• Clinical Research •

Abnormalities in retinal vascularity and blood perfusion associated with early syphilis revealed by optical coherence tomography angiography

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Abstract

• **AIM:** To explore the feasibility of optical coherence tomography angiography (OCTA) in the early detection of syphilis and syphilitic chorioretinopathy.

• **METHODS:** Patients with newly diagnosed syphilis were enrolled from September 2022 to November 2023. All the participants underwent serological examinations including rapid plasma reagin (RPR) test and treponema pallidum particle agglutination (TPPA) test, as well as macular OCTA scanning. Quantitative indicators including macular vessel flow density (VFD), vessel length density (VLD), and foveal avascular zone (FAZ) were measured and analyzed.

• **RESULTS:** A total of 44 participants were recruited in this study, including 24 patients in the syphilis group (14 males, mean age: 30.83±9.59y) and 20 healthy individuals in the control group (6 males, mean age: 29.6±11.86y). Compared with the control group, the syphilis group presented significantly higher macular VLD and VFD (P<0.05), as well as an increased FAZ perimeter. Subgroup analysis was performed based on RPR titers, with patients divided into the low-titer subgroup (1:2–1:4) and high-titer subgroup (1:8–1:128). Both subgroups showed elevated VLD and VFD (excluding inner VFD) relative to controls (all P<0.05). Moreover, significant elevation of VFD was only observed in the high-titer subgroup. Receiver operating characteristic analysis identified outer VLD as the optimal indicator for distinguishing syphilis patients from controls, with an area under the curve of 0.802 (95%CI: 0.667–0.937).

• **CONCLUSION:** Syphilis patients with either low or high RPR titers show increased macular VLD and VFD in the absence of obvious visual impairment, indicating the potential of OCTA microvascular parameters for early auxiliary diagnosis of syphilitic ocular lesions.

• **KEYWORDS:** optical coherence tomography angiography; syphilis; microvascular morphology
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INTRODUCTION

Syphilis, a sexually transmitted infection caused by the bacterium *Treponema pallidum*. Recent decades have seen a concerning resurgence in global syphilis rates, including ocular syphilis (syphilis affecting the eyes)[1]. Ocular syphilis can manifest at any stage of infection and presents with diverse clinical features, including conjunctivitis, episcleritis, scleritis, optic neuritis, and chorioretinitis, as well as iridocyclitis, retinitis, and uveitis[2]. Among these, chorioretinopathy is the

most frequently observed manifestation, typically presenting with exudates, hemorrhages, retinal and choroidal necrosis, and vitreous opacities, which can result in optic nerve atrophy or permanent destruction of macular photoreceptor outer segments, ultimately leading to vision loss, especially in cases showing poor visual improvement after initial treatment[3].

Syphilitic chorioretinopathy may be misdiagnosed due to non-specific symptoms[4]. As the "great pretender", syphilis infection can lie dormant for long periods and then unpredictably manifest with acute symptoms such as optic nerve retinopathy[5]. The presumptive diagnosis of syphilis relies on serological testing for both treponemal and nontreponemal antibodies, so asymptomatic infection may remain undetected until acute manifestations of advanced syphilis, a condition with generally poor prognosis. During this period, syphilis can also be transmitted to the fetus *via* the placental circulation[6-7]. Ocular syphilis with active inflammation responds well to penicillin treatment as long as it is diagnosed early and treated appropriately and promptly[8]. Unfortunately, as ocular manifestations mimic those of other ophthalmic diseases, including non-infectious diseases, the condition may be misdiagnosed or erroneously treated with steroids, which can lead to irreversible vision loss[4]. Therefore, early diagnosis of syphilitic chorioretinopathy is critical for improved outcome, but few have attempted to detect initial ocular signs in early-stage syphilis.

Ocular syphilis may arise as the only presenting feature within 6wk of transmission[9]. Unfortunately, older ophthalmic examination technologies were insufficient for detecting the underlying chorioretinopathy at these early stages, so imaging data were of limited value for diagnosis[10]. Early detection is of growing importance as syphilis incidence has increased and with it the incidence of syphilitic chorioretinopathy[11]. Eandi *et al*[12] reported that syphilitic chorioretinopathy manifested as scattered hypofluorescent spots on fluorescence angiography (FA) or as "leopard spotting", followed by progressive hyperfluorescence. While fluorescein fundus angiography (FFA) is an important diagnostic tool for syphilitic chorioretinopathy, it is invasive and some patients may be allergic to the contrast medium. Thus, early diagnosis of syphilitic chorioretinopathy remains challenging in clinical practice. Nonetheless, ocular manifestations, including syphilitic chorioretinopathy, are potentially valuable diagnostic features for facilitating early treatment of potential fatal tertiary syphilis and neurosyphilis, so ophthalmologists have the opportunity to markedly improve outcomes[13].

Optical coherence tomography angiography (OCTA) based on optical interferometry enables high-resolution, noninvasive, and label-free imaging of living ocular tissues, and can be used to identify structural abnormalities compared to healthy tissue and healthy matched individuals during disease progression. Thus, OCTA may be particularly effective for the screening, early diagnosis, and monitoring of ocular syphilis, thereby preventing advanced-stage disease and reducing the risk of vision loss. However, there are few reports on OCTA in early syphilitic chorioretinopathy, and it is not clear whether the imaging features of OCTA will assist in clinical diagnosis. To further improve the early diagnosis of syphilitic chorioretinopathy, we investigated the diagnostic performance of OCTA parameters among patients with syphilis stratified by rapid plasma reagin (RPR) titer.

PARTICIPANTS AND METHODS

Ethical Approval The study follows the Declaration of Helsinki and exempt from ethical review by the Committee on Medical Ethics, First Affiliated Hospital, University of South China (No.2025ll0320001). The requirement for informed consent was waved as the examinations were routine and did not influence treatment programs, while all results were anonymized.

Syphilis patients first diagnosed at the Department of Dermatology, First Affiliated Hospital, University of South China, were enrolled between Sep. 2022 and Nov. 2023. Diagnosis was based on RPR test with confirmatory *Treponema pallidum* hemagglutination assay (TPHA). In addition, recruited patients were screened for non-treponemal infection by the venereal disease research laboratory test. The following clinical data were collected at baseline (prior to antibiotic treatment): age, sex, human immunodeficiency virus (HIV) serological status, RPR/TPHA results, best corrected visual acuity (BCVA), intraocular pressure (IOP), slit-lamp and fundus examination results, and OCTA. Best-corrected visual acuity was measured using a standard visual acuity scale, and converted to the logarithm (logMAR VA). Diagnostic confirmation required more than two positive RPR or TPHA test results and the final patient cohort excluded those with comorbid HIV infection. Other exclusion criteria were as follows: 1) poor quality images on OCT with a signal strength index less than six or significant motion artifacts; 2) ocular vasculitis or glaucoma, age-related macular degeneration, trauma, retinal detachment, and other congenital or genetic diseases; 3) current clinical manifestations of ocular syphilis (*e.g.*, uveitis); 4) history of ocular disease or steroid use or surgery, uncontrolled hypertension, coronary heart disease, pregnancy, mental illness, or neurosyphilis; 5) diagnosis of uveitis and extremes of axial length (*e.g.*, <22 mm or >26 mm). A healthy controls group was recruited at the same time. The healthy controls individuals without syphilis or HIV.

All OCTA images were acquired using the CIRRUS OCT platform (ZEISS CIRRUS 5000, Carl Zeiss Meditec Inc, Dublin, CA, USA), each covering a 6 mm×6 mm macular

area centered on the macula. According to the Early Treatment Diabetic Retinopathy Study (ETDRS) standards: the macular is divided into the center subfield (a circular area centered on the fovea with a radius of 0.5 mm), the inner ring (the annular area between circles of radius 0.5 and 1.5 mm), and the outer ring (the annular area between circles of radius 1.5 and 3.0 mm). Imaging metrics included ganglion cell layer (GCL), retinal nerve fiber layer (RNFL), and macular foveal thickness, average volume thickness [the device software automatically computed the average thickness by dividing the total volume (sum of all pixel-wise thickness values) by the scan area], and cube volume (cube volume was derived by multiplying the scan area by the average thickness). We also compared microvascular parameters between syphilis patients and healthy controls. Vascular length density (VLD) was defined as the linear length of blood vessels in a given region divided by area, microvascular flow density (VFD) as the total vessel area per unit total area, and the avascular area of macular fovea (FAZ) as macular fovea area with no blood vessels. FAZ boundaries were identified using ZEISS CIRRUS 5000 with 6 mm×6 mm scans centered on the fovea. FAZ was defined as the avascular area bordered by the terminal capillaries of the superficial capillary plexus (SCP). FAZ was automatically segmented by the device software with manual correction for artifacts. Total FAZ area (mm^2) calculated by the software based on the delineated boundary. The perimeter identified as total length (mm) of the FAZ boundary. Circularity index: Calculated as a value of 1.0 indicates a perfect circle. FAZ parameters (area, perimeter, and circularity) were automatically determined using the built in segmentation algorithm of the Zeiss Angioplex OCTA system (software version 6.8.0.8308). FAZ was automatically segmented by the device software with manual correction for artifacts. In addition, patients were stratified into 2 groups according to RPR titer: 1:2–1:4 (low), 1:8–1:128 (high). An automated tracking function was employed to produce a consistent image set and directly read from the CIRRUS OCT device's built-in software, thereby ensuring image field consistency and accuracy of parameter measurements. Further, all examinations were completed in the same examination environment by the same examiners (Luo XY and Li JH). Two independent retinal specialists (Liu QP and Zhu YQ) reviewed and analyzed OCTA images, and any disagreement was adjudicated by a third person (Liu ZG).

Statistical Analysis All data were analyzed using SPSS for Mac, version 22.0 (IBM Corp, Armonk, NY, USA). Measurement data were first tested for homogeneity of variance using the Shapiro-Wilk test and subsequently expressed as mean±standard deviation (SD). Qualitative variables are expressed as percentages and compared by χ^2 tests. Layer thickness values [RNFL, fovea, ganglion cell complex (GCC)] and vascular metrics [VLD, VFD, and FAZ parameters (area, perimeter, morphology)] were compared between groups by independent samples *t*-test. Multiple groups/subgroups were compared by analysis of variance (ANOVA) with host-hoc Dunn's or Tukey's multiple comparisons tests. Receiver operating characteristic (ROC) curves were constructed for each OCTA-derived vascular morphologic parameter to assess efficacy in distinguishing healthy from syphilitic eyes. A $P<0.05$ was considered statistically significant for all tests.

Table 1 Demographic and clinical characteristics of study participants

Parameters	Syphilis	Healthy	*P*
Participants, *n*	24	20	
Age, y, mean±SD	30.83±9.59	29.6±11.86	
Sex, *n* (%)			
Male	14 (58.33)	6 (30)	
Female	10 (41.67)	14 (70)	
RPR titer, *n* (%)			
1:2–1:4	10 (41.67)	NA	
1:8–1:128	14 (58.33)	NA	
Eye, *n*	48	40	
logMAR VA	0.00±0.02	0.00±0.00	0.196
IOP, mm Hg	14.3±1.73	13.6±1.81	0.070
RNFL thickness, μm	104.90±10.32	106.08±11.09	0.607
Superior	130.77±19.49	117.95±13.93	0.001
Inferior	135.15±13.58	132.85±15.605	0.463
Temporal	80.71±14.49	79.68±15.01	0.744
Nasal	71.77±14.38	72.98±12.97	0.684
Fovea thickness	243.5±15.83	246.45±19.15	0.431
Fovea cube volume	10.26±0.37	10.24±0.41	0.849
Fovea volume thickness	278.5±25.39	276.55±27.71	0.732
GCC thickness	85.71±4.47	85.48±4.89	0.816

All values are presented as the mean±SD. RPR: Rapid plasma regain; logMAR VA: Logarithm of the minimum angle of resolution visual acuity; RNFL: Retinal nerve fiber layer; IOP: Intraocular pressure; GCC: Ganglion cell complex; SD: Standard deviation; NA: Not applicable.

RESULTS

Baseline Characteristics of Patient and Healthy Controls

The patient and healthy controls were well matched for age, with similar averages and ranges from young adult to middle age. The proportion of females was higher in the healthy controls group. All participants in both groups completed the entire examination battery.

There were no significant group differences in BCVA and IOP. However, various VLD and VFD parameters were significantly greater in the syphilis group compared to healthy controls. The RNFL was also thicker in the superior quadrant of syphilis patients, while the thickness of all other RNFL quadrants as well as fovea thickness, fovea cube volume, fovea volume thickness, GCC thickness, FAZ area, and FAZ morphology did not differ between groups (Table 1, Figure 1). The blood flow was stronger in syphilis patients than healthy controls, and the syphilis group exhibited more numerous distorted (highly nonlinear) vessels than healthy controls (Figure 2).

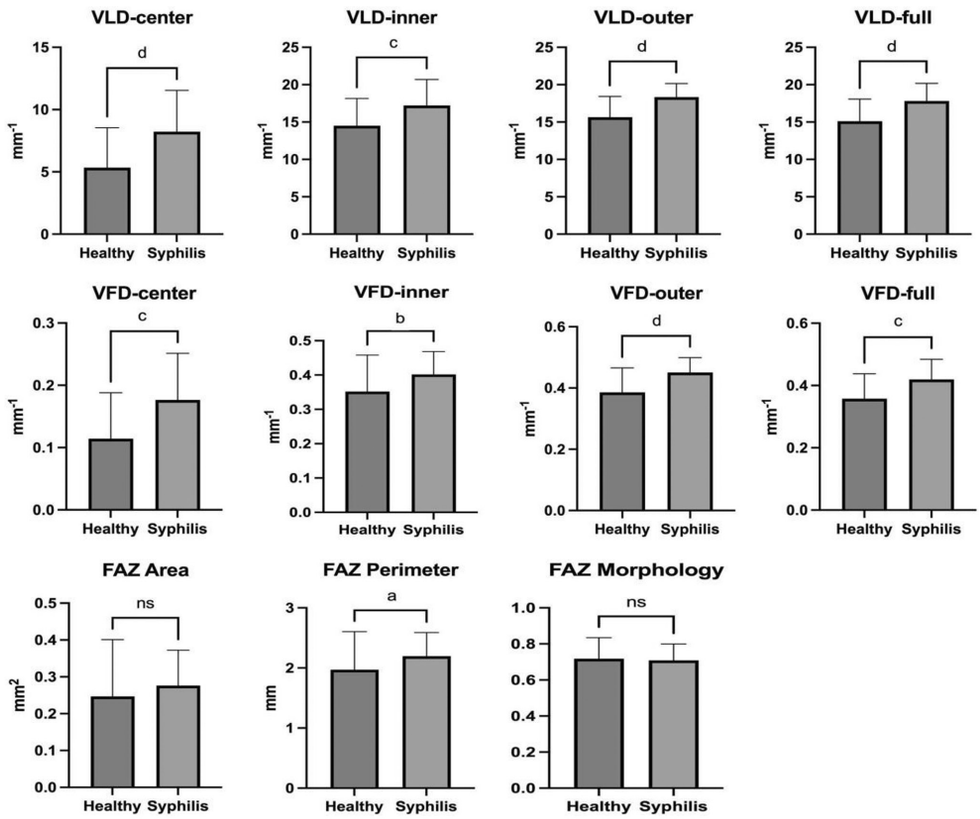

Figure 1 Comparisons of vascular parameters VLD, VFD, and FAZ between healthy controls and syphilis groups VLD: Vascular length density; VFD: Vascular flow density; FAZ: Avascular area of macular fovea. [a]*P*<0.05, [b]*P*<0.01, [c]*P*<0.001, [d]*P*<0.0001.

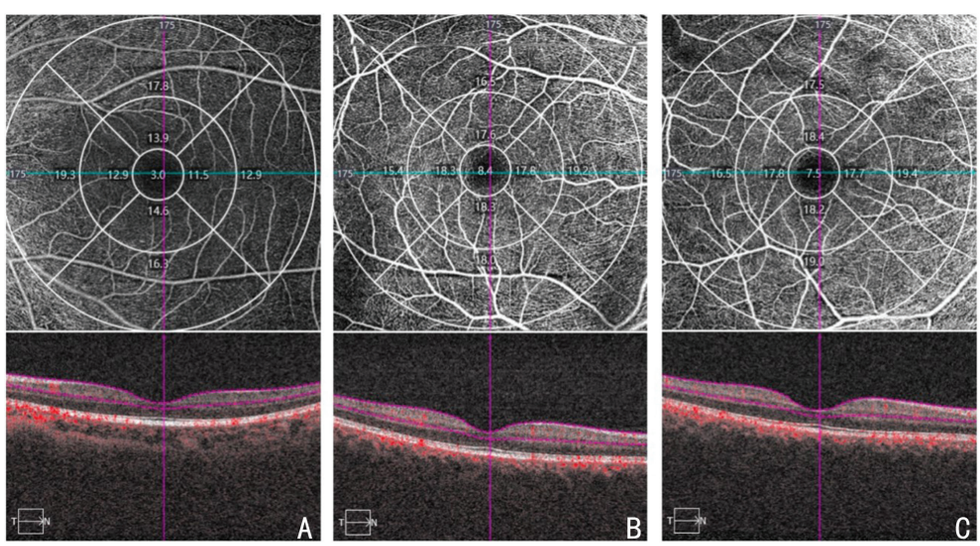

Figure 2 OCTA images from healthy controls group eyes (A) and syphilis patients stratified by RPR test titer as 1:2 (low; B) and 1:128 (high; C) The syphilis group exhibited greater blood flow and vascular twisting. OCTA: Optical coherence tomography angiography; RPR: Rapid plasma reagin.

Comparison of Vascular Parameters Between Healthy Controls and Syphilis Patients Stratified by RPR Test Titer The RPR titer was low (1:2–1:4) in 41.67% of syphilis patients, high (between 1:8 and 1:128) in 58.33%. The syphilis group was divided into low-titer and high-titer groups (Table 2). The VLD values for the entire scanned area (full) and all three subregions (center, inner and outer ring) were higher in the low-titer and high-titer patient group than the healthy controls group (P<0.05). Although there was no significant difference within the group, the trend line showed that retinal blood linear length was still on an upward or stable trend (except outer ring). The VFD appears the same, implying the higher the titer and the greater the perfusion. It is mainly concentrated in the central, outer and full rings, and there is no significant change in the inner ring. In addition, FAZ parameters did not differ between groups (Figure 3).

Prediction of Syphilis by ROC Curve Analysis Based on Vascular Morphology Parameters Based on the

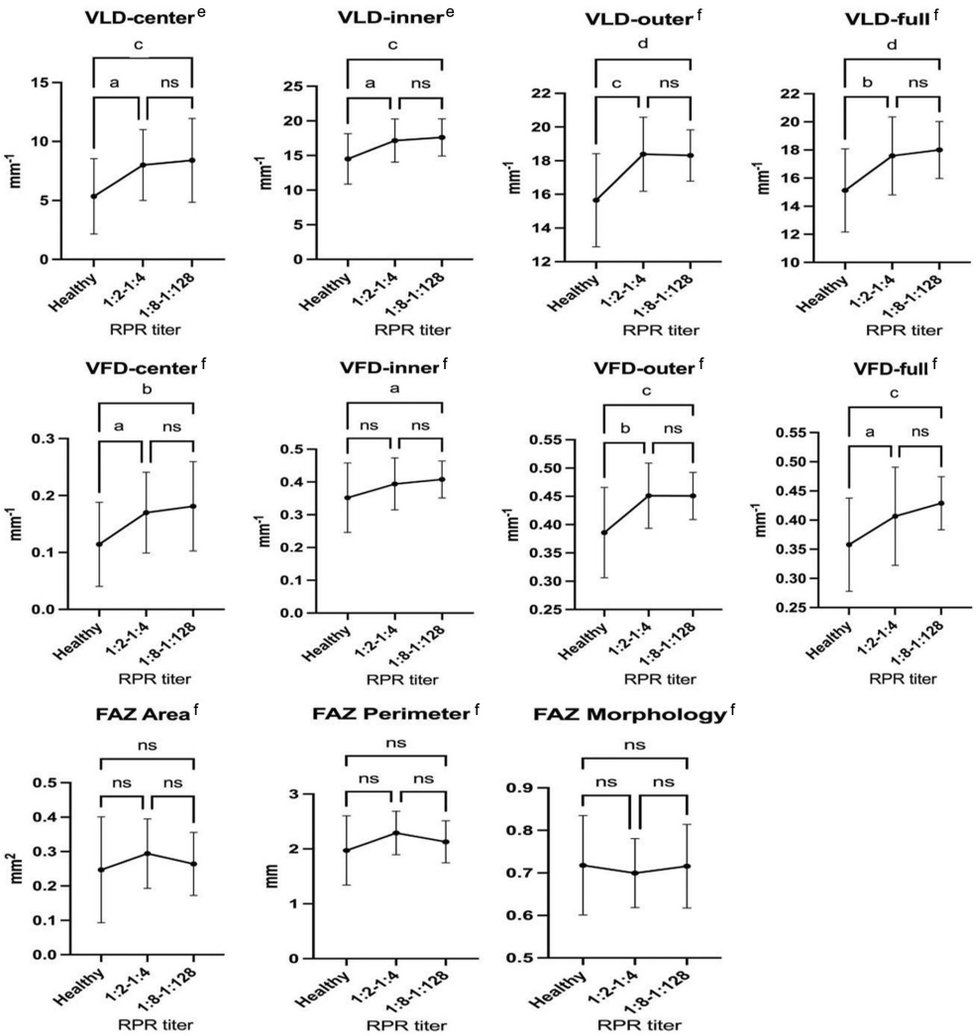

Figure 3 Comparison of vascular parameters between the healthy controls group and syphilis subgroups stratified by RPR test titer VLD: Vascular length density; VFD: Vascular flow density; FAZ: Avascular area of macular fovea; RPR: Rapid plasma reagin. [a]*P*≤0.05, [b]*P*≤0.01, [c]*P*≤0.001. [d]*P*≤0.0001. [e]Dunn's multiple comparisons test; [f]Tukey's multiple comparisons test.

Table 2 Characteristics of syphilis participants

Parameters	Low syphilis (between 1:2 and 1:4)	High syphilis (between 1:8 and 1:128)	*P*
Participants, *n*	10	14	
Age, y, mean±SD	33.7±12.12	29.29±7.25	
Gender, *n* (%)			
Male	4 (40)	10 (71.43)	
Female	6 (60)	4 (28.57)	
Eye, *n*	20	28	
logMAR VA	0.00±0.01	0.00±0.03	0.231
IOP, mm Hg	13.67±3.00	14.43±1.87	0.462

IOP: Intraocular pressure; VA: Visual acuity; SD: Standard deviation.

aforementioned group differences, all regional VLD values and all regional VFD values except for VFD of the inner subregion may be fundus microvascular markers for ocular syphilis. Receiver operating characteristic curves constructed for VLD, VFD, and FAZ (Table 3) revealed significant group differentiation by center VLD [area under the curve (AUC): 0.737 (0.632–0.842) *P*<0.001], inner VLD [AUC: 0.767 (0.627–0.908) *P*=0.002], outer VLD [AUC: 0.802

Table 3 Accuracies of OCTA vascular parameters for distinguishing syphilis patients from healthy controls according to ROC analysis

Parameter	AUC (95%CI)	*P*
VLD		
Center	0.737 (0.632, 0.842)	0.000
Inner	0.767 (0.627, 0.908)	0.002
Outer	0.802 (0.667, 0.937)	0.000
Full	0.766 (0.627, 0.906)	0.000
VFD		
Center	0.731 (0.587, 0.874)	0.008
Inner	0.640 (0.487, 0.792)	0.105
Outer	0.754 (0.612, 0.895)	0.003
Full	0.716 (0.565, 0.866)	0.012
FAZ		
Area	0.570 (0.420, 0.719)	0.420
Perimeter	0.567 (0.410, 0.725)	0.436
Morphology	0.555 (0.402, 0.707)	0.526

VLD: Vascular length density; VFD: Vascular flow density; FAZ: Avascular area of macular fovea; OCTA: Optical coherence tomography angiography; ROC: Receiver operating characteristic; AUC: Area under the curve; CI: Confidence interval.

(0.667–0.937) P<0.001], full VLD [AUC: 0.766 (0.627–0.906) P<0.001], center VFD [AUC: 0.731(0.587–0.874), P=0.008], outer VFD [AUC: 0.754 (0.612–0.895), P=0.003], and full VFD [AUC: 0.716 (0.565–0.866), P=0.012]. The overall best performing parameter was the outer VLD (Figure 4) as the AUC was significantly higher than that of any other parameter. In contrast, FAZ area, perimeter, and morphology did not distinguish between healthy controls and syphilis patients in ROC curve analysis.

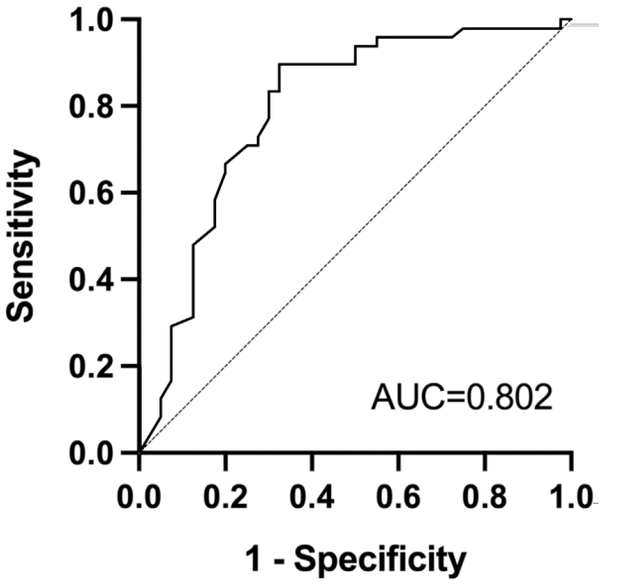

Figure 4 ROC curves for distinguishing healthy controls from syphilis patients according to the indicated vascular parameter measured by OCTA The outer VLD has he largest area under the curve (AUC) and is also the most significant independent risk factor. ROC: Receiver operating characteristic; OCTA: Optical coherence tomography angiography; VLD: Vessel length density.

DISCUSSION

We identified abnormalities in macular microvascular density and vessel morphology among syphilis patients without signs or symptoms of visual dysfunction. Both VLD and VFD were greater in these early syphilis patients than healthy controls as revealed by OCTA, but some values were slightly lower among patients with higher RPR titers, suggesting adaptation of retinal blood vessels to syphilis-induced retinal pathology. These findings suggest that OCTA-derived microvascular metrics may be useful for the detection of asymptomatic syphilis and risk of syphilitic chorioretinopathy, although additional studies are needed to confirm if they can be generalized to the greater patient population.

The cohort recruited for this study was younger than in a previous investigation[2], possibly because younger people are more willing to undergo medical examinations. However, young and asymptomatic early-stage patients are an important target population for research on syphilitic chorioretinopathy. About a quarter of all syphilis patients exhibit ocular syphilis as the only clinical manifestation[10], most frequently posterior uveitis, and a recent survey indicated that the majority of syphilitic uveitis cases occur after the primary stage[4]. Moreover, it is well-known that earlier exposure to syphilis can lead to adverse outcomes. Therefore, there is a critical need for greater awareness of syphilis risk among younger individuals[14], especially among males (Table 1)[15], and identification of markers for timely diagnosis.

There was no significant difference in BCVA between the two groups, indicating that few patients had progressive ocular syphilis at the time of examination. In accord with these findings, RNFL, central macular thickness, fovea cube volume, fovea volume thickness, and GCC thickness did not differ between syphilis and healthy controls groups (Table 1). Alternatively, there were significant differences in macular terminal blood vessel density and morphology, consistent with previous reports that vascular changes precede changes in retinal layer thickness[16]. Nonetheless, microvascular abnormalities in the macula can ultimately impair vision, as observed among diabetic retinopathy and glaucoma patients[17-20]. Previous studies have tended to focus on existing ocular syphilis, such as syphilitic uveitis[21], while we demonstrate that abnormalities in microvascular structure as measured by OCTA are evident prior to gross structural changes to the macula and the onset of ocular syphilis.

Optical coherence tomography angiography is a superior modality for detecting vascular abnormalities. In this study, OCTA detected increased VLD and VFD in the syphilis group (Figures 1 and 2), suggesting enhanced microvascular perfusion. The retina vascular system is regulated predominantly by local metabolism[22], so it is reasonable to speculate that the fundus vasculature can counteract the effects of syphilis through endogenous regulation. In fact, modulation of local regulation may explain why syphilis patients developed fundus microvascular changes. Previous studies reported that ocular syphilis was more likely in cases with higher RPR titer[8,23]. However, we found little difference among titer subgroups but slightly more severe changes in the high-titer subgroup (Figure 3). This pattern suggests that even a low titer will induce increased blood flow to prevent disease-related damage and that no further adaptation is possible.

Alternatively, there were no significant differences in FAZ area and morphology between total syphilis and healthy groups (Figure 1); however, FAZ perimeter differed significantly (Figure 3). It is supposed that the FAZ reflects the proportion of blood flow area relative to the total area and is mainly concentrated in the center and inner ring surrounding the macula[3]. The alteration in macular FAZ perimeter was mainly due to vessel distortion (Figure 2) and greater vessel diameter, likely enhanced flow. This implies that a high titer will affect

the inner structure and thereby the form of the FAZ.

We suggest that adaptation of the retinal vasculature to syphilis-associated stimuli improves at greater titers (*i.e.*, results in greater blood perfusion) as previously reported[24-25]. However, central VLD and VFD first increased at lower titers and then appeared an upward trend within increasing titer, but no noticeable difference between titers group, implying a limit to this adaption. If the titer exceeds the threshold at which compensation fails, syphilis-associated retinal disease is initiated[26]. Therefore, early ocular examinations are critical for prevention of ocular syphilis.

We measured VLD, VFD, and FAZ by OCTA to quantitatively characterize vascular morphology in the macula of patients with syphilis. These measures revealed small but significant changes in retinal vessel diameter, length, and tortuosity as well as blood flow density among syphilis patients without ocular symptoms. Thus, these changes could be useful microvascular markers of early-stage syphilis. Indeed, these metrics can reveal subtle changes in retinal vascular circulation not easily detected during early disease[27-28]. For example, uncontrolled overperfusion and a decrease in autoregulatory capacity were found to contribute to the pathogenesis of diabetic retinopathy[29-31]. In ROC analysis (Table 3), regional VLD and VFD metrics (except inner VFD) demonstrated good to excellent diagnostic value for differentiating healthy controls eyes from the eyes of patients with syphilis. Of these, outer macular VLD demonstrated the best performance (Figure 4), suggesting that analysis of outer vessels may be more useful for detecting ocular syphilis. The vascular reactivity to eye stimulation frequently distinguishes healthy from disease eyes, and the severity of impaired vascular reactivity can be used to monitor disease progression or assess treatment[32-35]. Quantitative measurements of vascular morphology by OCTA may provide additional markers for syphilitic chorioretinopathy diagnosis and treatment evaluation.

Our study has several limitations. Due to the cross-sectional study design, we cannot conclude that these vascular changes are directly caused by syphilis or underlie syphilitic chorioretinopathy. In addition, the sample size was relatively small, which reduced statistical power, especially for the high- and low-titer subgroups. While our study demonstrates the potential diagnostic value of OCTA parameters, we did not compare these to traditional OCTA parameters such as choroidal vessels metrics. Furthermore, we scanned only a small 6 mm×6 mm region around the macula that did not include regions such as the optic radial peripapillary, where markers may have better diagnostic accuracy. Finally, we did not distinguish between superficial and deep blood vessels, which may show distinct changes during the progression of ocular syphilis Future studies should investigate the microvasculature of different retinal layers captured for clinical images. We also did not examine if these OCTA abnormalities reversed when syphilis titers returned to normal. Whether these changes are reversible or permanent has obvious implications for the utility of these markers in improving clinical outcome.

In conclusions, vascular abnormalities can be detected in the retinas of early-stage syphilis patients with normal vision by OCTA. Both VLD and VFD were increased in syphilitic eyes, particularly in the outer fovea, and outer VLD demonstrated good accuracy for distinguishing syphilitic from healthy controls eyes. Therefore, measuring retinal microvasculature abnormalities by OCTA may be a useful strategy for detecting early-stage asymptomatic syphilis and for monitoring progression and treatment responses.

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