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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

Sha Tian and Kun Chen have contributed equally to this work and share first authorship.

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.[1] SIOL may derive from systemic non-Hodgkin's lymphoma that metastasizes to the eyes.[2] 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.[3]

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% to 34% of VRL patients have concurrent PCNSL.[3] 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.[4,5] VRL usually occurs in adults between the ages of 24 and 85, with a median age of 63.[6] VRL can also be diagnosed in young people under the age of 16 years.[7] 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[3] 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).[6,8]

In recent years, ophthalmic imaging techniques, such as optical coherence tomography (OCT)[9] 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),[10] myeloid differentiation factor 88 (MYD88)-L265P mutation,[11] and PCNSL-based next-generation sequencing[12] 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.[13] Several subsequent studies have also reported successful differentiation between lymphoma and uveitis using IL-10 and IL-10/IL-6 ratios.[14,15] 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.[16] In contrast, low levels of IL-10 or IL-10/IL-6 ratios <1 do not necessarily exclude the diagnosis of lymphoma.[17] To improve the diagnostic efficacy of cytokines, Costopoulos et al.[18] 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.[19] 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: $-12.871+5.533^* \log([\text{IL-10}]+1) - 1.614\ ^*\log([\text{IL-6}]+1)$ for AH and $-12.208+4.648^* \log([\text{IL-10}]+1) - 1.669^* \log([\text{IL-6}]+1)$ 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–Wilk 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

p-value < 0.05 was considered statistically significant. Moreover, a logistic regression with IL-6 and IL-10 by binary logistic regression analysis using SPSS was used to classify uveitis and VRL and to estimate the probability of VRL. The Hosmer-Lemeshow test with $p > 0.05$ was considered a good fit by logistic regression analysis.

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 ± 10.15 years. Among the VH samples, there were 24 males and 25 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 andsix 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*log (IL-10 + 1) − 1.879*log (IL-6 + 1) and from this, the probability of PVRL occurrence was 1/(1 + EXP logistic (VH)). The equation for aqueous fluid was logistic (AH) = −0.273 + 3.85*log (IL-10 + 1)-1.969*log (IL-6 + 1) and the probability was 1/(1 + EXP logistic (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 [40.34–957.3] pg/ml) were higher than VRL (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, $p < 0.0001$). The IL-10/IL-6 ratios of patients with VRL (7.16 [2.38–22.26]) were significantly higher compared to patients with uveitis (0.04 [0.0025–0.17], $p < 0.0001$). 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], $p < 0.0001$).

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

3.3.2 | Diagnostic evaluation of the efficacy of intraocular lymphoma

The efficacy of vitreous IL-10 levels, the IL-10/IL-6 ratio, and ISOLD and the logistic regression model in diagnosis for lymphoma are shown in Table 4. We redefined the cut-off values for the IL-10 levels, the IL-10/IL-6 ratio, and ISOLD score bases on the ROC curve analysis (Figure1A). In VH, the cut-off value of IL-10 obtained from the ROC curve analysis was 26.275 pg/ml, with a specificity of 93.7% and a sensitivity of 89.8% for the diagnosis of VRL. The ISOLD cut-off value was −9.97, with a sensitivity of 95.9% and a specificity of 93.7%. Based on the cut-off value of the IL-10/IL-6 ratio of 0.885, the diagnosis of VRL had a sensitivity of 91.8% and a specificity of 93.7%. Furthermore, when the logistic regression cut-off value was 0.5015, the sensitivity was 95.9% and the specificity was 93.7%. The AUC values of IL-10, the IL10/IL6 ratio, the ISOLD, and the logistic regression model were 0.93, 0.954, 0.95, and 0.954, respectively.

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 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 VRL (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,

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	0.0059	<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	0.0161	<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		0.66	0.783	0.957				
	ISOLD	−10.115	0.957	0.87	0.953	0.027	0.9	1
	Logistic	−0.40229	1	0.87	0.967	0.023	0.922	1

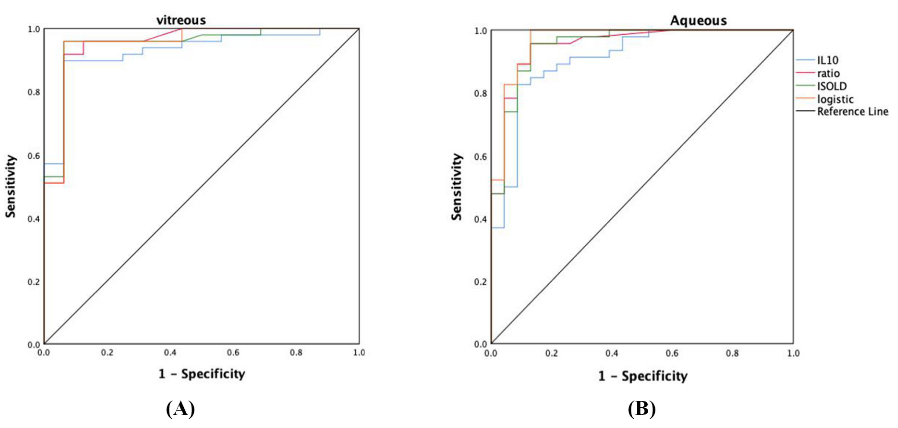

FIGURE 1 ROC curves of various indicators for diagnosis VRL. (A) showed ROC curves of various indicators in vitreous humor, and (B) represented in aqueous humors. The blue line stands for IL-10, the red line indicates the IL10/IL6 ratio, the green line represents the ISOLD score, and the orange line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

$p < 0.0001$). 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], $p < 0.0001$).

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 IL-10/IL-6 ratio, the ISOLD values, and the regression model by the ROC curve analysis (Figure1B). 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 IL-10/IL-6 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 IL-10/IL-6 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 the sensitivity to diagnosing VRL was 100% and the specificity was 87%. 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 (Figure2). 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 cytopathology 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.[17,20] 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.[21] 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[18] and the logistic regression model[19] 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.[22] 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.[23–25] 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.[26] Cassoux et al.[27] found 89% sensitivity and 93% specificity for IL-10 >50 pg/ml in aqueous fluids and 80% sensitivity and 99% specificity for IL-10 > 400 pg/ml in vitreous fluids. Furthermore, some studies have also shown that the IL-10/IL-6 ratio is a useful diagnostic tool, with a ratio >1 considered for the diagnosis of lymphoma; conversely, a IL-10/IL-6 ratio <1 is considered for the diagnosis of uveitis.[17,23] 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.

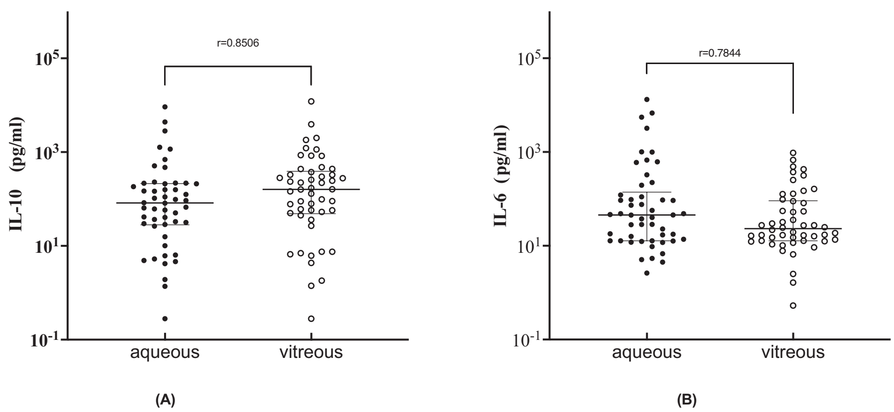

FIGURE 2 Correlation of IL-6 and IL-10 in aqueous humors (A)with IL-6 and IL-10 in vitreous fluids (B).IL-6 and IL-10 levels were performed using log-transformed values. r value denotes the correlation coefficient.

TABLE 5 Evaluation of the diagnostic efficacy of a logistic regression model for VH and AH at $p > 99\%$

	Sensitivity	Specificity	PPV	NPV
Vitreous	34.69%	100%	100%	32.65%
Aqueous	45.65%	100%	100%	47.92%

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 amyloidosis. 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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SUPPORTING INFORMATION

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

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