

# Correlations between Serum Immunoglobulin Levels and Retinal Structural Parameters in Patients with Newly Diagnosed, Acute Vogt–Koyanagi–Harada Disease—A Retrospective Data Study

Zhijan Jiang (✉ [jiang\\_zj82@126.com](mailto:jiang_zj82@126.com))

Shanghai Xuhui Central Hospital <https://orcid.org/0000-0002-0679-2788>

Nan Zhang

Shanghai Xuhui Central Hospital

Huiying Ji

Shanghai Xuhui Central Hospital

maoli zhu

Shanghai Xuhui Central Hospital

Jianhong Dong

Shanghai Xuhui Central Hospital

Min Zhou

Fudan University Eye Ear Nose and Throat Hospital Department of Ophthalmology

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## Research Article

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# Abstract

## background

IgE is an immune antibody involved in inflammatory response and serum IgE level elevated in some autoimmune diseases. VKH disease is autoimmune inflammatory disorder, IgE might be involved in VKH disease and high serum IgE level might related to the disease severity.

## Main body

Retrospective study. Foveal thickness (FT), serous retinal detachment (SRD), sensory retinal thickness (SRT), central foveal thickness (CFT), cube volume (V), and cube average thickness (AT) were measured by OCT. According to SRD, the patients were divided into high detachment group ( $>500\mu\text{m}$ ) and low detachment group ( $\leq 500\mu\text{m}$ ). Rate-scattering turbidimetry was used to measure the Immunoglobulins levels. Of 138 patients, 51 (36.96%) were included in the high detachment group. The proportion of males (2.122; 95% CI, 1.051–4.288;  $P = 0.035$ ) was greater and best-corrected visual acuity (BCVA) ( $-0.495$ ; 95% CI,  $-0.620$ – $-0.369$ ;  $P < 0.001$ ) was worse in the high detachment group. IgE level in the high detachment group (median: 83 IU/ml, interquartile range (IQR): 30–251) was significantly greater ( $P = 0.016$ ) than that in the low detachment group (median: 53 IU/ml, IQR:32–80). FT, SRD, CFT, V, and AT were significantly greater in the high detachment group. IgE level was positively correlated with SRD, CFT, and AT. Multivariable binary logistic regression analysis showed that male (2.447; 95% CI, 1.004–5.964;  $P = 0.049$ ) and serum IgE levels (0.997; 95% CI, 0.995–0.999;  $P = 0.014$ ) were independent risk factors for severe SRD.

## Conclusion

Male are more likely to have severe SRD, and the extent of detachment is associated with the serum IgE level. IgE may be involved in the progression of VKH disease.

## Background

Vogt–Koyanagi–Harada (VKH) disease is an autoimmune disease that is relatively common in China, and is characterized by ophthalmic, auditory, dermatologic, and neurologic manifestations. The most common ophthalmic manifestation of VKH disease is granulomatous intraocular inflammation. Serous retinal detachment (SRD) is the most common ocular manifestation in patients presenting in the acute phase of VKH disease [1, 2].

The etiology and pathogenesis of VKH disease are still unknown. One mechanism may involve an autoimmune response to melanocytes that is mediated by CD4 + T cells [3]. Changes in the ratio of CD4 + lymphocytes and CD4+/CD8 + cells were observed in skin lesions of patients with VKH disease. Histopathology of skin lesions showed that in addition to diffuse infiltration of activated T cells in the choroid membrane, the lesions contained infiltrations of plasma cells, multinucleated giant cells, and other cells, suggesting that humoral immunity also plays a role in the pathogenesis of VKH disease [4].

Immunoglobulins (Igs) are globulin proteins with antibody-like structures and important immune antibody activities. Upon stimulation by an antigen, B cells proliferate and differentiate into plasma cells, which secrete relevant immunoglobulin antibodies involved in the regulation of humoral immunity. Igs also play immunomodulatory roles by neutralizing specific antigens and activating complement [5]. Studies have demonstrated that serum IgG, IgA, and IgM also have notable roles in various diseases, including autoimmune hemolytic anemia, IgA nephropathy, and autoimmune hepatitis [6–8]. It was also reported that the serum IgG, IgA and IgM levels were significantly increased in patients with rheumatoid arthritis, and the changes in these Igs were associated with disease activity [9]. Elevated IgE levels were also detected in patients with other autoimmune diseases, such as systemic lupus erythematosus and bullous pemphigoid, and IgE autoantibodies were also detected in these patients [10, 11]. Several studies have also reported higher serum total IgE levels in patients with types of autoimmune uveitis, such as acute iridocyclitis, Eales' disease, pars planitis, and multifocal choroiditis, than in a normal control group [12, 13].

To date, however, no studies have measured Igs levels in patients with VKH disease, or examined the correlation between Igs levels and retinal structural parameters. Therefore, in this study, we reviewed the medical records of patients admitted to our hospital with acute VKH disease, and analyzed the serum Ig levels in patients according to the extent of SRD. We also examined the correlation between Ig levels and changes in retinal structure in acute VKH disease.

## Patients And Methods

### Patients

This was a retrospective clinical study. The study was approved by the Ethics Committee at Shanghai Xuhui Central Hospital Ethics Committee (Shanghai, China).

We retrieved the medical records of patients with newly diagnosed, acute VKH who were admitted to Shanghai Xuhui District Central Hospital between August 2015 and April 2020. Patients were eligible for this study if they satisfied the diagnostic criteria for acute VKH disease described in the section “Diagnostic criteria for acute VKH disease.” Patients with corneal disease, glaucoma, eye trauma, history of eye surgery, eye developmental abnormalities, or genetic diseases were excluded. Patients with asthma, urticaria, systemic lupus erythematosus, bullous pemphigoid, and other systemic immune diseases were also excluded. Furthermore, we excluded patients who did not cooperate with the examinations or patients with corneal or lenticular opacity. The best-corrected visual acuity (BCVA) and time from onset to admission were retrieved from the patients' medical records. The OCT and serum data were also retrieved from the medical records and they were measured at the same time as BCVA.

### Diagnostic criteria for acute VKH disease

The diagnostic criteria for acute VKH are as follows [2]: (A) no history of ocular trauma or intraocular surgery; (B) bilateral ocular involvement (onset within 2 weeks in both eyes); (C) no evidence of uveitis, accompanying systemic rheumatic disease, or other ocular diseases; (D1) signs of diffuse choroiditis and exudative retinal detachment; (D2) SRD on optical coherence tomography (OCT) or B-scan ultrasonography; (D3) choroidal thickening on enhanced depth imaging OCT; (D4) early punctate staining and late subretinal dye pooling on

fundus fluorescein angiography (FFA); (D5) hyperfluorescence of the optic disc on FFA. Only patients who satisfied criteria A–C plus D1, or D2 and D3, or D4 were considered to have acute VKH disease.

### **OCT examination of the macular area**

OCT was done at the time of admission to hospital. The pupils were dilated with compound tropicamide (0.5% tropicamide and 0.5% deoxyepinephrine hydrochloride) eye drops before the examination. The macular areas were scanned using an OCT scanner (Cirrus HD-OCT 4000, Zeiss, Germany) with software version 4.0. All patients were scanned in both the macular cube mode and with a five-line raster.

The macular cube mode (512 × 128) scanned a square region (6.0 × 6.0 mm) centered on the fovea. The central foveal (central 1 mm subfield) thickness (CFT), cube volume (V), and cube average thickness (AT) were automatically measured by the software (Fig. 1A).

In the five-line raster scanning mode, the distance between each line was 0.25 mm and the transverse scans were centered on the fovea. The software's caliper function was used to manually measure foveal thickness (FT), SRD, and sensory retinal thickness (SRT). The FT boundaries were set as the internal limiting membrane and the inner boundary of the retinal pigment epithelium (RPE) layer. SRD was defined as the distance from the inner boundary of the sensory layer to the internal boundary of the RPE layer in the fovea. SRT was defined as the distance from the inner boundary membrane in the fovea to the inner boundary of the sensory layer (Fig. 1B). Each measurement was repeated twice, and the mean value was recorded. The patients were divided into two groups based on the SRD: high detachment group (>500 μm) and low detachment group (≤500 μm).

### **Measurement of serum Ig, C-reactive protein, and tumor necrosis factor α levels**

Fasting venous blood samples were obtained at the time of admission, and the sera were separated and stored at -20 °C until testing. Rate-scattering turbidimetry was used to measure the Ig levels on an automatic analyzer (BN II, Siemens, Germany). C-reactive protein (CRP) and tumor necrosis factor α (TNF-α) levels were measured using enzyme-linked immunosorbent assay kits (R&D Systems).

### **Statistical analysis**

SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. The variables were tested for a normal distribution using the Kolmogorov–Smirnov test. Variables that did not conform to a normal distribution are represented as the median. The Mann–Whitney *U* test was used to compare variables between the two groups. Pearson's  $\chi^2$  test was used to test categorical variables. In all analyses,  $P < 0.05$  was considered statistically significant.

## **Results**

### **General clinical characteristics**

Our study included 138 patients, of whom 67 were male (48.55%). The mean age was 41.65 years (14 to 76 years) and the mean time from onset to admission was 17.71 days (2 to 90 days). The mean BCVA (logarithms of the minimum angle of resolution) was 0.76(SD, 0.56).

Of 138 patients, 51 were included in the high detachment group, 30 of whom were male (58.82%). The other 87 patients were included in the low detachment group, of which 35 were male (40.23%). In the high detachment group, the median age was 42 years (interquartile range, 28-52) and the medial mean time from onset to admission was 10 days (interquartile range, 7-20). The medial mean BCVA (logarithms of the minimum angle of resolution) was 1.0 (interquartile range, 0.6-1.3). In the low detachment group, the media age was 41 years (interquartile range, 28-50) and the medial mean time from onset to admission was 14 days (interquartile range, 7-21). The medial mean BCVA (logarithms of the minimum angle of resolution) was 0.5 (interquartile range, 0.3-0.7).

The proportion of males (2.122; 95% CI, 1.051-4.288;  $P=0.035$ ) and the BCVA (-0.495; 95% CI, -0.620–0.369;  $P <0.001$ ) were significantly different between the two groups. By contrast, there were no differences in the age of onset (0.661; 95% CI, -4.123-5.450;  $P = 0.841$ ) or time from onset to admission (-0.646; 95% CI, -8.011-6.719;  $P = 0.535$ ) between the two groups.

### **Serum Ig, CRP and TNF- $\alpha$ levels**

The serum IgA, IgG, IgM, IgE, CRP, and TNF- $\alpha$  levels of the two groups are compared in Table 1. There were no differences in the serum levels of IgA, IgG, IgM, CRP, or TNF- $\alpha$ . However, the serum IgE level was significantly greater in the high detachment group than in the low detachment group.

### **Comparison of macular area morphologic characteristics**

Table 2 compares the FT, SRD, SRT, CFT, V, and AT between the two groups. FT, SRD, CFT, V, and AT were significantly greater in the high detachment group than in the low detachment group. However, SRT was not significantly different between the two groups. While not statistically significant, there was a trend that SRT is greater in high detachment group (Median SRT, 141 vs 134 $\mu$ m).

### **Correlations among IgE, visual acuity, and macular characteristics**

Correlations among the IgE, BCVA, and OCT data are shown in Table 3. The serum IgE levels were positively correlated with SRD, CFT, and AT. Moreover, the BCVA was positively correlated with FT, SRD, SRT, CFT, V, and AT.

### **Analysis of risk factors for severe SRD**

Multivariable binary logistic regression was performed using IgA, IgG, IgM, IgE, CRP, and TNF- $\alpha$  as the independent variables and severity of SRD (SRD  $>500 \mu$ m = 1; SRD  $\leq 500 \mu$ m = 0) as the dependent variable. Age, sex (male = 1, female = 2), and time from onset to admission were also included for adjustment. In this analysis, male (2.447; 95% CI, 1.004-5.964;  $P=0.049$ ) and IgE level (0.997; 95% CI, 0.995-0.999;  $P=0.014$ ) were independent risk factors for severe SRD (Table 4). The receiver operating characteristic curve analysis revealed that the area under the curve for IgE as a diagnosis of severe SRD was 0.623 ( $P = 0.016$ ).

## **Discussion**

All of the patients included in this study were of Chinese Han nationality. The mean age at onset of VKH disease was 41.65 years (range 14 to 76 years). The percentage of females were lower than previous reports, only 51.45%. Possible explanations may include the differing sample sizes or racial differences [3]. Despite this,

the proportion of males was significantly greater in the high detachment group than in the low detachment group, and the regression analysis showed that male sex was a significant risk factor for SRD in this cohort of patients with VKH disease. These results suggest that, among Chinese Han, males with acute VKH disease are more likely to present with severe SRD.

VKH disease is one of the common types of panuveitis. With the development of choroidal inflammation, it first affects the adjacent RPE layer, causing the RPE layer to crease. As choroidal vascular permeability increases, inflammatory choroidal fluid accumulates beneath the neuroepithelium to cause neuroepithelial detachment. FFA and indocyanine green angiography can be used to detect any leaks from retinal blood vessels that lead to SRD. SRD is a common manifestation of VKH disease that indirectly reflects the severity of inflammation [1]. OCT, a non-invasive imaging modality, can provide clear tomographic images that reveal the microstructure of the retina [14]. The extent of SRD can be quantified using various OCT parameters. In our study, the age at onset and time from onset to admission were not significantly different between the high and low detachment groups. However, FT, SRD, CFT, V, and AT were significantly greater in the high detachment group than in the low detachment group, indicating that the leakage caused by inflammation was more severe in the high detachment group. By contrast, SRT was not significantly different between the two groups, which indicates that in the acute stage, the inflammatory process had not caused marked changes in the sensory layer of retina. While not statistically significant, there was a trend that SRT is greater in high detachment group. The BCVA was significantly worse in the high detachment than the low detachment group, and it was significantly correlated with FT, SRD, SRT, CFT, V, and AT. These findings demonstrate that OCT scans in patients with acute VKH disease not only depict changes in the retinal structure, but also indirectly reflect the patient's disease severity and BCVA.

We found no significant differences in the serum IgA, IgG, IgM, CRP, or TNF- $\alpha$  levels between the two groups. However, the serum IgE level was significantly greater in the high detachment group. IgE synthesis is regulated by a variety of factors, including T lymphocytes, B lymphocytes, and various cytokines [15]. The interaction between CD40 on the surface of B lymphocytes and CD40L expressed by CD4 + T lymphocytes is critical for mediating antigen-specific IgE responses in vivo. The IgE response is dependent on T lymphocytes because the activation of B lymphocytes requires the additional T lymphocyte factors interleukin (IL)-4/IL-3 [16]. IgE is highly sensitive to the T-cytokine environment because it is regulated by cytokines secreted by CD4 + T cells [15]. The most recognized pathogenesis of VKH disease involves autoimmune inflammation mediated by CD4 + T cells targeting melanocytes [3]. Thus, elevated IgE levels may also be involved in the autoimmune inflammation mediated by CD4 + T cells.

IgE is recognized as the antibody mediating parasitic immunity and type I hypersensitivity. Many studies have shown that the serum IgE level is elevated in patients with various autoimmune disease, and IgE autoantibodies are also detected in many patients [10, 12]. A retrospective study of 1583 patients found that allergic diseases (53.14%) and autoimmune diseases (47.37%) were associated with the highest percentages of patients with elevated serum IgE levels [17]. The correlation between the serum total IgE level and autoimmunity disease severity is the same as that for specific IgE autoantibodies [10]. Moreover, most studies showed that elevated serum total IgE levels were closely associated with activity of diseases, such as systemic lupus erythematosus and bullous pemphigoid [18–20]. Permin and Wiik also confirmed that, while immune complexes comprised IgE autoantibodies, IgE itself increased vascular permeability by mediating the release of vasoactive amines [21]. In

our study, the serum IgE level in the high detachment group was significantly greater than that in the low detachment group, and it was positively correlated with SRD, CFT, and AT. Logistic regression analysis showed that IgE was an independent risk factor for severe SRD. We speculate that the high IgE level led to a marked increase in vascular permeability, which progressed to severe SRD. This suggests that high serum IgE levels might contribute to the severe condition of patients with acute VKH disease.

To the best of our knowledge, this was the first study to investigate the relationship between SRD and IgE in patients with acute VKH disease. However, this study has some limitations. First, due to the limitations of the Cirrus 4000 OCT scanner, the images of the choroid were unclear. Disease inflammation also made it difficult to measure the relevant choroid parameters. Second, we measured the serum total IgE level, but did not test for IgE autoantibodies, in patients with acute VKH disease.

In summary, males with acute VKH disease were more likely to present with severe SRD. Furthermore, the severity of SRD was associated with high serum IgE levels, which suggests that IgE may be involved in the pathogenesis and/or progression of VKH disease.

## Abbreviations

Vogt–Koyanagi–Harada ☒VKH

Foveal thickness ☒FT

serous retinal detachment ☒SRD

sensory retinal thickness ☒SRT

central foveal thickness ☒CFT

cube volume ☒V

cube average thickness ☒AT

best-corrected visual acuity ☒BCVA

interquartile range ☒IQR

Immunoglobulins ☒Igs

optical coherence tomography ☒OCT

fundus fluorescein angiography ☒FFA

retinal pigment epithelium ☒RPE

C-reactive protein ☒CRP

tumor necrosis factor  $\alpha$  ☒TNF- $\alpha$

# Declarations

## Funding information

This study was financially supported by Medical Project of Xuhui Central Hospital (2019-019).

## Competing interests

The authors declare that there is no competing interest.

## Availability of data and material

The data and material used during the current study are available from the corresponding author upon reasonable request.

## Author Contribution Statement

Jianhong Dong and Min Zhou were responsible for the conception and design of the work, final approval of the version to be published. Zhijian Jiang and Nan Zhang were responsible for extracting and analyzing data, interpreting results and drafting the work. Huiying Ji contributed to the data extraction and revising it critically for important intellectual content. Maoli Zhu contributed to data extraction and provided feedback on the work.

## Ethics Statement

Ethics approval for this study was obtained from the Shanghai Xuhui Central Hospital Ethics Committee of Shanghai Xuhui Central Hospital.

## Consent for publication

The participant has consented to the submission of case report to the journal.

## Acknowledgements

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## Tables

**Table 1** comparison of serum IgA, IgG, IgM, IgE, CRP and TNF- $\alpha$  between the high detachment group and the low detachment group

	High detachment group	Low detachment group	<i>P</i> value
IgA, median (IQR), g/L	2.04 (1.77, 2.59)	2.26 (1.74, 3.08)	0.304
IgG, median (IQR), g/L	1120 (9.74, 13.05)	11.69 (10.20, 13.76)	0.208
IgM, median (IQR), g/L	1.23 (0.92, 1.64)	1.24 (0.86, 1.67)	0.865
IgE, median (IQR), IU/ml	83.00 (30.00, 251.00)	53.00 (32.00, 80.00)	0.016
CRP, median (IQR), mg/L	1.04 (0.50, 2.02)	0.67 (0.30, 3.00)	0.082
TNF- $\alpha$ , median (IQR), pg/ml	4.60 (4.00, 6.43)	4.21 (4.00, 5.47)	0.099
IgA: immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M; IgE: immunoglobulin E; CRP: C-reactive protein; TNF- $\alpha$ : tumor necrosis factor $\alpha$			

**Table 2** Comparison of FT, SRD, SRT, CFT, V and AT between the high detachment group and the low detachment group

	High detachment group	Low detachment group	<i>P</i> value
FT, median (IQR), μm	864.00 (661.00, 1247.25)	324.50 (232.00, 446.25)	<0.001
SRD, median (IQR), μm	701.00 (421.75, 997.25)	162.00 (96.00, 282.00)	<0.001
SRT, median (IQR), μm	141.00 (124.00, 161.25)	134.00 (118.00, 158.50)	0.052
CFT, median (IQR), μm	813.00 (606.75, 1016.25)	362.00 (268.75, 445.50)	<0.001
V, median (IQR), mm <sup>3</sup>	17.60 (14.70, 20.38)	11.80 (10.90, 13.00)	<0.001
AT, median (IQR), μm	489.50 (408.00, 566.75)	327.50 (320.75, 360.25)	<0.001
FT: foveal thickness; SDR: serous retinal detachment; SRT: sensory retinal thickness; CFT: central fovea thickness; V: cube volume; AT: cube average thickness			

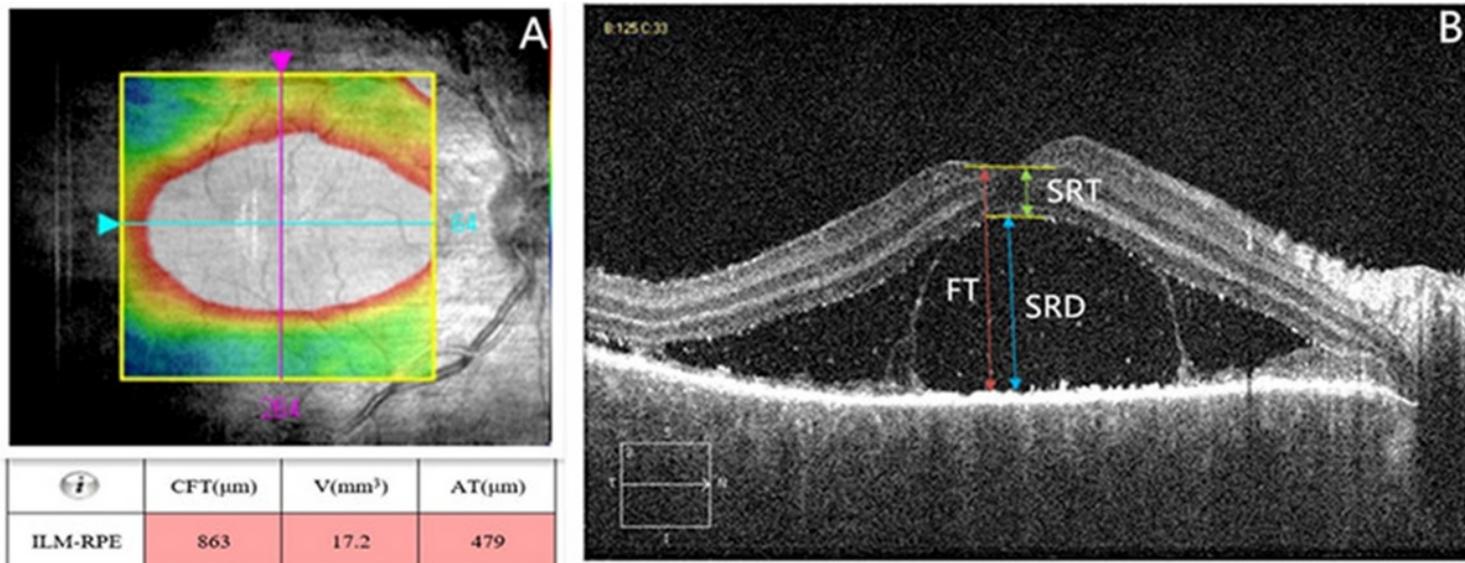
**Table 3** Correlations among IgE, BCVA and OCT macular parameters

		IgE	BCVA (logMAR)	FT	SRD	SRT	CFT	V	AT
IgE	Pearson Correlation	1	0.067	0.110	0.136	-0.041	0.137	0.113	0.125
	Sig. (2- tailed)		0.269	0.067	0.024	0.500	0.023	0.061	0.038
BCVA (logMAR)	Pearson Correlation	0.067	1	0.644	0.618	0.160	0.588	0.596	0.554
	Sig. (2- tailed)	0.269		<0.001	<0.001	0.008	<0.001	<0.001	<0.001
IgE: immunoglobulin E; BCVA: best corrected visual acuity; FT: foveal thickness; SDR: serous retinal detachment; SRT: sensory retinal thickness; CFT: central fovea thickness; V: cube volume; AT: cube average thickness									

**Table 4** analysis of risk factors for severe SRD

Item	<i>B</i> value	<i>Wald</i> value	<i>P</i> value	<i>OR</i> value (95% <i>CI</i> )
gender	2.447	3.876	0.049	1.004~5.964
age	0.996	0.089	0.766	0.968~1.024
Admission time	1.001	0.014	0.906	0.982~1.02
IgA	1.284	1.146	0.284	0.812~2.029
IgG	0.972	0.15	0.698	0.842~1.122
IgM	0.754	0.945	0.331	0.427~1.333
IgE	0.997	6.034	0.014	0.995~0.999
CRP	1.034	0.151	0.698	0.875~1.221
TNF- $\alpha$	0.917	0.497	0.481	0.719~1.168
IgA: immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M; IgE: immunoglobulin E; CRP: C-reactive protein; TNF- $\alpha$ : tumor necrosis factor $\alpha$				

## Figures



**Figure 1**

Representative optical coherence tomography images of the fovea. A: The macular cube scan was used to automatically measure the central fovea thickness (CFT), cube volume (V) and cube average thickness (AT). B: The horizontal B scan was used to manually measure foveal thickness (FT), serous retinal detachment (SRD), and sensory retinal thickness (SRT).