.41 mm, respectively. The mean FAZ area of the female subjects was 0.41±0.11 mm^2, while that of male subjects was 0.32±0.11 mm^2. The average FAZ area of males was significantly smaller compared with that of females ($P < 0.01$). Moreover, males had a smaller FAZ
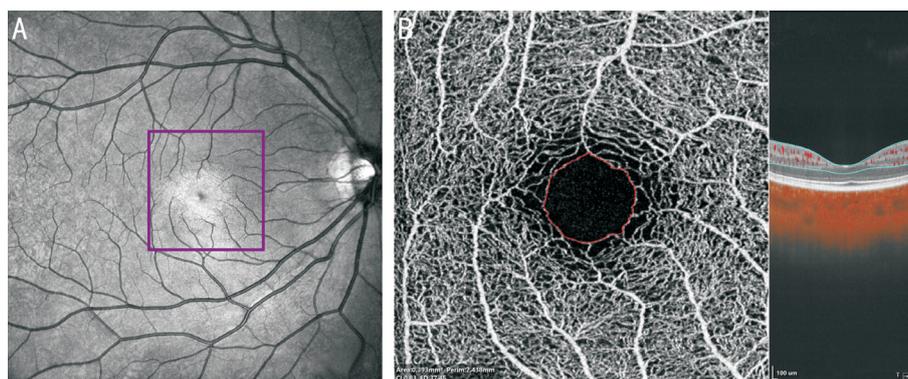
Figure 1 Foveal avascular zone analysis A: SS-OCTA scan region of 3×3 mm^2 centered on the fovea; B: Automatic analysis of FAZ by the instrument software. The area, perimeter, CI, and FD of FAZ are shown in the lower left corner of the image (Area: 0.393 mm^2, Perim: 2.428 mm, CI: 0.83, FD: 37.45). SS-OCTA: Swept-source optical coherence tomography angiography; FAZ: Foveal avascular zone; CI: Circularity index; FD: Fractal dimension.

Table 1 FAZ parameters and clinical characteristic variables by gender

Parameters	Total	Male	Female	P
Age (y)	29.50±8.22	29.77±9.15	29.26±7.31	0.936
Refractive error (D)	-3.59±2.48	-3.84±2.37	-3.36±2.56	0.4
AL (mm)	25.08±1.34	25.47±1.19	24.71±1.37	0.005
IOP (mm Hg)	16.41±2.43	16.75±2.49	16.09±2.34	0.125
Area (mm^2)	0.37±0.12	0.32±0.11	0.41±0.11	<0.001
Perimeter (mm)	2.42±0.41	2.27±0.41	2.55±0.37	<0.001
CI	0.77±0.05	0.75±0.05	0.78±0.04	<0.001
FD	43.11±4.88	42.76±4.80	43.43±4.98	0.463
CRT (μm)	254.52±24.11	261.70±17.57	245.76±17.08	<0.001
CCT (μm)	322.48±90.48	318.84±84.83	325.89±96.03	0.669
CVI	0.34±0.11	0.34±0.12	0.33±0.09	0.763
CVV (mm^3)	0.09±0.05	0.09±0.05	0.09±0.05	0.943

FAZ: Foveal avascular zone; AL: Axial length; IOP: Intraocular pressure; CI: Circularity index; FD: Fractal dimension; CRT: Central retinal thickness; CCT: Central choroidal thickness; CVI: Choroidal vascularity index; CVV: Choroidal vessel volume.

perimeter and CI compared with those of females (*P*<0.01). The FAZ parameters of the subjects are shown in Table 1.

Characteristics and Distribution of FAZ Pattern The shape of FAZ exhibited by SS-OCTA was found to be variable, in which most of the fundus images showed specific patterns. The round configuration was noted in 28 eyes (22%), while the quadrilateral configuration was present in 23 eyes (18%), pentagonal configuration in 20 eyes (16%), oval configuration in 15 eyes (12%), and triangular configuration in 6 eyes (5%). In addition, the irregular configuration was found in 35 eyes (28%). The characteristics and distribution of FAZ patterns are shown in Figures 2 and 3.

Subgroup Analysis Based on Refractive Error According to refractive error, subjects were divided into the emmetropia group (*n*=25) and myopia group (*n*=102). Next, the myopia group was divided into three subgroups: low degree myopia (*n*=26) with diopter (D) range from -0.75 to -3.00 D, medium myopia (*n*=53) with diopter range from -3.00 to -6.00 D and high myopia (*n*=23) with diopter range from -6.00 to -10.00 D. The mean AL in the three groups was 24.62±0.90 mm (23.06-

25.85 mm), 25.76±0.77 mm (23.68-27.18 mm), 26.24±0.67 mm (24.24-27.42 mm), respectively. All myopic eyes showed a smaller FAZ area and perimeter (*P*<0.01). Only the high myopia group exhibited a statistically significant lager CI and FD when compared with the emmetropia group (Figure 4). All myopic eyes possessed a thicker CRT than the emmetropic eyes, which changed according to myopia severity. In contrast, the myopia group was shown to have a statistically thinner CCT than normal. Additionally, the CVI and CVV were found to be statistically decreased in both the moderate and high myopia group compared with those of the normal group (*P*<0.01; Figure 5). The variables of different groups are shown in Table 2.

Univariate and Multivariate Regression Analysis The results of the univariate regression analyses for FAZ parameters are shown in Table 3. According to the univariate regression analysis, multiple factors were noted to be correlated with FAZ. Specifically, gender, refractive error, AL, CRT, CCT, CVI, and CVV were significantly related to FAZ area and perimeter in the study. Refractive error, AL and CRT were also
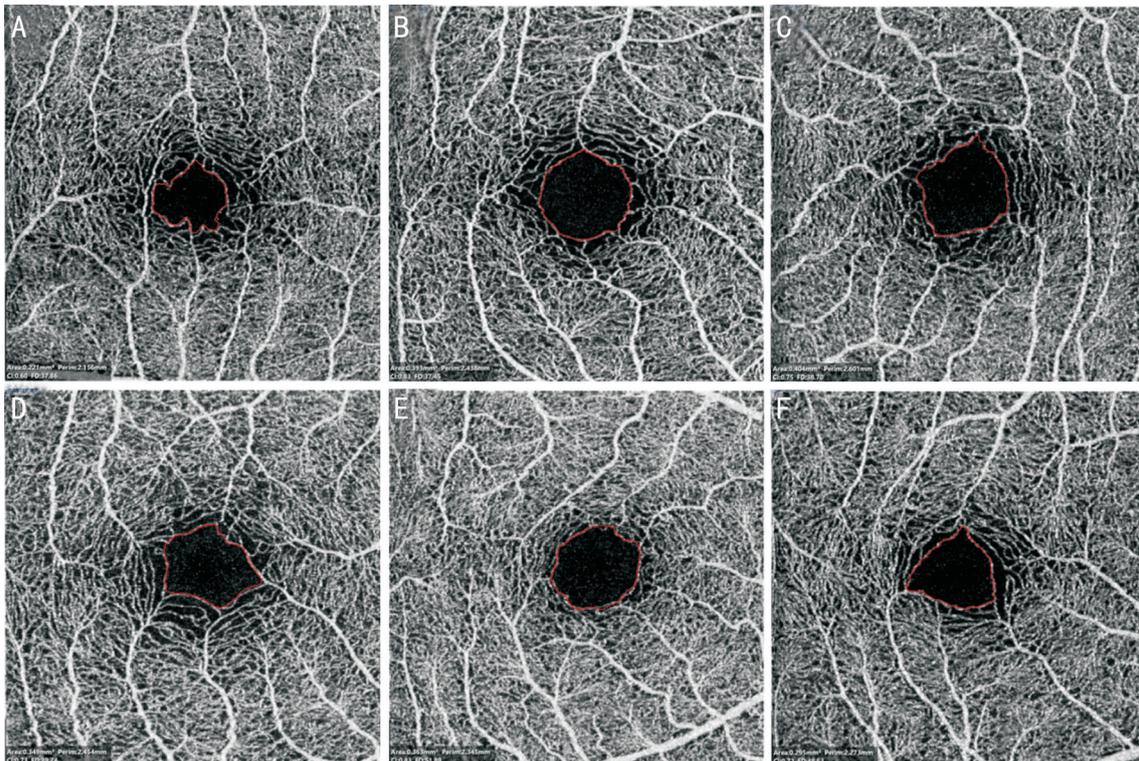
Figure 2 FAZ pattern exhibited by SS-OCTA A: Irregular configuration; B: Round configuration; C: Quadrilateral configuration; D: Pentagonal configuration; E: Oval configuration; F: Triangular configuration. FAZ: Foveal avascular zone; SS-OCTA: Swept-source optical coherence tomography angiography.
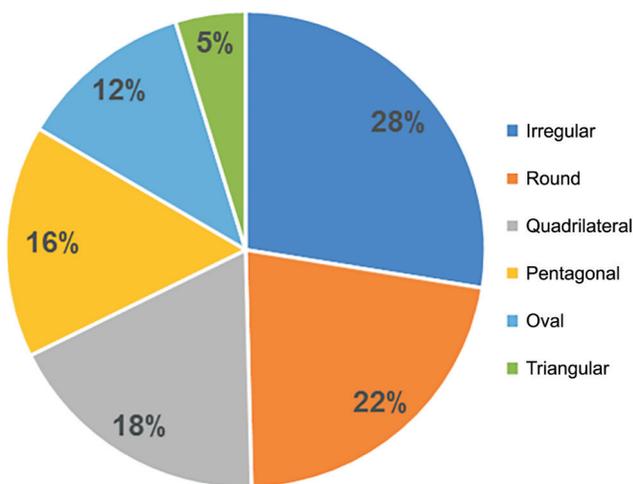

Figure 3 Distribution of FAZ pattern FAZ: Foveal avascular zone.

significantly related to the CI of FAZ. Moreover, refractive error and AL were significantly related to the FD of FAZ. CRT showed significant correlation with FAZ in multivariate regression analysis. In addition, a linear relationship was observed between CRT and FAZ area, perimeter, CI and FD. With a thinner CRT, FAZ area and perimeter exhibited an increasing trend ($P<0.01$). The linear relationship between CRT and FAZ is shown in Figure 6. No obvious correlation between age and FAZ parameters was present in the univariate or multivariate regression analysis.

DISCUSSION

This study provided a detailed quantitative analysis of FAZ. Accordingly, the six patterns of FAZ in normal Chinese adults with or without myopia were initially described, and the obtained results support previous studies pertaining to the association between gender, CRT and FAZ area. This study is also the first to report on the variation of FAZ according to different degree of myopia.

Eldaly *et al*[19] detected five different FAZ patterns: horizontally oval, rounded, pentagon, vertically oval and nonspecific configuration in an Egyptian population study, in which horizontally oval superficial FAZ was shown to be the most common pattern. In this study, six FAZ forms were observed in normal Chinese adults, with most having specific patterns, including round, oval, triangle, quadrilateral and pentagonal that reached up to 72%, while a few exhibited an irregular configuration accounted for 28%. To our knowledge, this is the first study using SS-OCTA to describe FAZ morphology in a normal Chinese population. The results showed that the morphology of FAZ was variable in normal adults.

Several previous studies have described FAZ area in Chinese subjects using different OCTA instruments. Zhou *et al*[20] evaluated young Chinese subjects with average age of 25.95±1.79y and found that the mean FAZ area was 0.30±0.11 mm^2 using the Optovue Fourier-domain OCTA
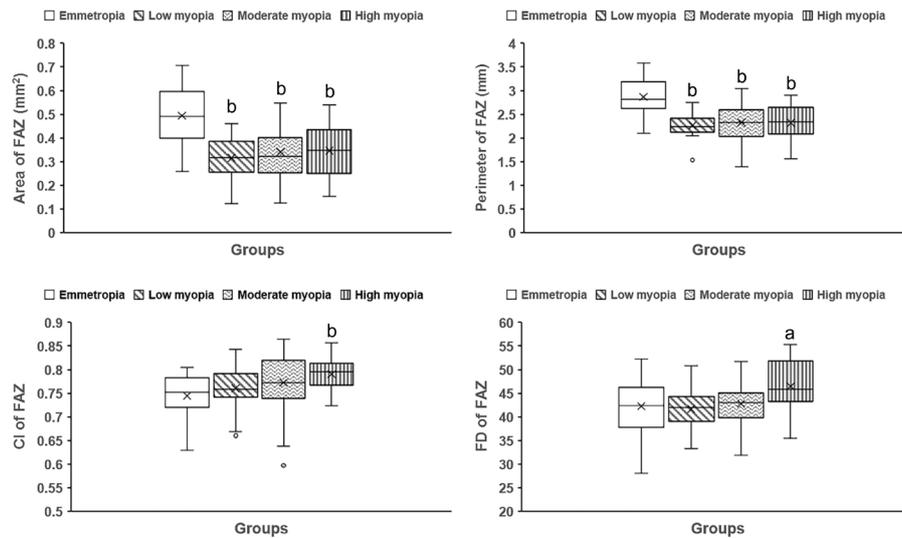
Figure 4 The area, perimeter, CI, and FD of FAZ in the four groups Compared with emmetropia [a]$P<0.05$, [b]$P<0.01$. CI: Circularity index; FD: Fractal dimension; FAZ: Foveal avascular zone.
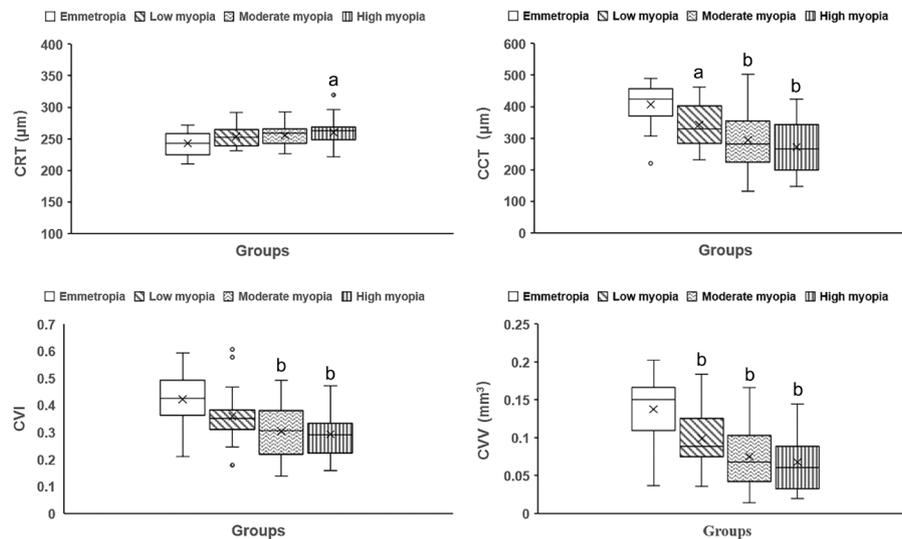

Figure 5 The CRT, CCT, CVI, and CVV of central fovea in the four groups Compared with emmetropia [a]$P<0.05$, [b]$P<0.01$. CRT: Central retinal thickness; CCT: Central choroidal thickness; CVI: Choroidal vascularity index; CVV: Choroidal vessel volume.
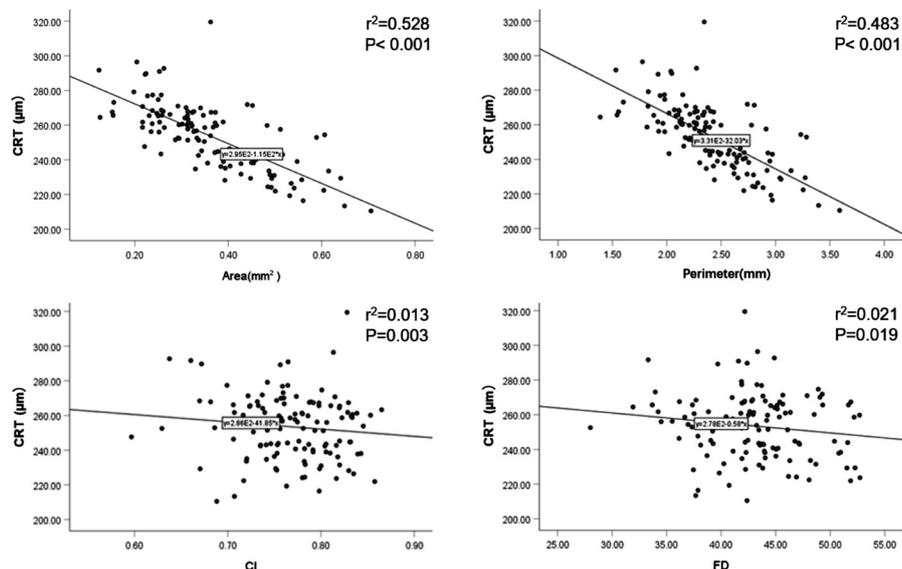

Figure 6 The linear relationship between CRT and FAZ CRT was negatively correlated with area, perimeter, CI, and FD of FAZ. CRT: Central retinal thickness; CI: Circularity index; FD: Fractal dimension; FAZ: Foveal avascular zone.

Table 2 Subgroup analysis of identified factors according to refractive error

Parameters	Emmetropia	Low myopia	Moderate myopia	High myopia	P
Age (y)	31.84±9.04	30.38±7.57	27.06±6.14	31.61±10.81	0.66
Refractive error (D)	0	-2.28±0.78	-4.33±0.67	-7.27±1.09	0
AL (mm)	23.10±0.40	24.62±0.90	25.76±0.77	26.24±0.67	0
IOP (mm Hg)	15.72±2.32	16.27±2.31	16.81±2.37	16.39±2.76	0.296
Area (mm^2)	0.49±0.12	0.32±0.08	0.34±0.11	0.35±0.11	0
Perimeter (mm)	2.87±0.36	2.26±0.28	2.33±0.37	2.32±0.35	0
CI	0.74±0.04	0.76±0.05	0.77±0.06	0.79±0.03	0.011
FD	42.25±5.23	41.71±4.34	42.75±4.17	46.48±5.38	0.002
CRT (μm)	242.74±19.42	254.12±16.22	255.53±16.69.42	260.21±22.46	0.009
CCT (μm)	406.52±64.78	343.03±68.42	294.88±87.47	272.25±78.96	0
CVI	0.42±0.11	0.36±0.09	0.30±0.10	0.29±0.08	0
CVV (mm^3)	0.14±0.04	0.10±0.04	0.07±0.04	0.07±0.03	0

AL: Axial length; IOP: Intraocular pressure; CI: Circularity index; FD: Fractal dimension; CRT: Central retinal thickness; CCT: Central choroidal thickness; CVI: Choroidal vascularity index; CVV: Choroidal vessel volume.

system. In a study of 262 normal Chinese volunteers whose age ranged between 5 and 89y, Zhou et al[21] reported that the mean FAZ area was 0.30±0.03 mm^2 in all eyes using Zeiss HD-OCT with Angioplex. Moreover, by employing the Optovue RTVue XR OCTA, Wang et al[22] found that the mean FAZ area was 0.35±0.12 mm^2 in 105 normal Chinese volunteers who had an average age of 35.9±13.8y. Notably, the mean FAZ area in the present study was found to be 0.37±0.12 mm^2, which was slightly greater than the above results. We believe that the main reason for the difference is the use of different instruments. Corvi et al[23] compared FAZ values using a 3×3 mm^2 volume scan pattern centered on the fovea with seven different OCTA devices and suggested that making comparisons between instruments is nearly impossible and the set of measurements from various instruments are not interchangeable. Therefore, it may be necessary to use a single device in order to reduce variability in clinical practice. Other reasons may involve differences regarding age and gender distribution.

CI and FD are another two quantitative indexes to evaluate FAZ morphology. Bigger CI and FD indicate more regular FAZ morphology and capillary distribution. Previous studies found that FD was significantly reduced in patients with DR, and FD was significantly associated with disease severity and visual acuity[24-25]. Therefore, accurate measurement of the shape and size of FAZ can be used as an important quantitative indicator for monitoring early morphological variation of the disease.

In this study, females possessed a significantly larger FAZ area compared with that of males. This result was found to be consistent with previous studies[13,20,26], which may be due to thinner fovea retinal thickness in females than males. There was no correlation between FAZ parameters and age, as reported by other researchers[13,26]. In fact, the association between age and FAZ area is always a controversial topic. Fujiwara et al[27] described a positive correlation between age and FAZ area among subjects aged 40 years or older. Moreover, Yu et al[28] reported that the FAZ area increased annually by 1.48%, and they speculated the main reason for the trend was relative reductions in oxygen and nutrient demand.

Various studies have shown that the FAZ area is related to retinal thickness under the macular fovea, but not to choroid thickness[19,29-30] which was supported in this study. Furthermore, the multivariate regression analysis demonstrated that CRT was significantly correlated with FAZ. A linear relationship was also present between CRT and FAZ area, perimeter, CI, and FD. AL is another important factor that may influence FAZ measurement. Previous studies have shown that AL was negatively correlated with FAZ area[21-22,25,31]. According to univariate regression analysis, AL was found to be correlated with the area and perimeter of FAZ; however, in the multivariate regression analysis, there was no significant correlation between AL and FAZ area. Fujiwara et al[27] also suggested AL was not significantly correlated with FAZ area. Therefore, this issue remains ambiguous and requires further study.

In this study, the subjects were detailed and grouped according to refractive errors. The variation of FAZ parameters in myopic eyes was also preliminarily discussed. All myopic eyes showed a smaller FAZ area and perimeter compared with those of the control ($P<0.01$). Additionally, FAZ area had an increasing trend with myopia severity. Previous studies have also shown that FAZ area was significantly enlarged in highly myopic eyes than in those with non-high myopia[32-33]. All myopic eyes exhibited thicker CRT and thinner CCT compared with that of emmetropic eyes. The CVI and CVV were also shown to be statistically decreased in the myopia groups. These results were

Table 3 Univariate analysis among factors and FAZ values

Independent variable	Dependent variable	Estimate	Standard error	t	P
Area	Gender				0
	Age (y)	0.003	0.001	1.961	0.052
	Refractive error (D)	0.015	0.004	3.728	0
	AL (mm)	-0.039	0.007	-5.263	0
	IOP (mm Hg)	-0.006	0.004	-1.419	0.158
	CRT (μm)	-0.003	0	-8.432	0
	CCT (μm)	0	0	2.826	0.006
	CVI	0.275	0.099	2.789	0.006
	CVV (mm³)	0.783	0.22	3.553	0.001
Perimeter	Gender				0
	Age (y)	0.007	0.004	1.66	0.099
	Refractive error (D)	0.06	0.014	4.308	0
	AL (mm)	-0.138	0.025	-5.573	0
	IOP (mm Hg)	-0.02	0.015	-1.296	0.198
	CRT (μm)	-0.01	0.001	-7.45	0
	CCT (μm)	0.001	0	3.009	0.003
	CVI	0.919	0.337	2.726	0.007
	CVV (mm³)	2.745	0.75	3.659	0
CI	Gender				0.001
	Age (y)	0.001	0.001	1.681	0.095
	Refractive error (D)	-0.006	0.002	-3.439	0.001
	AL (mm)	0.008	0.003	2.268	0.025
	IOP (mm Hg)	-0.001	0.002	-0.309	0.758
	CRT (μm)	0	0	-2.264	0.025
	CCT (μm)	-0.044	0	-1.271	0.206
	CVI	0.003	0.001	1.924	0.057
	CVV (mm³)	-0.126	0.098	-1.288	0.2
FD	Gender				0.463
	Age (y)	0.072	0.053	1.365	0.175
	Refractive error (D)	-0.538	0.17	-3.165	0.002
	AL (mm)	0.857	0.322	2.661	0.009
	IOP (mm Hg)	0.349	0.177	1.97	0.051
	CRT (μm)	-0.02	0.018	-1.085	0.28
	CCT (μm)	0.002	0.005	0.468	0.64
	CVI	8.022	4.081	1.966	0.052
	CVV (mm³)	8.022	4.081	1.966	0.052

Regression analysis was chosen for continuous variables and the Mann-Whitney U test was chosen for categorical variables. AL: Axial length; IOP: Intraocular pressure; CI: Circularity index; FD: Fractal dimension; CRT: Central retinal thickness; CCT: Central choroidal thickness; CVI: Choroidal vascularity index; CVV: Choroidal vessel volume.

also consistent with previous studies[34-38]. However, though a variation of FAZ in myopia group was noted, there was no significant correlation between the parameters and refractive error or AL in the regression analysis.

The main limitations of the present study are variability of refractive error and small sample size for subgroup. Therefore, it is necessary to further expand the sample size across different degrees of myopia so as to verify FAZ related variation. Furthermore, continuous monitoring of these indicators in the progression of myopia may provide more reference value for evaluation and prognosis of the disease.

This study described the morphological characteristics of FAZ and quantified the parameters of FAZ in normal Chinese adults with or without myopia using SS-OCTA. The patterns of FAZ exhibited various forms, including: round, oval, triangle, quadrilateral, pentagonal, and irregular configurations. The results suggest that the morphology of normal FAZ can be variable. Additionally, all myopic eyes showed a smaller FAZ area and perimeter compared with those of emmetropic eyes. To determine the exact correlation between the parameters and myopia, it is necessary to conduct longitudinal studies to explore the continuous variation of FAZ. However, detailed quantitative evaluation of FAZ parameters, such as FAZ area, will help us to identify early morphological changes of macula diseases. Specifically, establishing quantitative parameters of FAZ would not only provide details of macular pathophysiology but also could possibly contribute as a biomarker in disease staging.

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