Effect of acute primary angle closure glaucoma on the blood flow and macular structure: A prospective cohort study

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Research article

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Abstract

Background: Mounting evidence shows that vascular factors play an important role in the pathogenesis of glaucoma, while optical coherence tomography angiography (OCTA) can provide a better view for microvascular changes in glaucoma. Objective: This study aimed to assess the effect of the severity of acute primary angle closure glaucoma (APACG) on macular microcirculation and the diagnostic value of blood flow and macular structure for APACG using OCTA. Methods: Patients with APACG hospitalized at the Tianjin Eye Hospital from January to April 2019 were enrolled in this prospective cohort study. They were assigned to mean deviation (MD) ≤6 (35 eyes), 6 < MD ≤ 12 (41 eyes), MD >12 (33 eyes), primary angle closure suspect (PACS) (40 eyes), and age-matched age-related cataract (ARC) groups (33 eyes). OCTA was used to measure the vessel density (VD) and foveal avascular zone (FAZ) in different macular superficial areas. OCT was used to measure the retinal thickness (RT) and ganglion cell complex thickness (GCC). One-way analysis of variance was used to compare the differences in VD and FAZ for different degrees of APACG. Areas under the receiver operating characteristic curves (AUCs) were used to assess the diagnostic values of VD, RT, and GCC for APACG. Results: On comparing the ARC, PACS, and MD ≤6 groups with 6 < MD ≤ 12 and MD > 12 groups, differences in all parameters were found to be statistically significant. This indicated that VD gradually decreased and FAZ enlarged with the exacerbation of APACG. For the 6 < MD ≤ 12 group versus PACS group, the diagnostic value of VD was high (AUCs: 0.902–0.942), and that of RT was moderate (AUCs: 0.805–0.842). For the MD >12 group versus PACS group, the diagnostic values of VD (AUCs: 0.900–0.958) and RT (AUCs: 0.828-0.887) increased. Conclusions: With the exacerbation of APACG, the damage of VD in the macula was greater. VD had higher diagnostic accuracy, providing a new view for the diagnosis of APACG.

Introduction

Glaucoma is defined as a multifactorial optic neuropathy. Increasing evidence shows that vascular factors play an important role in the pathogenesis of this disease [1, 2]. Numerous studies have shown a reduction in blood perfusion of eyeballs among patients with primary open-angle glaucoma (POAG), normal tension glaucoma, and ocular hypertension [3-5]. However, the study on the blood flow of glaucoma remains a challenge due to the limitations of imaging methods [6, 7]. As a noninvasive imaging technique, optical coherence tomography angiography (OCTA) is a reproducible quantitative assessment method for the retinal and choroidal vascular systems [8], which are divided into superficial, deep, and outer retinas, and choroidal vascular layer. The study found that the vessel density (VD) measured using OCTA in the optic nerve head, peripapillary, and macular regions of patients with POAG significantly decreased. Also, the diagnostic value of peripapillary and macular VD was relatively high in untreated POAG [9, 10].

A large-sample epidemiological survey revealed that the incidence of primary angle closure glaucoma (PACG) was higher in Asians than in other areas, with more than 80% of those with PACG in Asia [11]. The

intraocular pressure (IOP) during the acute attack of acute primary angle closure glaucoma (APACG) was much higher than that in POAG. It also had a greater impact on the retinal microcirculation. Therefore, the APACG-affected eyes with a history of acute attack were examined, providing a unique opportunity to study the association between VD and glaucoma. The structural damage in glaucoma often precedes detectable visual field defects [12,13]. However, a few studies were available regarding the relation between VD damage and structural damage and their changes during the disease progression.

This study focused on the superficial capillary network (SCN) in the macula, because retina ganglion cells (RGCs) are important damage markers of glaucoma mainly present in the superficial retina [14], and approximately half of RGCs are located in 4.5 mm of the center fovea. Also, SCN provides the main nutrients for RGCs [15]. At the same time, OCTA also provides a new indicator, foveal avascular zone (FAZ), which is a nearly circular noncapillary region located in the central fovea of the macula and surrounded by interconnected capillary beds [16]. Histologically, the FAZ boundary is formed by a single layer of capillary arcade located inside the RGC layer. The main purpose of this study was to investigate the characteristics of changes in blood perfusion in the superficial macula for different degrees of APACG, and to assess the diagnostic value of blood perfusion and macular structure for APACG.

Participants And Methods

Participants

Patients with APACG hospitalized at the Tianjin Eye Hospital from January to April 2019 were consecutively enrolled. The study was approved by the Ethics Committee of Tianjin Eye Hospital. All the participants provided written informed consent (registration number of Chinese Clinical Trial Registry: ChiCTR1900021086; review approval of the Ethics Committee of Tianjin Eye Hospital: TJYYLL-2018-05). The inclusion criteria for APACG were as follows: (1) Patients with a previous history of acute primary angle closure (APAC), whose IOP was controlled within the normal range for two months after drug or laser treatment. APAC was defined based on the following criteria: (i) at least two symptoms from the following: eyeball pain; nausea, vomiting, or both; history of intermittent visual blurring; and (ii) IOP exceeding 21 mm Hg (Goldmann applanation tonometry was used for measurement) with at least three of the following signs: conjunctival congestion, corneal edema, moderate pupil dilation, shallow anterior chamber; and (iii) gonioscopy revealing angle closure [17,18]. (2) Patients with glaucoma-related optic nerve or visual field defects. The inclusion criteria for PACS were as follows(Applied to all subjects): (1) static angle closure >180°; and (2) IOP <21 mm Hg without glaucomatous optic neuropathy [19]. The exclusion criteria were as follows: patients with high myopia or high hypermetropia (mean diopter ≤ ±6D); patients with a long-term history of retinopathy, non-glaucomatous optic neuropathy, history of uveitis, ocular trauma, and ocular diseases seriously affecting the turbidity of refracting media of the eyeball; patients with a previous history of ocular surgery; and patients with poor drug-controlled hypertension and diabetes.

The mean deviation (MD) value was measured using standard automated perimetry (Humphrey Field Analyzer, 30-2; Carl Zeiss Meditec, CA, USA). According to the grading method of Hodapp–Parrish–Anderson (H-P-A) visual field damage, all patients with APACG were assigned to three groups: mild (MD ≤6dB, 35 eyes), moderate (6dB < MD ≤ 12dB, 41 eyes), and severe (MD>12dB, 33 eyes) groups [20], age-matched PACS group (40 eyes), and age-related cataract (ARC) group (33 eyes). Given that the average ages of the APACG and PACS patients included in this study were older, they all suffered from cataracts, which is one of the main factors affecting the signal strength index (SSI) of OCTA, patients with ARC of the corresponding age were used as the normal control group in the study.

All participants underwent complete ophthalmologic examinations, including best-corrected visual acuity, slit lamp, gonioscopy, and ophthalmoscopy, as well as IOP at OCTA. Lenstar LS900 (software version V4.2.1; Haag-Streit, Switzerland) was used to measure the axial length (AL), anterior chamber depth (ACD), and lens thickness (LT).

OCTA

After admission, all participants immediately underwent an OCTA examination using RTVue XR (software version 2016.1.0.26; Optovue, USA) instruments by two specially trained physicians, measuring VD of superficial retina (including inner limiting membrane, nerve fiber layer, ganglion cell layer, and inner plexiform layer) within 3 × 3 mm^2 centered on the macula. The measurement area was divided into macular fovea (F) and parafovea (Pf), which was further divided into superior hemiretina (SH), inferior hemiretina (IH), temporal (T), superior (S), nasal (N), and inferior (I), while automatically measuring the FAZ area. A light source with a wavelength of 840 nm was used for the OCTA examination, and the scanning speed was 70 kHz. Scanning was performed once in the horizontal and vertical directions. Patients were told to stare at the fixation eye point, without blinking. The system with eyeball tracking and motion correction function was initiated, and the final image quality was checked by the operator. The vessel connection was intact with no motion artifact, and SSI needed to be greater than 60; otherwise, it was not used. The retinal thickness (RT) in the corresponding region (i.e., the thickness of the inner limiting membrane to the retinal pigment epithelium layer) was obtained with the same protocol at the same time of VD measurement. The thickness of the ganglion cell complex (GCC) (i.e., the thickness of nerve fiber layer, ganglion cell layer, and inner plexiform layer) was measured using the GCC protocol of the system, and the average value of each subarea was automatically calculated (Fig. 1).

Statistical analyses

Using SPSS18.0 statistical software (SPSS Inc., Chicago, IL), the measurement data were confirmed to be in normal distribution by W test, calculated as mean and standard deviation, and the counting data, such as the gender ratio, were not in normal distribution, represented by the composition ratio. One-way analysis of variance was used to compare the differences in VD and FAZ in each macular area among the five groups. Pearson correlation analysis was used to compare the relation between VD and RT in the macula. Medcalc v18.2.1 (MedCalc Statistical Software, Marakierke, Belgium) was used for areas under the receiver operating characteristic curve (AUC) analysis to assess the diagnostic values of VD, RT, and GCC in the macula for APACG. *P* value <0.05 was considered statistically significant.

Results

The chi-square test was used for the constituent ratio of men and women in the five groups, and the difference was not statistically significant ($P > 0.05$). Age (*A*), IOP at OCTA, AL, ACD, and LT were analyzed by one-way analysis of variance (ANOVA). The difference in *A* ($P > 0.05$) SSI $P > 0.05$ was not statistically significant among the five groups. The differences in IOP ($P < 0.05$), AL ($P < 0.05$), ACD ($P < 0.05$), and LT ($P < 0.05$) were statistically significant among the five groups. Furthermore, Bonferroni *t* test was used for pairwise comparison, and the differences in IOP, AL, ACD, and LT among the mild, moderate, and severe groups were not statistically significant ($P > 0.05$) (Table 1).

Effect of different degrees of APACG on blood perfusion and FAZ in the macula

Using one-way ANOVA, differences in all the parameters were found to be statistically significant among the five groups ($P < 0.05$). The Bonferroni *t* test was further used for pairwise comparison. In the ARC, PACS, and mild groups, except for F VD and FAZ, differences in other parameters were not significantly different among the three groups ($P > 0.05$). Compared with the ARC and PACS groups, the F VD in the mild group significantly decreased and FAZ significantly increased, and the difference was statistically significant (P 0.05). Comparing the ARC, PACS, and mild groups with the moderate and severe groups, differences in all parameters were statistically significant ($P < 0.05$), indicating that with the exacerbation of APACG, VD gradually decreased and FAZ gradually enlarged. In the comparison between the moderate and severe groups, except for IH VD, T VD, and I VD, differences in other parameters were statistically significant ($P <0.05$), indicating that with the exacerbation of APACG, VD decreased and FAZ increased (Table 2).

Diagnostic value of AUCs in assessing blood perfusion and structural changes in the macula for APACG

The MedCalc software was used to compare the diagnostic value of VD and RT for APACG. For the mild versus PACS group, the diagnostic value of VD (AUC: 0.704–0.760) and RT (AUC: 0.613–0.672) in the macula was low, and the difference in AUCs between the two groups was not statistically significant ($P > 0.05$). For the moderate versus PACS groups, the diagnostic value of VD (AUC: 0.902–0.942) in the macular area was high, and that of RT (AUC: 0.805–0.842) was moderate. AUCs of SH VD, IH VD, T VD, S VD, N VD, and I VD were compared with those of RT in the corresponding area; the diagnostic value was high, and the difference was statistically significant ($P < 0.05$). For the severe versus the PACS groups, the diagnostic values of VD (AUC: 0.900–0.958) and RT (AUC: 0.828–0.887) in the macular area improved, and the difference between the two reduced. AUCs of Pf VD, SH VD, IH VD, S VD, and N VD were higher in the diagnostic value than those of RT in the corresponding region, and the difference was statistically significant ($P < 0.05$). With the exacerbation of APACG, the diagnostic values of VD and RT gradually improved. The diagnostic sensitivity of VD in the macular area to moderate and severe APACG was higher than that of the structural parameter RT (Table 3).

The MedCalc software was used to compare the diagnostic values of VD and GCC for APACG. For the mild versus PACS groups, the AUC value of SH VD and IH VD was larger than that of GCC in the corresponding area, but the diagnostic values of VD and RT were low, and the difference was not statistically significant ($P > 0.05$). For the moderate versus PACS and severe versus PACS groups, the diagnostic values of VD and RT improved, and the AUC values of SH VD and IH VD were still higher than those of GCC in the corresponding area, and the difference was not statistically significant ($P > 0.05$) (Table 4) (Figure 2).

Discussion

In recent years, increasing attention has been paid to the factors of abnormal intraocular blood flow or vascular regulation ability in the development and progression of various types of glaucoma. With the widespread use of OCTA technology in clinic, the further understanding was obtained regarding the retinal microcirculation state in these patients with normal IOP after APAC. In the present study, the OCTA technology was used to accurately segment the vascular structure of superficial retina in the macula, quantify microcirculation function, and assess its diagnostic ability to APACG compared with traditional retinal structural parameters.

In the present study, no statistical difference in IOP was found among the five groups on OCTA examination, indicating that IOP, the main influencing factor, was excluded. The VD and FAZ still showed significant changes with the exacerbation of APACG. In the macular area, VD gradually decreased and FAZ gradually increased. The differences in F VD and FAZ were statistically significant between the mild

group and the ARC and PACS groups, suggesting that the two parameters were sensitive indicators of the retinal microcirculation state in patients with APACG having a previous history of acute attack with mild visual field damage. At the same time, this study found that compared with RT, the diagnostic value of VD was higher. For the moderate versus PACS groups, the difference in AUCs between them in six areas was statistically significant. For the severe versus PACS groups, the difference in AUCs between them in the five areas was statistically significant, but the difference reduced. The difference in AUCs between VD and GCC in the macular area was not statistically significant in the three groups of APACG, indicating that compared with traditional structural parameter RT, VD had a higher diagnostic value for APACG. Also, compared with the classic indicator GCC for glaucoma damage, the diagnostic value of VD was higher.

This study focused on the macular area. Similar studies found that the VD around the optic nerve head after APAC was still low in the normal IOP [21]. Previously, due to limitations of examination methods, APACG was usually characterized by anterior segment ischemia, and 52.5% of patients with APACG had changes in iris ischemia [22]. It was believed that the iris stroma had the least anti-damage ability against IOP elevation during APAC. With the application of OCTA, the damage caused by transient IOP elevation to the retina was also significant. The decrease in VD in the retina and macular area led to chronic damage, such as ischemia and hypoxia. Of note, the VD obtained by OCTA was used to estimate the blood flow velocity. Instead, it should be understood as the two conditions of capillary detachment or slow blood flow velocity in the vessel. Therefore, in addition to the application of IOP-lowering drugs, those used for improving the retinal microcirculation should be given.

Related studies on POAG found that the retinal capillary density in a normal population was different from that in patients with moderate POAG. No difference was found in the comparison between patients with moderate and severe POAG[9], which was basically consistent with the change trend of VD in the macular area for different degrees of APACG in this study. Comparing the moderate and severe APACG groups with the ARC and PACS groups, the differences in all parameters were statistically significant. In the comparison between the moderate and severe groups, the difference in VD in the three areas was not statistically significant. This might be because early glaucoma was characterized by progressive microvascular changes, and as the disease progressed to a severe stage, the apoptosis of RGCs was predominant, and the microvascular changes were few. Therefore, the OCTA parameters had a better ability for the early diagnosis of the disease than the late diagnosis [23].

The parameter FAZ is progressively enlarged under conditions of advancing age, diabetic retinopathy, retinal vein obstruction, and so forth [24-26]. This is because the macular capillary loss, as a marked characteristic of ischemic and vascular occlusive retinal disease, can lead to significant changes in FAZ, which can be assessed according to the area, perimeter, and so forth, of the FAZ [27-29]. At present, little is known about the association between FAZ and glaucoma. Studies have shown that patients with glaucoma having central visual field defects have larger and irregularly shaped FAZ compared with those with normal or peripheral visual field defects, but there was no significant difference in FAZ area between

peripheral and central visual field defects [30, 31]. At the same time, patients with NTG have a larger FAZ area and decreased peripheral vascular density. The OCTA technology has been used to further demonstrate that NTG is an ischemic disease characterized by vascular dysfunction [32]. In the present study, FAZ significantly changed in the early stage of APACG, indicating that it was a sensitive indicator of APACG-induced changes in retinal circulation.

Prior studies have shown that VD measured by OCTA can be used as an indicator to identify healthy eyes and glaucoma, and also distinguish between healthy people and those with suspicious glaucoma [10, 33]. Henry et al. studied the AUCs of glaucoma and healthy eyes. They showed that the retinal nerve fiber layer (RNFL; 0.95) and GCC (0.95) had the highest values, followed by the macular VD (0.94) and peripapillary VD (0.93) [34], indicating that the diagnostic value of VD in the macular area was similar to that of other known indicators, such as RNFL and GCC, which was consistent with the results of this study. The advantages of using the macular VD in the diagnosis and assessment of APACG were as follows. First, the damage of early glaucoma might occur more clearly on the omentum away from the optic nerve head [35], and therefore early changes in peripapillary VD or RNFL may not be detected. Second, early retinal edema after an acute attack caused no difference in GCC and RNFL thickness between APACG and PACS eyes. Third, the myopic optic disks, especially high myopia, were usually characterized by a slanted appearance and atrophy of the temporal optic nerve head, and the perfusion of retina of the optic nerve head was less than that of the emmetropic eye, impeding the differential diagnosis of APACG and normal eyes [36, 37].

This study had some limitations. The study showed that the scan pattern of 6 ´ 6 mm^2 region in the macular area was more accurate than that of 3 ´ 3 mm^2 region in terms of diagnostic accuracy. The smaller scan range might miss part of the GCC area [9]. However, most of the patients with APACG having a history of acute attack were treated with 1% pilocarpine eye drops. Also, pupils of the affected eyes were small, and the scan pattern of 3 ´ 3 mm^2 region was more reasonable. The IOP-lowering eye drops have a potential confusing effect on eyeball hemodynamics and retinal vascular autoregulation. For example, carbonic anhydrase inhibitor and prostaglandin analogues could result in vessel dilatation and increased blood flow [38, 39], but the effect took 1–4 weeks to be removed after discontinuing IOP-lowering eye drops. Therefore, it was not discontinued on examination. No measurement of the blood pressure of participants or recording of their antihypertensive medications was performed. However, a previous study also suggested no correlation between blood pressure readings and VD of the optic nerve head on OCTA [33]. Several studies found that the decrease in VD of the optic nerve head and the corresponding macular area could be detected in patients with glaucoma having unilateral visual field defects [40]. VD (59.0% and 51.1%) in the hemi-optic nerve head and macular areas for the intact visual field was higher than that for the affected visual field (54.7% and 48.3%, respectively), but lower than that of healthy eyes (62.4% and

53.8%). These findings suggested that vascular changes might occur before detectable visual field defects. Therefore, the correlation between VD and visual fields in patients with APACG needs further investigation.

In conclusion, for patients with APACG and IOP returning to normal after treatment, the VD and FAZ in the macular superficial layer were still lower than normal, and the damage of VD and FAZ aggravated with the exacerbation of APACG. The VD in the macular superficial layer showed higher diagnostic ability than RT, which was equivalent to that of GCC. These findings provided new insights into the pathophysiological study of patients with APACG having a history of acute attack, and also new indicators for the clinical diagnosis of APACG.

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Authors' contributions

Rui Wang: data collection, analysis and interpretation, drafting the article. Jin Yang: data collection, analysis and interpretation. Xuan Li: design of the work, critical revision and final approval of the article to be published.

Ethics approval and consent to participate

This study followed the tenets of the Declaration of Helsinki and was approved by the ethics committee of Tianjin Eye Hospital(TJYYLL-2018-05). Registration number of Chinese Clinical Trial Registry was ChiCTR1900021086. Informed written consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Due to technical limitations, tables 1 - 4 are only available as a download in the supplemental files section.

Figures

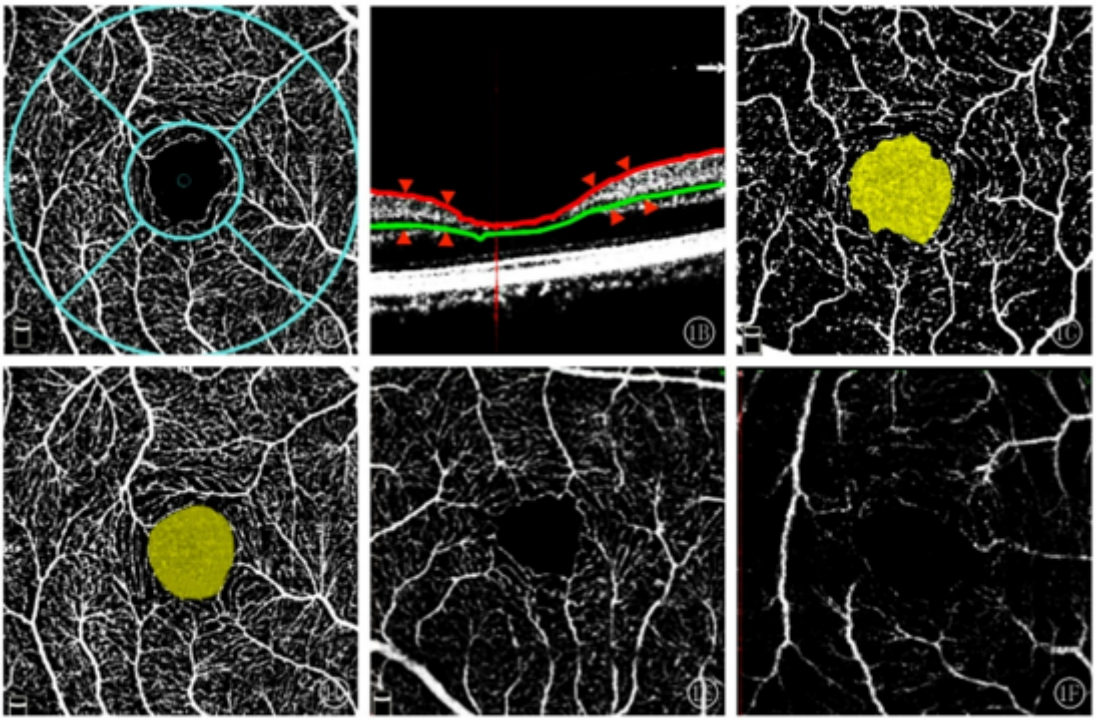

Figure 1. Image captured by OCTA. (A) The zonal image of the VD in the macula was divided into the macular central fovea and four paracentral foveae (temporal, superior, nasal, and inferior). The paracentral foveae were located in two concentric circles of 1 mm and 2.5 mm diameter. (B) The measurement range of VD, including the thickness of the inner limiting membrane, nerve fiber layer, ganglion cell layer, and inner plexiform layer. (C) In the APACG group, the capillaries around FAZ were sparse and anfractuous in trend, and the arch ring was enlarged with irregular morphology. (D) In the normal control group, the capillaries around FAZ were arachnoid, and the arch ring was complete and regular in morphology. (E) At the image capture, the image was obviously shifted due to factors, such as blinking, and was not used. (F) The scanning signal intensity was less than 60. The image had a poor effect, and therefore it was not used.

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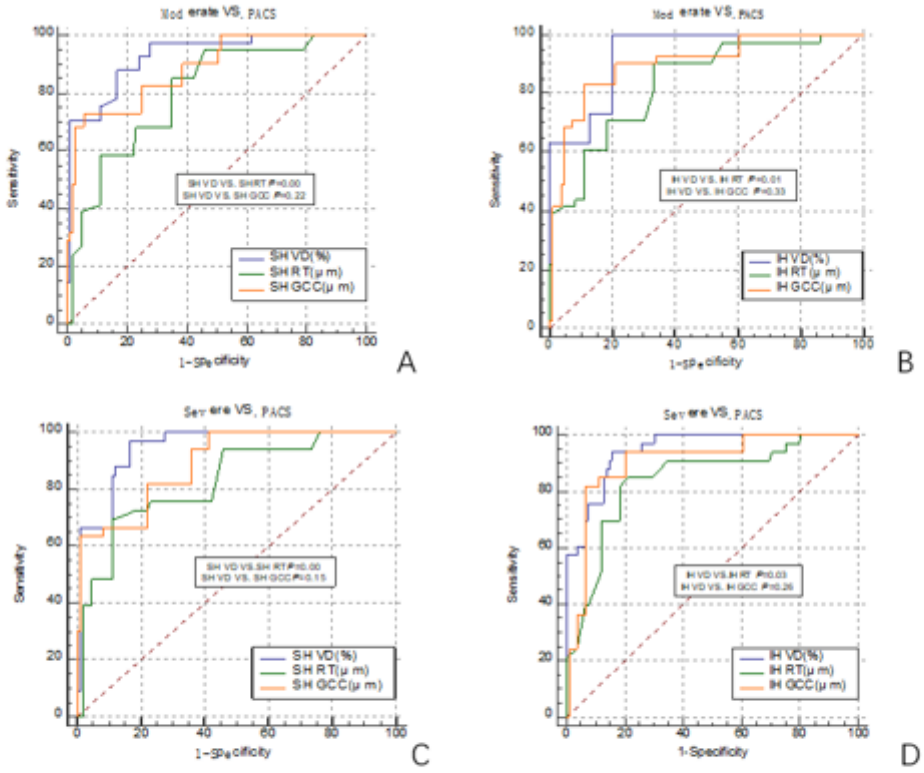

Figure 2. Receiver operating characteristic (ROC) curve. In the moderate versus PACS groups, (A) comparison of ROC curves between SH VD and RT and GCC; (B) comparison of ROC curves between IH VD and RT and GCC. In the severe versus PACS groups, (C) comparison of ROC curves between SH VD and RT and GCC. (D) comparison of ROC curves between IH VD and RT and GCC.

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Receiver operating characteristic (ROC) curve. In the moderate versus PACS groups, (A) comparison of ROC curves between SH VD and RT and GCC; (B) comparison of ROC curves between IH VD and RT and GCC. In the severe versus PACS groups, (C) comparison of ROC curves between SH VD and RT and GCC. (D) comparison of ROC curves between IH VD and RT and GCC.

Supplementary Files

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- Table3.jpg
- Table1.jpg
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