Logistic regression models of cytokines in differentiating vitreoretinal lymphoma from uveitis

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Abstract

Background: Vitreoretinal lymphoma (VRL) can commonly masquerade as chronic idiopathic uveitis due to its nonspecific clinical presentation. Thus, its early diagnosis is difficult. In this study, new logistic regression models were used to classify VRL and uveitis. Additionally, the diagnostic performance of interleukin (IL)-10, the IL-10/IL-6, and the Interleukin Score for IntraOcular Lymphoma Diagnosis (ISOLD) are evaluated.

Methods: Sixty-nine aqueous humors (AH) (46 VRL, 23 uveitis) and 65 vitreous humors (VH) (49 VRL, 16 uveitis) were collected from a single-center retrospective cohort. Logistic regression models were conducted based on IL-6 and IL-10. The cut-off values, area under the receiver operating characteristic curve (ROC) curve (AUC), sensitivity and specificity of IL-10, the IL-10/IL-6, the ISOLD, and the models were calculated from the ROC. Furthermore, Spearman’s rank correlation analysis was performed to determine cytokine levels in VH and AH.

Results: We redefined the cut-off values of IL-10, the IL-10/IL-6, the ISOLD, and the logistic regression models. In AH, the AUC values of IL-10, ISOLD, IL10/IL6, and the model were 0.91, 0.953, 0.952, and 0.967. In VH, they were 0.93, 0.95, 0.954, and 0.954, respectively. IL-6 ($r = 0.7844$) and IL-10 ($r = 0.8506$) in AH and VH showed a strong correlation.

Conclusions: IL-6 and IL-10 levels were introduced into new logistic regression models. The diagnostic efficacy of the models improved compared to the indicators mentioned above among Chinese patients. Additionally, the models could predict the probability of VRL more accurately. A strong correlation of cytokine levels showed the great potential of AH as prioritized auxiliary diagnostic for VRL.

Keywords
IL-6, IL-10, ISOLD, logistic regression models, uveitis, vitreoretinal lymphoma
1 | INTRODUCTION

Intraocular lymphoma (IOL) has two different forms, including primary IOL (PIOL) and secondary IOL (SIOL). PIOL refers mainly to primary central nervous system lymphoma (PCNSL) involving the eyes. SIOL may derive from systemic non-Hodgkin's lymphoma that metastasizes to the eyes. Depending on the site of occurrence IOL is classified into vitreoretinal lymphoma (VRL) and uveal lymphoma, the latter of which can be further subdivided into choroidal, ciliary body, or iris lymphoma. VRL is the most common IOL and involves the retina, subretinal space, vitreous, or optic nerve. VRL is a rare subtype of PCNSL, and diffuse large B cell lymphoma (DLBCL) is its most common pathology, with only a small proportion of VRL derived from T cells or natural killer (NK) cells. At the time of presentation, 16%-34% of VRL patients have concurrent PCNSL. Approximately 15%-20% of patients with PCNSL have or will develop an ocular manifestation of their lymphoma, and 50%-90% will develop PCNSL within 16-24 months on average. VRL usually occurs in adults between the ages of 24 and 85, with a median age of 63. VRL can also be diagnosed in young people under the age of 16 years. Whether VRL has sex-based differences has not yet been consistently established.

The clinical presentation of VRL is non-specific and commonly presents as blurred vision, decreased visual acuity, and flying mosquito syndrome and often even masquerades as various types of uveitis. Furthermore, the use of steroids makes the diagnosis of VRL more difficult, with an average time to initial diagnosis of up to 40 months (range: 1-144 months). In recent years, ophthalmic imaging techniques, such as optical coherence tomography (OCT) and intraocular fluid-based complementary diagnostic techniques, such as polymerase chain reaction (PCR) for the detection of immunoglobulin heavy chain (IGH) and immunoglobulin light chain (IGL) clonal rearrangements (IgH-PCR and Igl-PCR, respectively), myeloid differentiation factor 88 (MYD88)-PCR for the detection of immunoglobulin heavy chain (IGH) and immunoglobulin light chain (IGL) clonal rearrangements (IgH-PCR and Igl-PCR, respectively), and cytokine analysis have improved the early diagnosis of VRL. Of these, cytokines have been studied most extensively. The presence of high levels of IL-10 in the vitreous fluid of patients with B-cell PVRL was first reported by Chan et al. in 1995. Several subsequent studies have also reported successful differentiation between lymphoma and uveitis using IL-10 and IL-10/IL-6 ratios. Therefore, elevated IL-10 in vitreous or aqueous or elevated IL-10/IL-6 ratios are usually considered indirect evidence of the presence of VRL. However, some studies have also shown that high levels of IL-10 are also produced in acute retinal necrosis syndrome or toxoplasmosis, which may lead to false positives. In contrast, low levels of IL-10 or IL-10/IL-6 ratios <1 do not necessarily exclude the diagnosis of lymphoma. To improve the diagnostic efficacy of cytokines, Costopoulos et al. proposed the Interleukin Score for IntraOcular Lymphoma Diagnosis (ISOLD), a model that evaluated the probability of PVRL based on IL-6 and IL-10 levels in a large multicenter European cohort with high sensitivity (93%) and specificity (95%). Later, Kuo et al. trained and validated a single-centered logistic regression model based on the score. These findings showed that intraocular cytokine analysis by logistic regression may be a promising approach to assist in cytopathology.

In this study, we evaluated the clinical value of IL-6, IL-10, the IL-10/IL-6 ratio, and the ISOLD score applied in a single-center retrospective cohort at The North Hospital of HuaShan Hospital, Fudan University. In addition, we trained and tested new logistic regression models in this cohort to assess the overall diagnostic performance of the models in VRL and the diagnostic efficacy of differentiating VRL from uveitis.

2 | MATERIALS AND METHODS

2.1 | Study population

This monocentric, retrospective study was conducted from September 2019 to February 2022 at the Department of Ophthalmology, The North Hospital of Huashan Hospital, Fudan University, Shanghai. Aqueous humor (AH) and vitreous humor (VH) were collected from VRL patients diagnosed by vitreous biopsy and subsequent histopathological confirmation, and from patients diagnosed with uveitis during the corresponding period. Calculated by the number of eyes, 69 AH were collected, including 46 VRL and 23 uveitis (four infectious and 19 non-infectious uveitis) and 65 VH were collected, including 49 VRL and 16 uveitis (nine infectious and seven non-infectious). Of these, 50 samples were matched. All samples were assayed for cytokines using a Cytometric Bead Array (CBA) assay (RAISECARE, Qingdao, China). The ISOLD score was determined according to the formula: $-12.871 + 5.533 \times \log([IL-10]+1) - 1.614 \times \log([IL-6]+1)$ for AH and $-12.208 + 4.648 \times \log([IL-10]+1) - 1.669 \times \log([IL-6]+1)$ for VH.

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Huashan Hospital, Fudan University. Patients and their families voluntarily underwent a clinical examination and signed an informed consent form.

2.2 | Statistical analysis

SPSS 26.0 and Prism 9 version 9.1.1 (GraphPad Software) statistical software were used for statistical analysis. The Shapiro–Wilks test was used to test the normal distribution of the data. Values conforming to normal distribution were expressed as mean ± SD. In case of a non-normal distribution, the data were expressed as median and interquartile range M (P25, P75). In addition, cytokine levels were compared with the Mann–Whitney U test between the uveitis and VRL groups. The optimal threshold values and the area under the curve (AUC) were calculated from the receiver operating characteristic (ROC) curve and the sensitivity and specificity at the optimal cut-off (maximal Youden index). In addition, a correlation analysis between IL-6 and IL-10 levels in AH and VH was performed using Spearman’s rank correlation. A
were 10 males and six females, with a mean age of 61.44 ± 8.23 years. In the uveitis group, there were 23 AH and 16 VH. Of these, the AH samples included 12 males and 11 females, with a mean age of 58.90 ± 10.84 years. In the uveitis group, there were 23 AH and 16 VH. Of these, the AH samples included 12 males and 11 females, with a mean age of 56.39 ± 14.25 years. Among the VH, there were 10 males and six females, with a mean age of 61.44 ± 8.23 years. As shown in Table 1, the baseline characteristics of the VRL and uveitis groups in the aqueous and VH were balanced and comparable.

3.2 Establishment of the logistic regression equations

IL-6 levels identified in aqueous and vitreous samples were converted to log (IL-6 + 1), and IL-10 of AH and VH converted to log (IL-10 + 1). As shown in Table 2, the equation for VH was established by binary logistic regression analysis using SPSS as logistic (VH) = 0.187 + 3.035 \times \log (IL-10 + 1) - 1.879 \times \log (IL-6 + 1) and from this, the probability of PVRL occurrence was 1/(1 + \exp \log (VH)). The equation for aqueous fluid was logistic (AH) = -0.273 + 3.85 \times \log (IL-10 + 1) - 1.969 \times \log (IL-6 + 1) and the probability was 1/(1 + \exp \log (AH)).

3.3 Vitreous humor

3.3.1 Comparison of different indicators of uveitis and lymphoma

In VH samples, IL-6 levels were higher in patients with uveitis than in patients with lymphoma (p < 0.01). In contrast, IL-10 levels, the IL-10/IL-6 ratio, the ISOLD, and the logistic regression model were significantly higher in lymphoma than in uveitis in VH samples (p < 0.0001) (Table 3). Table 3 shows the median and range of IL-6 and IL-10 levels, the IL-10/IL-6 ratio, the ISOLD, and the logistic regression model in VH samples for uveitis and lymphoma. IL-6 levels in patients with uveitis (137.3 [40.34–95.3] pg/ml) were higher than in VH (21.85 [12.79–89.41] pg/ml, p < 0.01). However, lymphoma patients had higher IL-10 levels (235 [59.11–507.9] pg/ml) than uveitis (5.28 [2.59–9.89] pg/ml, p < 0.0001). Furthermore, the ISOLD values in lymphoma patients with lymphoma (−4.18 [−5.93 to −2.34]) were higher than those with uveitis (−12.11 [−13.79 to −11.29], p < 0.0001). Further, the logistic regression model also showed higher levels in patients with lymphoma (4.05 [2.88–5.15]) than in those with uveitis (−1.758 [−3.74 to −0.74], p < 0.0001).

3.4 Aqueous humor

3.4.1 Comparison of different indicators of uveitis and lymphoma

In AH samples, IL-6 levels were higher in patients with uveitis than in patients with lymphoma (p < 0.05). In contrast, IL-10 levels, the IL-10/IL-6 ratio, the ISOLD, and the logistic regression model were significantly higher in lymphoma than in the uveitis in the AH (p < 0.0001) (Table 3). Table 3 shows the median and interquartile range of aqueous IL-6 and IL-10 levels, the IL-10/IL-6 ratio, the ISOLD values, and the logistic regression model for uveitis and lymphoma. IL-6 levels in patients with uveitis (251.6 [45.33–2836] pg/ml) were higher than in VH (42.56 [12.79–227.9] pg/ml, p < 0.05). However, lymphoma patients had higher IL-10 levels (104.0 [35.7–221.8] pg/ml) than patients with uveitis (2.96 [0.28–13.22] pg/ml,

3 | RESULTS

3.1 Study population

This study included a total of 69 AH and 65 VH samples, which were divided into VRL and uveitis groups. In the lymphoma group, there were 46 AH and 49 VH samples. Of these, the AH samples included 21 males and 25 females, with a mean age of 58.89 ± 10.84 years. In the uveitis group, there were 23 AH and 16 VH. Of these, the AH samples included 12 males and 11 females, with a mean age of 56.39 ± 14.25 years. Among the VH, there were 10 males and six females, with a mean age of 61.44 ± 8.23 years. As shown in Table 1, the baseline characteristics of the VRL and uveitis groups in the aqueous and VH were balanced and comparable.

TABLE 1 Study population demographics

| Group | Samples | Eyes | Sex (%male) | Mean age ± SD |
|-------|---------|------|-------------|---------------|
| VRL   | Aqueous | 46   | 21/25 (45.7%) | 58.89 ± 10.15 |
|       | Vitreous| 49   | 24/25 (48.98%)| 58.90 ± 10.84 |
| Uveitis| Aqueous | 23   | 12/11 (52.2%) | 56.39 ± 14.25 |
|       | Vitreous| 16   | 10/6 (62.5%)  | 61.44 ± 8.23  |
Furthermore, the IL-10/IL-6 ratios of patients with VRL (2.185 [0.83–5.92]) were significantly higher compared to patients with uveitis (0.01 [0.00–0.05], p < 0.0001) and the ISOLD levels in patients with lymphoma (−4.63 [−6.78 to −2.12]) were higher than in uveitis patients (−13.47 [−15.30 to −11.42], p < 0.0001). In addition, the logistic regression model also showed higher levels in lymphoma (4.9 [2.63–6.45]) than in uveitis (−1.962 [−3.80 to −0.71], p < 0.0001).

### TABLE 2  Vitreous and aqueous components in logistic regression analysis

| Group   | B     | Sig. | Exp(B) | OR (95% CI) |
|---------|-------|------|--------|-------------|
| Vitreous| Log (IL-10 + 1) | 3.035 | 0.00   | 20.803     | 4.241–102.045 |
|         | Log (IL-6 + 1) | −1.879 | 0.012  | 0.153     | 0.35–0.658  |
|         | Constant      | −0.187 | 0.883  | 0.829     |            |
|         | Log (IL-10 + 1) | 3.85  | 0.00   | 47.014     | 6.784–325.825 |
| Aqueous | Log (IL-6 + 1) | −1.969 | 0.001  | 0.14      | 0.042–0.469 |
|         | Constant      | −0.273 | 0.795  | 0.761     |            |

### TABLE 3  Levels of different indicators between cases of uveitis and VRL

|        | IL-6(pg/ml) | IL-10(pg/ml) | IL-10/IL-6 | ISOLD | Logistic |
|--------|-------------|--------------|------------|-------|----------|
| Vitreous VRL | 21.85 (12.79–89.41) | 235 (59.11–507.9) | 7.16 (2.38–22.26) | −4.18 (−5.93 to −2.34) | 4.05 (2.88–5.15) |
| Uveitis | 137.3 (40.34–957.3) | 5.28 (2.59–9.89) | 0.04 (0.0025–0.17) | −12.11 (−13.79 to −11.29) | −1.758 (−3.74 to −0.74) |
|         | p Value     | <0.0001      | <0.0001    | <0.0001   | <0.0001  |
| Aqueous VRL | 42.56 (12.79–227.9) | 104.0 (35.7–221.8) | 2.185 (0.83–5.92) | −4.63 (−6.78 to −2.12) | 4.9 (2.63–6.45) |
| Uveitis | 251.6 (45.33–2836) | 2.96 (0.28–13.22) | 0.01 (0.00–0.05) | −13.47 (−15.30 to −11.42) | −1.962 (−3.80–0.71) |
|         | p Value     | <0.0001      | <0.0001    | <0.0001   | <0.0001  |

Note: Values are indicated as medians with interquartile range.

### TABLE 4  Diagnostic efficacy assessment of VRL in vitreous and aqueous humors

|        | Cut-off | Sensitivity | Specificity | Area | Std. Error | Lower bound | Upper bound |
|--------|---------|-------------|-------------|------|------------|-------------|-------------|
| Vitreous IL-10 | 26.275  | 0.898       | 0.937       | 0.93 | 0.034      | 0.863       | 0.997       |
| IL-10/IL-6 | 0.885  | 0.918       | 0.937       | 0.954| 0.032      | 0.892       | 1           |
| ISOLD  | −9.97   | 0.959       | 0.937       | 0.95 | 0.032      | 0.886       | 1           |
| Logistic | 0.5015 | 0.959       | 0.937       | 0.954| 0.032      | 0.891       | 1           |
| IL10  | 29.74   | 0.826       | 0.913       | 0.91 | 0.038      | 0.835       | 0.985       |
| IL-10/IL-6 | 0.065  | 0.957       | 0.87        | 0.952| 0.027      | 0.9         | 1           |
| Aqueous ISOLD | 0.66    | 0.783       | 0.957       |      |            |             |             |
| Logistic | −10.115 | 0.957       | 0.87        | 0.953| 0.027      | 0.9         | 1           |

FIGURE 1 ROC curves of various indicators for diagnosis VRL. (A) showed ROC curves of various indicators in vitreous humor, and (B) represented in aqueous humors. The blue line stands for IL-10, the red line indicates the IL10/IL6 ratio, the green line represents the ISOLD score, and the orange line shows the logistic regression model.
3.4.2 | Diagnostic evaluation of the efficacy of intraocular lymphoma

The efficacy of IL-10 levels, the IL-10/IL-6 ratio, the ISOLD, and the logistic regression model for lymphoma are shown in Table 4. In this study, we redefined the cut-off values for IL-10 levels, the IL10/IL6 ratio, the ISOLD values, and the regression model by the ROC curve analysis (Figure 1B). In AH, the cut-off value for IL-10 was 29.74 pg/ml, with a specificity of 91.3% and a sensitivity of 82.6% for the diagnosis of VRL. In the ISOLD model, a cut-off value of -10.115 resulted in a 95.7% sensitivity and 87% specificity. When the threshold value of the IL10/IL6 ratio was calculated using the Jorden index was 0.065, which had a sensitivity of 95.7% and a specificity of 87%. To further improve the specificity of the IL10/IL6 ratio, we set the threshold value to 0.66. Its specificity increased significantly from 87% to 95.7%, while its sensitivity decreased to 78.3%. The threshold value of the logistic regression model was -0.40229, and from 87% to 95.7%, while its sensitivity decreased to 78.3%. Furthermore, the AUC values for IL-10 levels, the ISOLD value, the IL10/IL6 ratio, as well as the logistic regression model, were 0.91, 0.953, 0.952, and 0.967, respectively.

3.5 | Correlation analysis

In 50 paired aqueous and vitreous fluids samples, the correlation analysis for IL-6 and IL-10 levels was performed using log-transformed values (Figure 2A). A significant correlation could be found between the levels of IL-6 and IL-10 in AH and VH. The IL-10 level in vitreous fluid showed a strong correlation with IL-10 in AH, \( r = 0.8506 \) (0.7460–0.9142), \( p < 0.0001 \) (Figure 2A). In addition, IL-6 in VH and IL-6 in AH also showed a strong correlation, \( r = 0.7844 \) (0.6425–0.8743), \( p < 0.0001 \) (Figure 2B).

3.6 | Assessment of the diagnostic efficacy of the model

As shown in Table 5, the logistic regression prediction model in VH had a sensitivity of 34.69%, a specificity of 100%, a positive predictive value (PPV) of 100%, and a negative predictive value (NPV) of 32.65% for the diagnosis of VRL when the probability of evaluation was higher than 99%. The sensitivity of the logistic regression model in AH for the diagnosis of VRL was 45.65%, the specificity was 100%, the PPV was 100%, and the NPV 47.92%.

4 | DISCUSSION

The low prevalence and highly nonspecific clinical presentation of VRL pose a significant challenge. Vitreous cytology remains the gold standard for its diagnosis, and despite ongoing improvements in novel cytological techniques, false negatives are still common due to the fragility, destruction, and loss of tumor cells. Additionally, vitrectomy is an invasive procedure that can result in a number of complications, including vitreoretinal traction or hemorrhage, retinal detachment, and late cataract formation. Several auxiliary tests are used to help diagnose VRL, with interleukin 6 and interleukin 10 in particular showing potential. In addition, researchers are exploring more sophisticated methods for intraocular cytokine analysis in efforts to achieve better and more consistent diagnostic performance. Recently, the ISOLD score and the logistic regression model showed high sensitivity and specificity in diagnosing PVRL.

IL-10 is a B lymphocyte growth and differentiation factor secreted by activated B cells, especially malignant B cells. Because most VRL is of B-cell origin, IL-10 levels are elevated in the VH and AH of patients with VRL compared to patients with uveitis. IL-6 is produced by a variety of cells, including T and B lymphocytes, monocytes, epithelial cells, endothelial cells, and fibroblasts known to play a pivotal role in uveitis. Cassoux et al. found 89% sensitivity and 93% specificity for IL10 >50 pg/ml in aqueous fluids and 80% sensitivity and 99% specificity for IL10 >400 pg/ml in vitreous fluids. Furthermore, some studies have also shown that the IL10/IL-6 ratio is a useful diagnostic tool, with a ratio >1 considered for the diagnosis of lymphoma; conversely, a IL10/IL-6 ratio <1 is considered for the diagnosis of uveitis. These thresholds are significantly higher than the values found in our study for both VH and AH samples. Therefore, in this study, we redefined the threshold values in accordance with the national criteria to achieve better diagnostic performance.
This is the first study in China to train and validate a logistic regression prediction model for VRL diagnosis based on IL-6 and IL-10 levels, which have high diagnostic efficacy. The AUC of AH was 96.7%, which was higher than the ISOLD score (95.3%), the IL-10/IL-6 ratio (95.2%), and IL-10 levels (91%), and the AUC of VH was 95.4%, which was consistent with the IL-10/IL-6 ratio (95.4%) with a higher sensitivity than this ratio and better than the ISOLD score (95%) and IL-10 (93%). Furthermore, we analyzed the diagnostic efficacy of the logistic regression model for VH and AH when the probability of the diagnosis of VRL was greater than 99%. If the probability was higher than 99%, the PPV and specificity were both 100% for AH or VH. Moreover, cytokine levels between AH and VH are strongly correlated. Therefore, it can be concluded that vitrectomy can be avoided as the probability of VRL is greater than 99%, when combined with its history and imaging diagnosis.

A significant limitation of this study is the small sample size and we need more data to develop a more reliable logistic regression model. Using VH, this model misclassified two VRL as uveitis, both cases had levels of IL-10 < 5 pg/ml and were the early stages of the disease process. Further, our model misclassified two uveitis as VRL, with one showing abnormally elevated IL-10 cytokine levels and a history of tuberculosis, and the other with IL-6 and IL-10 levels <5 pg/ml, which was diagnosed as early-stage vitreous amylodiosis. Using AH samples, this model misclassified three VRL as uveitis, two of which paired with VH showing IL-10 levels <5 pg/ml, and the other had an abnormal elevation of IL-6 > 10,000 pg/ml. This model also misclassified two uveitis as VRL, one of which paired with vitreous humor with a history of tuberculosis, and the other was an acute retinal necrosis syndrome. Therefore, when we suspect that a patient has VRL, we should first evaluate the cytokine model of aqueous fluid, and if extreme abnormalities in cytokines are present, we should not rely solely on the model, but should consider vitrectomy in combination with other ancillary tests to clarify the diagnosis.

### 5 CONCLUSIONS

The logistic regression prediction model developed in this study showed better diagnostic efficacy than IL-10 levels, the IL-10/IL-6 ratio, or ISOLD values, demonstrating its potential to aid in the diagnosis of VRL in the future. Second, the strong correlation of cytokines between AH and VH fluid demonstrated that AH can be used as a substitute for VH for priority factor testing and logistic regression analysis to estimate the probability of having VRL, and if the logistic regression model diagnoses VRL with a probability higher than 99%, vitrectomy can be avoided in conjunction with medical history and imaging diagnosis.

### AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Sha Tian and Kun Chen supervised the experimental work, analyzed the data, and wrote the manuscript; Jianjiang Xiao and Xian Zhou analyzed and interpreted the data; Huimin Shi, Yi Li, and Hehe Huang helped to write the manuscript; Yanchun Ma performed cytokines analysis; Bobin Chen, Qingping Wang, and Ming Guansupervised this experimental work. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

### CONFLICT OF INTEREST

As shown in Appendix S1, the authors have no relevant financial interests to disclose.

### DATA AVAILABILITY STATEMENT

Research data are not shared.

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### REFERENCES

1. Farrall AL, Smith JR. Eye involvement in primary central nervous system lymphoma. Surv Ophthalmol. 2020;65(5):548-561.
2. Karakawa A, Taoka K, Kaburaki T, et al. Clinical features and outcomes of secondary intraocular lymphoma. Br J Haematol. 2018;183(4):668-671.
3. Chan CC, Rubenstein JL, Coupland SE, et al. Primary vitreoretinal lymphoma: a report from an international primary central nervous system lymphoma collaborative group symposium. Oncologist. 2011;16(11):1589-1599.
4. Sagoo MS, Mehta H, Swamplllai AJ, et al. Primary intraocular lymphoma. Surv Ophthalmol. 2014;59(5):503-516.
5. Pe'er J, Hochberg FH, Foster CS. Clinical review: treatment of vitreoretinal lymphoma. Ocul Immunol Inflamm. 2009;17(5):299-306.
6. Grimm SA, Pulido JS, Jahnke K, et al. Primary intraocular lymphoma: an international primary central nervous system lymphoma collaborative group report. Ann Oncol. 2007;18(11):1851-1855.
7. Sobrin L, Dubovy SR, Davis JL, Murray TG. Isolated, bilateral intraocular lymphoma in a 15-year-old girl. Retina. 2005;25(3):370-373.
8. Cassoux N, Merle-Beral H, Leblond V, et al. Ocular and central nervous system lymphoma: clinical features and diagnosis. Ocul Immunol Inflamm. 2000;8(4):243-250.
9. Pichi F, Dolz-Marco R, Francis JH, et al. Advanced OCT analysis of biopsy-proven vitreoretinal lymphoma. Am J Ophthalmol. 2021;238:16-26.
10. Coupland SE, Hummel M, Müller HH, Stein H. Molecular analysis of immunoglobulin genes in primary intraocular lymphoma. Invest Ophthalmol Vis Sci. 2005;46(10):3507-3514.
11. Takase H, Arai A, Iwasaki Y, et al. Challenges in the diagnosis and management of vitreoretinal lymphoma – Clinical and basic approaches. Prog Retin Eye Res. 2022;101053.
12. Bonzheim I, Sander P, Salmerón-Villalobos J, et al. The molecular hallmarks of primary and secondary vitreoretinal lymphoma. Blood Adv. 2020;4(5):1598-1607.
13. Chan CC, Whitcup SM, Solomon D, Nussenblatt RB. Interleukin-10 in the vitreous of patients with primary intraocular lymphoma. *Am J Ophthalmol.* 1995;120(5):671-673.

14. Frenkel S, Pe’er J, Kaufman R, Maly B, Habot-Wilner Z. The importance of cytokines analysis in the diagnosis of vitreoretinal lymphoma. *Acta Ophthalmol.* 2020;98(6):e668-e673.

15. Carbonell D, Mahajan S, Chee SP, et al. Consensus recommendations for the diagnosis of vitreoretinal lymphoma. *Ocul Immunol Inflamm.* 2021;29(3):507-520.

16. Fisson S, Ouakrim H, Touitou V, et al. Cytokine profile in human eyes: contribution of a new cytokine combination for differential diagnosis between intraocular lymphoma or uveitis. *PLoS One.* 2013;8(2):e52385.

17. Kimura K, Usui Y, Goto H. Clinical features and diagnostic significance of the intraocular fluid of 217 patients with intraocular lymphoma. *Jpn J Ophthalmol.* 2012;56(4):383-389.

18. Costopoulos M, Touitou V, Golmard JL, et al. ISOLD: a new highly sensitive interleukin score for intraocular lymphoma diagnosis. *Ophthalmology.* 2016;123(7):1626-1628.

19. Kuo DE, Wei MM, Knickelbein JE, et al. Logistic regression classification of primary vitreoretinal lymphoma versus uveitis by interleukin 6 and interleukin 10 levels. *Ophthalmology.* 2020;127(7):956-962.

20. Rodriguez EF, Sepah YJ, Jang HS, Ibrahim M, Nguyen QD, Rodriguez FJ. Cytologic features in vitreous preparations of patients with suspicion of intraocular lymphoma. *Diagn Cytopathol.* 2014;42(1):37-44.

21. Gupta OP, Weichel ED, Regillo CD, et al. Postoperative complications associated with 25-gauge pars plana vitrectomy. *Ophthalmic Surg Lasers Imaging.* 2007;38(4):270-275.

22. Khatri VP, Caligiuri MA. A review of the association between interleukin-10 and human B-cell malignancies. *Cancer Immunol Immunother.* 1998;46(5):239-244.

23. Ohta K, Sano K, Imai H, Kikuchi T. Cytokine and molecular analyses of intraocular lymphoma. *Ocul Immunol Inflamm.* 2009;17(3):142-147.

24. Cassoux N, Merle-Beral H, Lehoang P, Herbort C, Chan CC. Interleukin-10 and intraocular-central nervous system lymphoma. *Ophthalmology.* 2001;108(3):426-427.

25. Merle-Béral H, Davi F, Cassoux N, et al. Biological diagnosis of primary intraocular lymphoma. *Br J Haematol.* 2004;124(4):469-473.

26. Matas J, Llorenç V, Fonollosa A, et al. Systemic regulatory T cells and IL-6 as prognostic factors for anatomical improvement of Uveitic macular edema. *Front Immunol.* 2020;11:579005.

27. Cassoux N, Giron A, Bodaghi B, et al. IL-10 measurement in aqueous humor for screening patients with suspicion of primary intraocular lymphoma. *Invest Ophthalmol Vis Sci.* 2007;48(7):3253-3259.

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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