

Original Research

# The Value of Optical Coherence Tomography Angiography in Pituitary Adenomas

Yang Tang<sup>1</sup>, Xiaofang Liang<sup>1</sup>, Jing Xu<sup>1</sup>, Kaiyue Wang<sup>1</sup>, Wang Jia<sup>2,\*</sup>

<sup>1</sup>Department of Ophthalmology, Beijing Tiantan Hospital, Capital Medical University, 100070 Beijing, China

<sup>2</sup>Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, 100070 Beijing, China

\*Correspondence: [jwtyy@126.com](mailto:jwtyy@126.com) (Wang Jia)

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## Abstract

**Objective:** This study aims to explore the value of retinal vessel density (VD) in diagnosing optic nerve injuries in patients with pituitary adenomas using optical coherence tomography angiography (OCTA). **Methods:** In this cross-sectional retrospective study, 100 patients with pituitary adenomas and 71 participants for normal controls, who visited the Beijing Tiantan Hospital from January 2019 to May 2021, were enrolled. The OCTA was used to measure retinal thickness and VD, and the correlation of these parameters with visual field (VF) factors was analyzed. Receiver operating characteristic curves were used to compare the value of the above parameters in diagnosing VF abnormalities in the patients with pituitary adenomas; the differences in retinal VD between 41 patients with pituitary adenomas who had normal retinal thicknesses and 41 patients in the normal control group with no statistical differences in gender and age were compared. **Results:** The radial peripapillary capillary (RPC) density, superficial retinal capillary plexus (SRCP) density, retinal nerve fiber layer thickness, and ganglion cell layer complex thickness correlated with VF parameters ( $p < 0.05$ ). The RPC density in the temporal quadrant had the highest capability in diagnosing VF abnormalities, with an area under the curve = 0.821,  $p < 0.001$ , with 72.3% sensitivity and 82.7% specificity. The mean RPC density and RPC density in the nasal and temporal quadrants in the 41 patients with pituitary adenomas who had normal retinal thicknesses were reduced compared with the normal control group ( $49.95\% \pm 1.86\%$  vs.  $51.30\% \pm 1.87\%$ ,  $p = 0.002$ ;  $49.09\% \pm 3.13\%$  vs.  $50.41\% \pm 3.90\%$ ,  $p = 0.034$ ;  $54.33\% \pm 3.14\%$  vs.  $55.89\% \pm 3.08\%$ ,  $p = 0.020$ ) and other parameters had no statistical differences compared with the normal control group. **Conclusions:** The density of the RPC and SRCP may also be sensitive and specific indicators of VF damage in patients with pituitary adenomas. Measuring retinal VD in patients with pituitary adenomas may be a supplement to help identify VF impairments. In addition, abnormal retinal vascular density may indicate VF impairment in patients who are unable to cooperate with VF examinations.

**Keywords:** pituitary adenoma; visual field; vessel density; radial peripapillary capillary density; optical coherence tomography angiography

## 1. Introduction

Pituitary adenomas are common tumors that represent 15% of intracranial tumors, with clinical manifestations that include abnormal pituitary hormone secretion and symptoms caused by compression from tumor growth on surrounding tissues. The latter presentation mainly causes optic chiasm compression, resulting in vision loss, visual field (VF) damage, and optic disc changes in patients. Normal pituitary tissue is anterior and inferior to the bilateral optic nerves and optic chiasm. Pituitary adenomas can gradually grow backward and upward, eventually compressing the optic chiasm, resulting in retinal ganglion cell axonal retrograde degeneration and VF defects in one or both eyes; the incidence of VF defects caused by pituitary adenomas ranges from 9% to 32% [1]. However, VF examinations cannot distinguish between dead or dysfunctional ganglion cells [2], which may affect doctors' determinations of whether pituitary adenomas have damaged the optic nerves.

With the clinical application of the optical coherence tomography (OCT) technique, ganglion cell complex

(GCC) thickness in patients with pituitary adenomas is recognized as an effective and sensitive means of diagnosing visual function. Previous studies using OCT have found that thinning of the GCC before VF changes can be a sensitive indicator in assessing optic nerve injuries, but GCC thickness may remain normal in the case of an acute optic nerve injury [3]. However, OCT and GCC parameters are reliable only for diagnosing slow-growing lesions; in the case of an acute injury, OCT parameters can still be within a normal range, even with a definitive clinical diagnosis [4].

Optical coherence tomography angiography (OCTA) is a non-invasive examination to quantitatively measure vessel density (VD) in the retinal macular and peripapillary areas and is extensively used for retinal and other optic nerve diseases, with high repeatability and stability [5–19]. Recent studies [2,20–26] found that radial peripapillary capillary (RPC) and superficial retinal capillary plexus (SRCP) densities were reduced in patients with pituitary adenomas compared with normal control groups, and retinal VD did not only correlate with VF changes but also reti-



nal thickness. Some scholars have proposed [27] that blood flow density changes occur earlier than fundus optic nerve changes and visual function.

This study aimed to explore the value of retinal VD in diagnosing optic nerve injuries in patients with pituitary adenomas through OCTA. Then, the retinal VD of the patients with pituitary adenomas with a normal retinal thickness and the control group who were gender- and age-matched were compared to determine whether the retinal VD were the sensitivity and specificity indicators similar to retinal nerve fiber layer (RNFL) and GCC thicknesses.

## 2. Materials and Methods

This study was a cross-sectional study approved by the institutional review board of Beijing Tiantan Hospital, Capital Medical University (KYSQ 2018-128-01), with data collection following the principles of the Declaration of Helsinki. Written consent was obtained from all participants before the study. Some of these participants were also included in another study [28] in the same department, but the data were not duplicated.

### 2.1 Subjects

Patients with pituitary adenomas with complete clinical data visited the Department of Neurosurgery and Department of Ophthalmology at Beijing Tiantan Hospital, Capital Medical University, from January 2019 to May 2021. Following the criteria, 100 patients and 71 participants for the normal control group were enrolled in this study. All patients received head magnetic resonance imaging (MRI), visual acuity, intraocular pressure, slit lamp, fundus, VF, and OCTA examinations. Inclusion criteria: patients initially diagnosed with intracranial space-occupying tumors confirmed by head MRIs, which were further confirmed as pituitary adenomas through postoperative pathological diagnosis; patients who had clear consciousness and could cooperate in the VF and OCTA examinations; patients with an intraocular pressure of  $<21$  mmHg, a diopter of  $-3.00$  to  $+3.00$  D (spherical equivalent), and astigmatism  $<3.0$  D; OCTA image quality score of more than 60. Exclusion criteria: patients with a history of brain surgery; a family history of glaucoma or a history of other eye diseases; diabetes or other systemic diseases that could affect the retina and optic nerve; the presence of papilledema. Only a single eye (the one with the worst VF defects) based on each patient's mean deviation (MD) was selected for the analysis. There were 41 patients with pituitary adenomas with a normal RNFL and GCC layer thicknesses selected for further analysis and comparison of retinal VD parameters in 41 eyes/participants in the normal control group with no differences in age or gender and diopter.

The inclusion criteria of the normal control group included normal visual acuity, an intraocular pressure  $\leq 21$  mmHg, and a normal optic disc. The exclusion criteria of

the normal control group participants included those suffering from any neurological disease, systemic vasculitis, glaucoma, a diopter greater than  $+3.0$  degrees (spherical equivalent) or less than  $-3.0$  degrees, astigmatism greater than  $3.0$  degrees, amblyopia, epiretinal membrane, age-related macular degeneration, diabetic retinopathy, retinal arterial/retinal vein obstruction, optic neuropathy, or previous retinal surgery affecting the inner retinal thickness. The right eye data of the normal control group with an OCTA image quality score of 60 or higher were selected for the study.

### 2.2 Measurement Methods

(1) An automatic VF examination was conducted using the Humphrey fully automatic perimeter and central 24-2 threshold detection program (version 1.4.1.5) (Carl Zeiss Meditec, Inc, Dublin, CA, USA). The results of the automatic VF examinations with clinical significance ensured that the false negative and false positive rates were  $<33\%$  and that the fixation loss was  $<20\%$ . A normal VF is defined as an MD value greater than or equal to  $-3$  dB within 95% of the age-matched normal value [25,26].

(2) The OCT and OCTA examinations were conducted using the Optovue system (version A2017, 1, 0, 155) (Optovue, Inc., Fremont, CA, USA) to analyze the thickness and VD in the macular and optic nerve papilla areas. The optic nerve head scan was centered on the optic papilla (diameter 3.45 mm) to assess RNFL thickness, and the GCC scan was centered on the macular fovea (diameter 3 mm, inner limiting membrane/inner plexiform layer [ILM/IPL]) to assess GCC thickness. They were divided into four subsectors: superior, inferior, nasal, and temporal sectors automatically. The RPC scan was centered on the optic disc, with a diameter of 4.5 mm and a scanning depth of ILM/NFL; the SRCP was centered on the macular fovea, with a diameter of 3 mm and a depth of  $10\ \mu\text{m}$  upward from ILM/NPL, while the deep retinal capillary plexus (DRCP) was centered on the macular fovea, with a diameter of 3 mm and a depth of  $10\ \mu\text{m}$  downward from  $10\ \mu\text{m}$ -outer plexiform layer (OPL). All OCT and OCTA examinations were performed one week prior to the tumor resection surgery, and patients remained quiet for half an hour before examinations. Retinal VD was defined as the percentage of the capillary area within the local area, and normal RNFL and GCC thicknesses were defined as within 95% of the age-matched normal value.

The visual acuity, intraocular pressure, VF, fundus, and OCTA of all patients and the normal control group were examined on the same day. All VFs and OCTAs were examined by a fixed examiner.

(3) Tumor morphology: Head MRI was performed one week before surgery. Based on the form of the pituitary adenoma compressing the optic chiasm at the T1 sagittal position of the head, patients were divided into those with undeformed ( $n = 43$ ) or deformed ( $n = 57$ ) optic chiasms. In

**Table 1. Retinal vessel density among optic chiasm undeformed, optic chiasm deformed and normal control groups.**

	Normal control (group 1)	Optic chiasm undeformed (group 2)	Optic chiasm deformed (group 3)	<i>p</i> -value (1 versus 2)	<i>p</i> -value (1 versus 3)	<i>p</i> -value (2 versus 3)
RPC, %						
Whole image	57.23 ± 2.64	56.61 ± 2.95	52.34 ± 5.49	0.216	0.000	0.000
Superior	53.14 ± 3.54	53.40 ± 3.70	48.65 ± 8.47	0.718	0.001	0.000
Inferior	55.22 ± 3.78	54.75 ± 4.24	49.94 ± 7.99	0.545	0.000	0.000
Nasal	49.54 ± 3.65	47.96 ± 4.35	41.61 ± 8.38	0.041	0.000	0.000
Temporal	55.38 ± 3.01	54.38 ± 3.69	48.07 ± 7.82	0.122	0.000	0.000
SRCP, %						
Whole image	51.64 ± 3.13	51.29 ± 3.93	48.28 ± 4.36	0.615	0.000	0.001
Superior	54.07 ± 5.22	54.74 ± 5.31	51.47 ± 5.99	0.528	0.014	0.009
Inferior	54.31 ± 4.21	54.06 ± 5.52	51.23 ± 5.30	0.792	0.001	0.016
Nasal	52.84 ± 4.79	52.86 ± 5.98	49.07 ± 5.87	0.990	0.000	0.003
Temporal	53.44 ± 4.17	54.10 ± 4.74	51.07 ± 5.30	0.459	0.006	0.006
DRCP, %						
Whole image	54.18 ± 6.33	54.04 ± 5.69	51.89 ± 7.13	0.910	0.063	0.129
Superior	57.38 ± 5.37	56.33 ± 5.77	56.76 ± 4.83	0.345	0.513	0.700
Inferior	54.18 ± 6.33	54.04 ± 5.69	51.89 ± 7.13	0.199	0.200	0.949
Nasal	54.18 ± 6.33	54.04 ± 5.69	51.89 ± 7.13	0.447	0.038	0.268
Temporal	54.18 ± 6.33	54.04 ± 5.69	51.89 ± 7.13	0.534	0.175	0.537

the undeformed group, the upper edge of the tumor touched the optic chiasm, but it was not deformed. In the deformed group, the superior margin of the tumor compressed and deformed the optic chiasm.

### 2.3 Statistical Analysis

Normally distributed data were expressed as mean ± standard deviation, non-normally distributed data were expressed as median ± interquartile range, and best corrected visual acuity (BCVA) was converted to a logarithmic scale. The Student's *t*-test was used for normally distributed data, and the Mann–Whitney U test was used for non-normally distributed data. Receiver operating characteristic (ROC) curves were depicted to determine the diagnostic performance of significant measurements to discriminate eyes with abnormal VFs from normal. The area under the ROC curve (AUC) values were recorded. When the Youden index (sensitivity + specificity – 1) was maximized, the optimal cutoff value and the corresponding sensitivity and specificity were also determined. Spearman's correlation analysis was used to study the correlation between MD and pattern standard deviation (PSD) and VF index (VFI), RNFL, GCC, RPC, SRCP, and DRCP. *p*-values < 0.05 were considered statistically significant. All statistical analyses were performed with the SPSS version 23.0 software (IBM Corp., Chicago, IL, USA).

## 3. Results

(1) Patient characteristics: Among the selected patients with pituitary adenomas, 100 eyes/patients met the inclusion criteria, which included 50 eyes/males and 50 eyes/females; 47 eyes (47.00%) had a normal VF, 66 eyes (66.00%) had a normal RNFL, and 43 eyes (43.00%) had a

normal GCC. The patients were between 12 and 76 years old, with an average age of 48.33 ± 12.79. The selected normal control group included 24 eyes/males and 47 eyes/females between 25 to 76 years old, with an average age of 45.10 ± 12.02. Among the 41 eyes/patients with pituitary adenomas with a normal RNFL and GCC, there were 21 eyes/males and 20 eyes/females. The patients were between 19 and 76 years old, with an average age of 48.98 ± 12.54. Among the 41 eyes/individuals in the normal control group, there were 21 eyes/males and 20 eyes/females. Participants were between 20 and 69 years old, with an average age of 48.29 ± 10.51.

(2) The retinal VD among the undeformed and deformed optic chiasms and normal control groups: We found that only the nasal segment of the RPC was different between the normal control and undeformed optic chiasm groups. The VD of the RPC, SRCP, and the nasal segment of the DRCP was different between the normal control and deformed optic chiasm groups. There were differences between the undeformed and deformed optic chiasm groups in the VD of RPC and SRCP. The results are presented in Table 1.

**Table 2. Correlation of retinal thickness parameters, retinal vessel density parameters and visual field parameters.**

	MD	<i>p</i> value	PSD	<i>p</i> value	VFI	<i>p</i> value
RNFL	0.469	0.000	–0.467	0.000	0.483	0.000
GCC	0.508	0.000	–0.455	0.000	0.474	0.000
RPC	0.474	0.000	–0.484	0.000	0.468	0.000
SRCP	0.314	0.001	–0.243	0.015	0.273	0.006
DRCP	0.132	0.190	–0.064	0.524	0.125	0.214

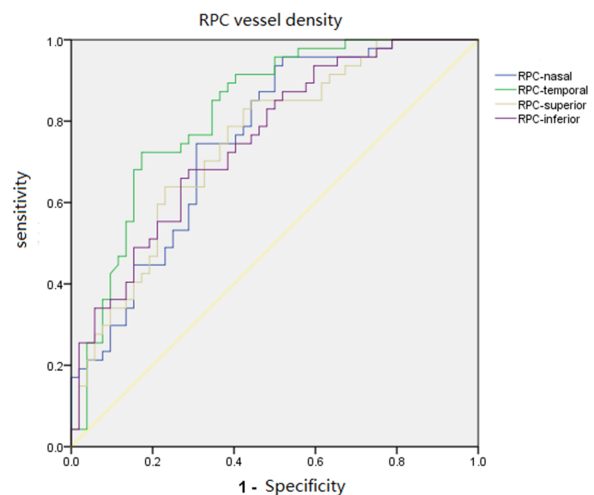
**Table 3. ROC Curves of each parameter.**

	AUC	<i>p</i> value	95% confidence interval	Cut off	Sensitivity	Specificity
RNFL thickness ( $\mu\text{m}$ )						
Average	0.77	0.000	(0.68, 0.87)	100.5	74.5%	73.6%
Superior	0.78	0.000	(0.69, 0.88)	128.5	74.5%	81.1%
Inferior	0.72	0.000	(0.62, 0.82)	117.5	85.1%	52.8%
Nasal	0.68	0.002	(0.57, 0.79)	61.65	95.7%	37.7%
Temporal	0.73	0.000	(0.64, 0.83)	68.6	91.5%	49.1%
GCC thickness ( $\mu\text{m}$ )						
Average	0.799	0.000	(0.71, 0.89)	94.5	89.4%	60.4%
Superior	0.795	0.000	(0.71, 0.88)	103.45	80.9%	67.3%
Inferior	0.804	0.000	(0.72, 0.89)	103.75	83.0%	67.2%
Nasal	0.808	0.000	(0.72, 0.89)	97.55	91.5%	71.2%
Temporal	0.775	0.000	(0.69, 0.87)	94.60	85.1%	63.5%
VD of RPC (%)						
whole image	0.805	0.000	(0.72, 0.89)	49.75	83.0%	71.2%
Superior	0.747	0.000	(0.65, 0.84)	51.48	85.1%	55.8%
Inferior	0.752	0.000	(0.66, 0.85)	54.78	68.1%	71.2%
Nasal	0.753	0.000	(0.66, 0.85)	43.83	95.7%	48.1%
Temporal	0.821	0.000	(0.74, 0.90)	54.84	72.3%	82.7%
VD of SRCP (%)						
whole image	0.668	0.004	(0.56, 0.78)	50.95	66.0%	69.2%
Superior	0.658	0.007	(0.54, 0.77)	57.05	46.8%	90.4%
Inferior	0.617	0.045	(0.51, 0.73)	55.80	38.3%	84.6%
Nasal	0.687	0.001	(0.58, 0.80)	53.35	63.8%	76.9%
Temporal	0.655	0.008	(0.54, 0.77)	53.85	63.8%	71.2%
VD of DRCP (%)						
whole image	0.556	0.337	(0.44, 0.67)	-	-	-
Superior	0.514	0.814	(0.40, 0.63)	-	-	-
Inferior	0.519	0.739	(0.40, 0.64)	-	-	-
Nasal	0.591	0.117	(0.48, 0.70)	-	-	-
Temporal	0.563	0.281	(0.45, 0.68)	-	-	-

(3) The correlation between VD parameters, VF parameters, RNFL and GCC thickness in patients with pituitary adenomas was analyzed. The VD of the RPC and SRCP was positively correlated with MD and VFI and negatively correlated with PSD. The VD of DRCP had no correlation with VF parameters. The results are shown in Table 2.

(4) Each parameter's ROC curve was used to diagnose whether the VFs were abnormal. According to the AUC of the abnormal VF diagnosed with each parameter, the highest diagnostic ability was RPC temporal quadrant vessels with an AUC = 0.821 and a *p*-value < 0.001. The second highest was the nasal GCC thickness, with an AUC = 0.808 and a *p*-value < 0.001. The VD of the DRCP had no diagnostic value. The cut off value of VD in the RPC temporal segment was 54.84%, with 72.3% sensitivity and 82.7% specificity. The results are shown in Table 3, Figs. 1,2.

(5) After comparing the differences of various parameters between 41 eyes/patients with pituitary adenomas who had a normal retinal thickness and 41 eyes/patients in the normal control group with no statistical differences in age and gender, the RNFL and GCC thicknesses and VD of the SRCP and DRCP had no statistical differences.

**Fig. 1. ROC curves for each quadrant of the VD of RPC.**

In the RPC VD in the pituitary adenoma group, the mean RPC VD (whole image capillary) and the RPC VD in the nasal and temporal quadrants were statistically significantly lower than the normal control group, as shown in Table 4.

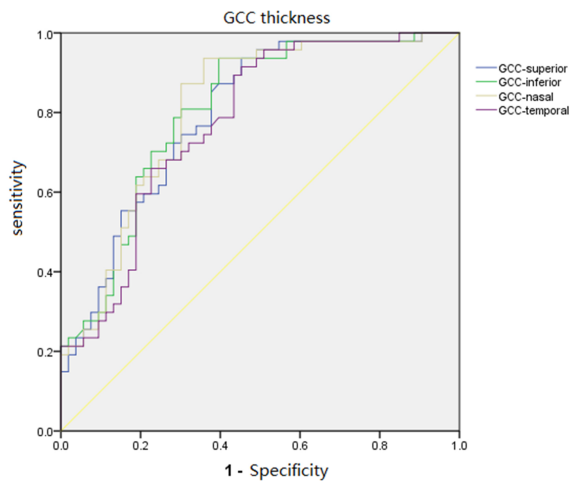


Fig. 2. ROC curves for each quadrant of GCC thickness.

Table 4. Comparison of retinal vessel density differences in pituitary adenoma patients with normal retinal thickness and normal control group.

	Case Group	Control Group	<i>p</i> value
Age (year)	48.98 ± 12.54	48.29 ± 10.51	0.79
Gender (M/F)	21/20	21/20	1.00
RNFL (average) (μm)	104.79 ± 7.80	105.39 ± 7.86	0.729
GCC (average) (μm)	98.69 ± 5.18	98.29 ± 6.30	0.753
VD of RPC (%)			
Whole image	49.95 ± 1.86	51.30 ± 1.87	0.002
Superior	53.00 ± 3.08	53.92 ± 3.20	0.188
Inferior	55.09 ± 3.42	56.11 ± 3.73	0.199
Nasal	49.09 ± 3.13	50.41 ± 3.90	0.034
Temporal	54.33 ± 3.14	55.89 ± 3.08	0.020
VD of SRCP (%)			
Whole image	51.48 ± 2.69	52.09 ± 2.59	0.299
Superior	55.20 ± 3.94	54.89 ± 3.27	0.704
Inferior	54.57 ± 3.27	54.48 ± 3.10	0.898
Nasal	53.01 ± 4.55	53.40 ± 2.85	0.900
Temporal	54.47 ± 3.06	53.59 ± 3.14	0.203
VD of DRCP (%)			
Whole image	53.16 ± 6.17	55.18 ± 5.19	0.131
Superior	56.01 ± 5.95	58.13 ± 4.31	0.131
Inferior	55.39 ± 5.39	57.40 ± 4.23	0.128
Nasal	57.31 ± 5.47	59.32 ± 3.40	0.156
Temporal	57.64 ± 3.96	58.78 ± 3.16	0.156

## 4. Discussion

This study compared the diagnostic value of OCTA and OCT parameters to determine whether retinal VD was sensitivity and specificity indicators identified VF defects in patients with pituitary adenoma. We found that the retinal VD parameters of patients with optic chiasmatic compression caused by intracranial tumors were lower than those of healthy people, and there was a correlation between VF, retinal VD, and retinal thickness parameters. Retinal VD parameters with the same as GCC and RNFL thickness were

sensitivity and specificity indicators that could be used to identify visual impairments.

Previous research has suggested that the growth of pituitary tumors results in optic chiasm compression, leading to reduced axoplasmic transportation and blood supply [29,30]. The resulting nerve fiber atrophy and apoptosis of ganglion cells may lead to reduced oxygen demand in the retina, thus leading to blood vessel atrophy. Our study found that the patients' retinal VD decreased with increased compression on the optic chiasm by the pituitary adenoma. First, the nasal segment of the RPC showed a significant statistical decrease in the undeformed optic chiasm group compared with the healthy control group. Then, the VD of the RPC and SRCP, and the nasal segment of the DRCP decreased in the deformed optic chiasm group compared with the healthy control group. We also found that the VD of the RPC and SRCP were different between the undeformed and deformed optic chiasm groups.

After studying 36 patients with brain tumors and optic chiasm compression, Lee *et al.* [21] found that the density of capillaries in the optic disc and around the macular fovea was significantly lower than in healthy people, and retinal blood VD was correlated with VF and retinal thickness. Wang *et al.* [24] found that the RPC vascular density in the nasal and temporal quadrants was correlated to the RNFL thickness in the corresponding quadrants in 31 patients with brain tumors with optic chiasm compression. After studying 12 patients with brain tumors with optic chiasm compression, Ghezala *et al.* [29] found that their RPC was significantly lower than healthy people. Our results support these previous results. We also found that similar to the band atrophy of the nerve fibers in the pituitary patients, in patients with normal RNFL and GCC thickness, their nasal and temporal segments of RPC VD were decreased compared with the healthy group.

Our study used the ROC curve of the retinal thickness and VD parameters to diagnose VF impairments in patients with pituitary adenomas. The temporal segment of RPC vessel density's AUC was slightly higher than the GCC and RNFL thickness. Its cut off point was 54.84%, with 72.3% sensitivity and 82.7% specificity, while the nasal segment of the GCC thickness had 91.5% sensitivity and 71.2% specificity, proving that RPC vascular density may also be a specific and sensitive indicator used for diagnosing VF impairments caused by pituitary adenomas. To date, we have not seen a report similar to our study method.

In our further comparison of retinal VD in patients with pituitary adenomas who had a normal retinal thickness and the normal control group, we found that even though the ganglion cell and nerve fiber layers were within the normal range, the VD in the nasal and temporal quadrants of the patients' optic discs were significantly lower than in the normal control group, which has never been reported in previous studies. The nasal and temporal segments of RPC VD may decrease in the early stage of pituitary adenoma, even



before the layers of nerve fibers change. Further longitudinal studies are needed to confirm this.

Our study had the following limitations: First, this was a single-center study, including only Chinese people, so our results may not apply to other ethnic groups. Second, this was a retrospective study, which only quantitatively measured the changes in retinal blood flow parameters in patients with pituitary adenomas. The causal relationship between the retinal blood flow differences in patients with different degrees of optic nerve injuries and the prognosis of visual function recovery was not explored, so further research is required. Third, we could not rule out the possibility of undetected micro-swelling in the optic disc affecting the VD assessment, which may cause some measurement errors.

## 5. Conclusions

In patients with pituitary adenomas, retinal VD decreased with increased compression on the optic chiasm by the pituitary adenoma. The capillary density in the optic disc is lower than in a normal eye; the retinal VD change correlates with the VF change. Therefore, similar to the GCC and RNFL thicknesses, the RPC VD can be used as a sensitive and specific indicator for assessing optic nerve injuries. Based on the VF and OCT parameters, measuring retinal VD combined with OCTA can help clinicians detect visual impairments in patients earlier. In addition, abnormal retinal vascular density may indicate visual function impairment in patients who cannot cooperate with a VF examination.

## Author Contributions

Conception and design of the research: YT, WJ. Acquisition of data: XL, JX, KW. Analysis and interpretation of the data: YT. Statistical analysis: YT. Obtaining financing: WJ. Writing of the manuscript: YT. Critical revision of the manuscript for intellectual content: YT, XL, JX, KW. All authors read and approved the final draft.

## Ethics Approval and Consent to Participate

This study was conducted with approval from the Ethics Committee of Beijing Tiantan Hospital (KYSQ 2018-128-01). This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

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## Conflict of Interest

The authors declare no conflict of interest.

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