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Clinical characteristics and outcomes of acute retinal necrosis at different stages: a retrospective study

Haoli Fu[1], Qingqin Tao[1], Fuhua Yang[1] and Xiaomin Zhang[1*]

Abstract

Background To examine the clinical features and treatment outcomes of patients with acute retinal necrosis (ARN) at different disease stages and identify the risk factors associated with a poor prognosis.

Methods This retrospective study included 39 patients (44 eyes) with ARN who were treated at a single center. The eyes were divided into three stages based on the ocular findings and clinical course at the initial diagnosis. The main outcome measures were the incidence of retinal detachment (RD) and final visual acuity (VA). Regression analyses were performed to investigate the risk factors associated with the main outcomes.

Results Nine, 10, and 25 eyes were in the early, middle, and late stages, respectively. Eyes in the early stage had the shortest symptom duration ($P=0.019$). At the first visit, the intraocular pressure (IOP) was elevated in half the patients; 29 eyes (65.9%) had keratic precipitates (KPs) and five (11.6%) had iris nodules. The final VA improved in early-stage eyes ($P=0.008$) and decreased in late-stage eyes ($P=0.004$) after treatment. RD was not common with early diagnosis. Five (50%) and 17 (68%) eyes in the middle and late stages developed RD, respectively. Independent predictors of RD included the vitritis grade ($P=0.046$) and clock hours of retinitis ($P=0.045$). Initial VA at presentation ($\beta=0.291$, $P=0.009$), the occurrence of RD ($\beta=0.209$, $P=0.033$), and clock hours of retinitis ($\beta=0.323$, $P=0.008$) were identified as associated with final VA.

Conclusion Early diagnosis and treatment are associated with positive clinical outcomes. Anterior segment signs (e.g., mildly or moderately elevated IOP, KPs, and iris nodules) are important for early diagnosis.

Keywords Early diagnosis, Retinal detachment, Acute retinal necrosis, Ocular characteristics, Visual acuity

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Introduction

Acute retinal necrosis (ARN) is an infectious retinitis characterized by peripheral retinal arteritis and necrotizing retinitis which eventually progresses to retinal detachment (RD) [1]. In the UK, the annual incidence of ARN is estimated to be between 0.5 and 0.63 new cases per million population [2, 3]. ARN is caused by infection with viruses belonging to the herpes virus family and mainly occurs in immunocompetent patients [2–4]. The Executive Committee of the American Uveitis Association proposed a standardized diagnostic reference in 1994 based on clinical characteristics [5]. Currently, there is no standard protocol treatment for ARN; the mainstay of treatment is a combination of systemic and intravitreal antivirals [6–8]. Some researchers have suggested that prophylactic laser photocoagulation and pars plana vitrectomy (PPV) may prevent RD [9, 10]; however, the efficacy remains controversial.

The overall clinical prognosis of ARN is poor after antiviral therapy [3, 11, 12]. However, most studies have reported that ARN is fulminant and has a poor therapeutic response mainly because many patients have more advanced disease at the time of diagnosis [13, 14]. The Japanese ARN Study Group proposed that early diagnosis and early initiation of antiviral therapy are associated with improved prognosis [13]. The group developed new diagnostic criteria in 2015, which included early stage ocular findings—especially anterior segment manifestations—and the clinical course of ARN [13, 15]. We also observed in clinical practice that patients with ARN who are diagnosed early have limited lesions and positive clinical outcomes. Nevertheless, few studies have examined cases diagnosed early [16]. Further, although several studies have investigated the clinical characteristics and outcomes of ARN [15, 17, 18], most did not stratify the patients by clinical severity. Hence, the role of early diagnosis and characteristic early features remain unclear. Therefore, to identify representative ocular presentations of ARN and determine whether early diagnosis leads to a better clinical prognosis, it is necessary to analyze the clinical characteristics and outcomes of different disease courses.

In this retrospective study, we stratified eyes with ARN based on the disease course at presentation and analyzed the clinical manifestations and outcomes after treatment. The risk factors related to poor outcomes were also examined.

Materials and methods

Inclusion criteria and data collection

We retrospectively reviewed the medical records of patients with ARN who visited and were treated at Tianjin Medical University Eye Hospital (TMUEH) between August 2013 and August 2023. All patients satisfied the criteria for ARN defined by the American Uveitis Association and were followed up with for at least 3 months. The causative viral agent was identified using a polymerase chain reaction (PCR) assay of the aqueous humor. Patients with no or negative PCR results but met the diagnostic criteria for ARN were also included in the analysis. In cases of bilateral ARN, both eyes were included in the study. Ethical approval for this study was granted by the TMUEH. All patients were informed that their participation was voluntary and informed consent was obtained.

At our institution, patients were treated in the Ocular Immunology and Retina Department. Medical records were reviewed to collect the following data: demographic characteristics (age and sex), immune status (immunocompetent or immunosuppressed due to glucocorticoid use, pre-existing immunologic condition, or ongoing chemotherapy in patients with cancer or a history of diabetic mellitus), intraocular pressure (IOP), ocular symptoms and signs at presentation, duration of symptoms, extent of retinitis (graded by the number of total clock-hours of involvement [through the center of the fovea]), involved zone (I, II, and III), medical and surgical therapies used, length of follow-up, visual acuity (VA) at presentation and at the final visit, and the occurrence of RD. We derived estimates of the extent and involved zones of retinitis from fundus photography if they had not been documented in the medical records. All patients who first consulted the Ocular Immunology Department had complete data on intraocular inflammation levels. Zone I was defined as the area within 1500 μm of the optic nerve or within 3000 μm of the fovea; zone II included the area extending from zone I to the equator; and zone III included the area anterior to the equator [19].

Staging system of ARN based on the clinical course

Based on the vitritis grade, extent of the retina involved, and typical characteristics of spread, we roughly divided ARN into three stages based on previously reported methods [13, 20, 21]: (1) early stage: KPs (Fig. 1A) and Koeppe nodules (Fig. 1B). The vitreous haze grading is typically 0–1. Isolated yellow-white granular or patchy lesions and surrounding retinal vasculitis in the peripheral retina can be found via fundus examination or photography (Fig. 1C, D). Retinal lesions may be confluent but involving less than three clock hours; (2) middle stage: vitreous haze grade increases to 2 or 3. The retinal lesions involve more than three clock hours (Fig. 1E, F); and (3) late stage: vitreous haze is usually severe and grade 4. Retinal lesions expand circumferentially (usually ≥ six clock-hours) and central vascular sheathing of the arteries can be easily seen (Fig. 1G, H). Many large breaks develop due to vitreous traction and thinning of

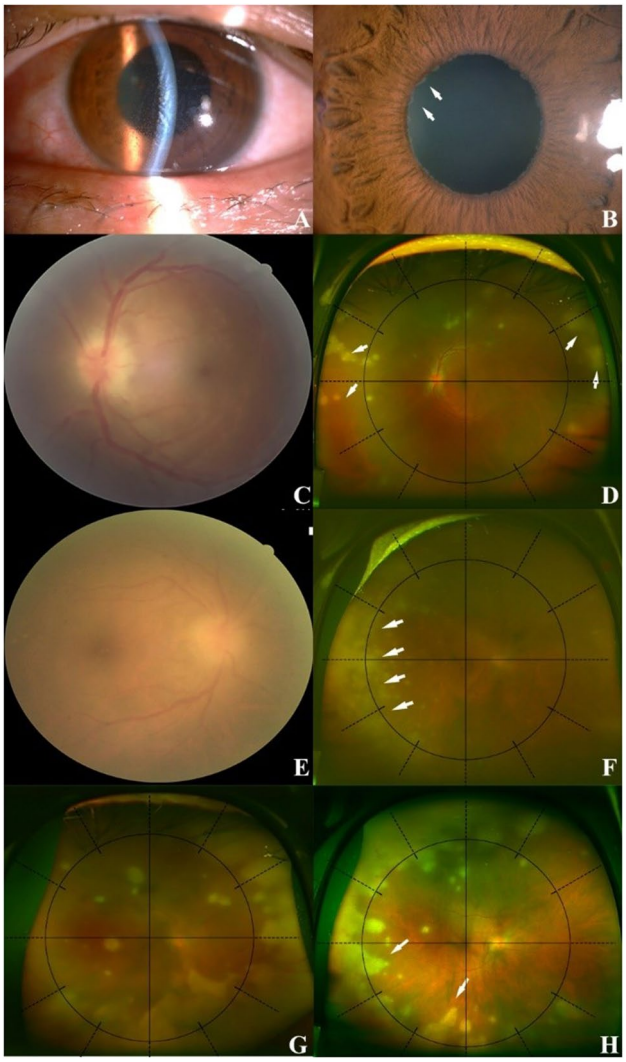

Fig. 1 Representative images showing the clinical characteristics of patients with ARN. **(A)** Mutton-fat (flattened-form) KPs were observed in patients with ARN at the first visit; **(B)** Fluffy white iris nodules were found in a 35-year-old male; he had blurred vision and a red eye for 7 days and his right eye was diagnosed with ARN; **C**, **D)** A 32-year-old male patient with early stage ARN (symptom duration from diagnosis = 10 days). The vitreous haze grading was 1 and scattered yellow-white patchy lesions (arrows) could be seen in the periphery retina. **E**, **F)** A 67-year-old female patient with middle stage ARN (symptom duration from diagnosis = 13 days). The vitreous haze grading was 3 and granular lesions begin to merge and involve nearly four clock-hours; **G)** A 59-year-old male patient with late stage ARN (symptom duration from the first visit = 16 days). The vitreous haze grading was 4 and retinitis diffused to zone II; **H)** A 63-year-old male patient with late stage ARN (symptom duration from the first visit = 15 days). The fan-shaped retinal lesions (arrows) expanded circumferentially and involved more than 6 clock hours. * The clock-hours of involvement are represented by the black line in the figure. ARN, acute retinal necrosis; KPs, keratic precipitates

the retina, resulting in rhegmatogenous retinal detachment (RRD).

Treatment regimen

All patients with ARN were initially treated with systemic antiviral agents after diagnosis: intravenous ganciclovir (5 mg/kg every 12 h) for 10–21 days followed by oral valacyclovir and intravitreal ganciclovir (2–4 mg/0.1 ml) injections (the number of injections varied depending on the patient's response and clinical improvement). Systemic corticosteroids (oral prednisolone 0.5–1 mg/kg/day) were prescribed to most patients (the decision of whether to treat with oral corticosteroids was dependent on the treating physician's particular practice). Routine surgery involved 25-gauge PPV and silicone oil tamponade was performed in the presence of RD. Prophylactic PPV was usually performed when severe vitritis or retinitis did not improve after systemic and intravitreal antiviral therapy, but in the absence of RD.

Statistical analysis

Statistical analysis was conducted using SPSS software version 26.0 (SPSS Inc., Chicago, Illinois, USA). VA was converted to the logarithm of the minimum angle of resolution (logMAR) for statistical analysis. Non-numerical vision was assigned logMAR scores of 1.70, 2.00, 2.30, and 3.00 for counting fingers, hand movements, perception of light acuity, and no perception of light, respectively [21–23]. The clinical data are presented as numerical, categorical, or ordinal data. Since the numerical data were not normally distributed, nonparametric tests including the Chi-square test, Kruskal–Wallis test, Wilcoxon test, and Mann–Whitney U test were used. To compare the clinical outcomes and selected potential factors, the Chi-square test and Spearman correlation coefficient (r) were used. Multiple logistic regression analysis was used to ascertain the effects of the selected clinical or therapeutic factors. The log-rank test was used to evaluate the differences in the risk of RD over time between subgroups, and the Kaplan–Meier survival estimates were plotted. The data are shown as mean ± standard deviation unless otherwise noted. The level of significance was set at $P < 0.05$.

Results

Demographic and clinical characteristics of the patients

A total of 44 eyes of 39 patients (24 males and 15 females) with ARN were included in the analysis, and 23 of the patients (25 eyes) first consulted with the Ocular Immunology Department. The demographic information and basic clinical characteristics of the patients are summarized in Table 1.

The mean age at presentation was 51.8 ± 2.8 years and 61.5% of the eyes belonged to males (Fig. 2). None of the

Table 1 Clinical characteristics of 44 eyes of 39 patients with acute retinal necrosis at presentation for both the total cohort and subgroups of different clinical stages

Characteristic	Total	Early stage	Middle stage	Late stage	*P*-value
Number of eyes	44	9	10	25	-
Male	24 (61.5)	7 (77.8)	4 (40)	17 (68)	0.207
Laterality, right	23 (52.3)	4 (44.4)	7 (70)	12 (48)	0.509
Age[a]	51.8 ± 2.8	42.6 ± 7.2	49.4 ± 6.3	55.3 ± 3.3	0.307
Duration of symptoms (days) [b]	14.8 ± 2.1	9.2 ± 1.9	12.2 ± 3.2	17.9 ± 3.2	0.019
Topical corticosteroids before initial visit	26(59.1)	2(22.2)	8(80)	16(64)	0.063
Bilateral involvement	5 (12.8)	-	-	-	-
Identifiable viral cause					1.000
HSV	2 (4.5)	1 (11.1)	1 (10)	0 (0)	
VZV	19 (43.2)	6 (66.7)	6 (60)	7 (28)	
NA	23 (52.3)	2 (22.2)	3 (30)	18 (72)	
IOP at presentation, mmHg[a]	22.1 ± 1.7	17.9 ± 2.1	30.5 ± 4.9	19.9 ± 1.6	0.08
> 21 mmHg	22 (50)	3 (33.3)	8 (80)	11 (44)	0.09
Intraocular inflammation					
AC cells					0.746
0–1+	13 (29.5)	4 (44.4)	2 (20)	7 (28)	
2–3+	13 (29.5)	3 (33.3)	5 (50)	6 (24)	
4+	0 (0)	0 (0)	0 (0)	0 (0)	
NA	18 (41)	2 (22.3)	4 (40)	12 (48)	
KPs	29 (65.9)	6 (66.7)	7 (70)	16 (64)	0.944
Iris nodules	5 (11.4)	2 (22.2)	1 (10)	2 (8)	0.476
Vitritis grade					0.001
0–1+	2 (4.5)	2 (22.2)	0	0	
2–3+	28 (63.6)	5 (77.8)	9 (90)	12 (48)	
4+	14 (31.9)	0 (0)	1 (10)	13 (52)	
Clock hours of retinitis[a]	5.6 ± 0.5	1.9 ± 0.3	3.6 ± 0.4	7.8 ± 0.4	< 0.001
Zone involved					< 0.001
Zone III	5 (11.4)	0 (0)	1 (10)	4 (16)	
Zone II	17 (38.6)	0 (0)	2 (20)	15 (60)	
Zone III	22 (50)	9 (100)	7 (70)	6 (24)	
Initial visual acuity, logMAR[a]	1.02 ± 0.09	0.78 ± 0.16	0.71 ± 0.15	1.22 ± 0.12	0.035
Initial visual acuity, categories					0.001
> 20/50	4 (9.1)	2 (22.2)	1 (10)	1 (4)	
20/50 to > 20/200	21 (47.7)	6 (66.6)	8 (80)	7 (28)	
20/200 or worse	19 (43.2)	1 (11.1)	1 (10)	17 (68)	
Final visual acuity, logMAR[a]	1.07 ± 0.13	0.17 ± 0.08	0.52 ± 0.24	1.61 ± 0.12	< 0.001
Follow-up duration, months[a]	13.1 ± 2.6	9.5 ± 2.6	15.7 ± 4.9	13.2 ± 4.0	0.425
Treatment regimen					
Systemic antiviral therapy	44 (100)		10 (100)	25 (100)	-
Ganciclovir injections[b]	3 (4)	9 (100)	6 (6)	3 (4)	0.004
Oral corticosteroids	34 (77.3)	3 (2)	5 (50)	21 (84)	0.08
Routine PPV	20 (45.5)	8 (88.9)	5 (50)	14 (68)	0.007
Prophylactic PPV	6 (13.6)	1 (12.5)	0 (0)	6 (24)	0.084
Complicated with retinal detachment	23 (52.3)	1 (12.5)	5 (50)	17 (68)	0.014
Duration from first visit until RD (days)[a]	82 ± 13	149	109 ± 43	65 ± 12	0.366

Abbreviations: IOP, intraocular pressure; VZV, varicella zoster virus; HSV, herpes simplex virus; logMAR, logarithm of the minimal angle of resolution; PPV, pars plana vitrectomy; RD, retinal detachment; NA, not available

Data are given as number (%) unless otherwise stated

[a] Data are given as mean ± standard deviation

[b] Data are given as median (interquartile range)

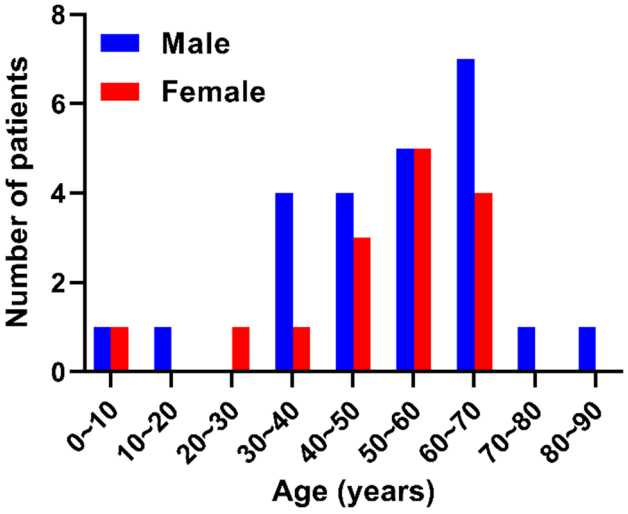

Fig. 2 Age and sex distributions of patients with acute retinal necrosis

patients were immunodeficient. Among the 39 patients, three (7.7%) exhibited bilateral ARN at first presentation, and two (5.1%) cases had delayed occurrence of ARN in the fellow eye after two months or 1 year. The mean symptom duration before diagnosis was 14.8 ± 2.1 days, and 59.1% of patients had already used topical corticosteroids before the initial visit. Twenty-two (50%) eyes had an elevated IOP (≥ 21 mmHg). The mean initial VA was 1.02 ± 0.09 logMAR. Twenty-nine eyes (65.9%) presented with KPs at the first visit. Five eyes (11.6%) had iris nodules and four out of five eyes exhibited a fluffy appearance. Thirteen eyes had anterior chamber (AC) cell grading values of 0–1+; 12 eyes had a grade of 2–3+; and none of the eyes had a grade of 4+. Vitritis grades 0–1 were detected in two eyes; grades 2–3 were detected in 28 eyes; and grade 4 was detected in 14 eyes. The mean number of clock hours of retinitis was 5.6 ± 3.1. The zones at presentation were zones I (11.4%, $n = 5$), II (38.6%, $n = 17$), and III (50%, $n = 22$). Based on the aqueous PCR results, the etiologies included varicella zoster virus (VZV) in 19 eyes (90.5%) and herpes simplex virus (HSV) in two eyes (9.5%). The mean follow-up duration was 13.1 months, with a minimum follow up time of 3 months and a maximum of 7.9 years.

Antiviral treatment and the outcomes of the total cohort

Ganciclovir was administered to all patients at a dosage of 5 mg/kg intravenously two times a day and continued for 10–21 days. The treatment was then followed by oral valacyclovir for 3–4 weeks. Intravitreal ganciclovir or foscarnet were administered with a median of three injections per eye. Systemic corticosteroids were administered to 34 patients (77.3%). Routine PPV was performed in 20 eyes (45.5%) within a few days after the occurrence of RD. Prophylactic vitrectomy was conducted in six eyes (13.6%, all eyes were initially at the late stage) after a mean of 16.7 days, with a range of 2–43 days after diagnosis.

Table 2 Univariate analysis of the clinical characteristics and therapeutic factors associated with RD in 44 eyes with acute retinal necrosis

Characteristic	Complicated with RD		*P*-value
	Yes ($N = 23$)	No ($N = 21$)	
Age	52.3 ± 4.3	51.2 ± 3.4	0.86
Male/Female	13/10	15/6	0.31
Duration from first visit	16.8 ± 3.6	12.7 ± 1.7	0.36
Identifiable viral cause			
HSV	2 (8.7)	0 (0)	
VZV	9 (39.1)	10 (47.6)	
NA	12 (52.2)	11 (52.4)	
Intraocular inflammation			
AC cells			0.22
0–1+	5 (21.7)	8 (38.1)	
2–3+	6 (26.1)	7 (33.3)	
4+	0 (0)	0 (0)	
NA	12 (52.2)	6 (28.6)	
KPs	14 (60.9)	15 (71.4)	0.34
Iris nodules	1 (4.3)	4 (19)	0.18
Vitritis grade			0.039
0–1+	0 (0)	2 (9.5)	
2–3+	13 (56.5)	15 (71.4)	
4+	4 (43.5)	4 (19)	
Clock hours of retinitis	6.5 ± 0.5	4.7 ± 0.7	0.036
Zone involved			0.21
Zone I	3 (13)	2 (9.5)	
Zone II	11 (47.8)	6 (28.6)	
Zone III	9 (39.2)	13 (61.9)	
Stages at presentation			0.04
Early	1 (4.3)	8 (38.1)	
Middle	5 (21.7)	5 (23.8)	
Late	17 (74.0)	18 (38.1)	
Initial visual acuity	1.17 ± 0.13	0.85 ± 0.12	0.046
Final visual acuity	1.4 ± 0.4	0.67 ± 0.19	0.002
Treatment regimen			
Ganciclovir injections	3 (3)	3 (5)	0.57
Oral corticosteroids	16 (69.6)	18 (85.7)	0.29
Prophylactic PPV	3 (13)	3 (14.3)	0.34

VZV, varicella zoster virus; HSV, herpes simplex virus; PPV, pars plana vitrectomy; RD, retinal detachment; NA, not available; logMAR, logarithm of the minimal angle of resolution

The mean final VA was 1.07 ± 0.13 logMAR. Eyes with ARN that developed RD had a worse final best corrected VA (Table 2). Of the 20 eyes that underwent routine vitrectomy, two (10%) had a VA better than 20/50 at the last follow-up, four (20%) had a VA of 20/50–20/200, and 14 (70%) had a VA of 20/200 or worse. Of the six eyes that underwent prophylactic vitrectomy, five (83.3%) had a final VA worse than 20/200, and one eye had a VA of 20/63 at the final visit.

In a cohort of 44 eyes with ARN, 23 (52.3%) developed RD. One patient presented with RD at the first visit. RD

was observed in 22 eyes during the follow-up period, occurring at a mean of 82 days (range 8–223 days) after diagnosis.

Comparison of the baseline characteristics between different stages

Of the 44 eyes, there were nine eyes in the early stage, 10 in the middle stage, and 25 in the late stage at the first visit, according to our staging system (Table 1). Age, sex and causative viral agent did not differ between the groups. Eyes in the early stage had the shortest symptom duration ($P=0.019$) and the mildest vitritis ($P=0.001$). Of the eyes, 33.3%, 70%, and 44% in the early, middle, and late stages showed IOP elevation (>21 mmHg), respectively. The late-stage eyes had the worst initial VA ($P=0.035$). The clock hours of retinitis and zone of retinal involvement differed significantly among the three groups (both $P<0.01$). Regarding antiviral treatment, the middle-stage eyes received more intravitreal antiviral injections ($P=0.004$). There was a weak correlation between the duration of symptoms and clock hours of retinitis ($r=0.316$, $P=0.037$).

Comparison of the therapeutic outcomes between different stages

The mean final VA differed significantly between subgroups ($P<0.001$, Table 1). The worst visual outcome was observed in the late-stage group (20/200 or worse in 84%), with a mean final VA of 1.61 ± 0.12. The best final VA was seen in the early-stage group (better than 20/50 in 88.9%, with a mean of 0.17 ± 0.08 logMAR), and most eyes recovered to their pre-onset condition. In the middle-stage eyes, five (50%) had a final VA better than 20/50, three (30%) had a final VA of 20/50 to 20/200, and two (20%) had a final VA of 20/200 or worse. In addition, the mean final VA significantly improved in early stage eyes ($P=0.008$) and significantly decreased in late-stage eyes ($P=0.004$) after antiviral treatment (Fig. 3). The final VA slightly improved in the middle-stage eyes, although the difference was not significant ($P=0.307$).

Of the early stage eyes, only one patient (age 4 years) had RD and underwent vitrectomy several times due to proliferative vitreoretinopathy (PVR). Five eyes (50%) in the middle stage and 17 (68%) in the late stage developed RD. Survival analyses illustrated the timeline for RD development at the different stages (Fig. 4). Of the six late-stage eyes that underwent prophylactic vitrectomy, three (50%) had recurrent RD. Among them, two eyes detached again before the removal of silicone oil and one eye detached after the removal of silicone oil due to PVR. In these cases, silicone oil tamponade surgery was performed a second time and all eyes had a reattached retina at the final visit. Overall, the prophylactic PPV group showed no difference in the RD rate compared with the routine antiviral group ($P=0.33$, Fig. 5).

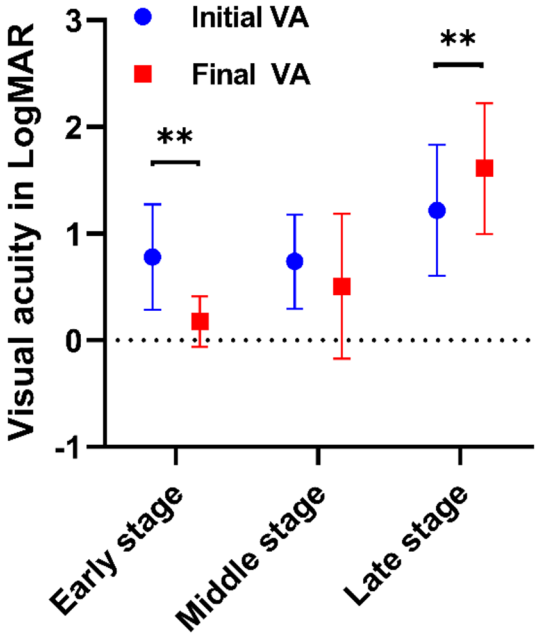

Fig. 3 LogMAR VA at presentation and at last follow-up of the involved eyes at different stages. VA, visual acuity

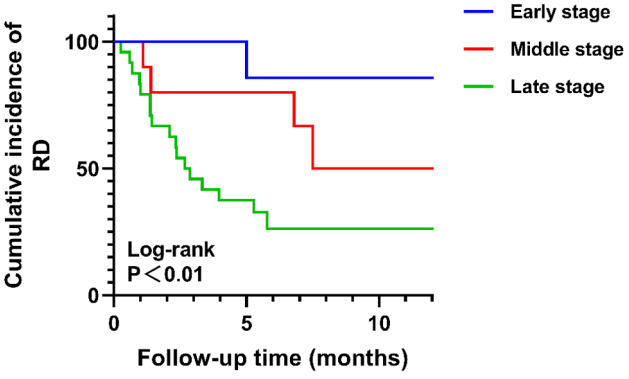

Fig. 4 Kaplan–Meier graph showing the cumulative incidence of RD in different stage eyes after antiviral treatment. RD, retinal detachment

Prognostic factors associated with RD and final VA

To account for the effects of select clinical factors, we assessed the potential clinical factors contributing to RD and the final VA outcome. Patients were divided into two groups based on the occurrence of RD. Univariate analyses showed that a vitritis grade > 3 was associated with an increased risk of RD ($P=0.039$) (Table 2). Worse initial VA demonstrated borderline significance for RD ($P=0.046$). More clock hours of necrotic retinitis were significantly related to a higher RD rate ($P=0.036$). Eyes at an earlier stage at diagnosis had a significantly lower RD rate ($P=0.004$). A logistic regression model that included possible clinical variables detected in the

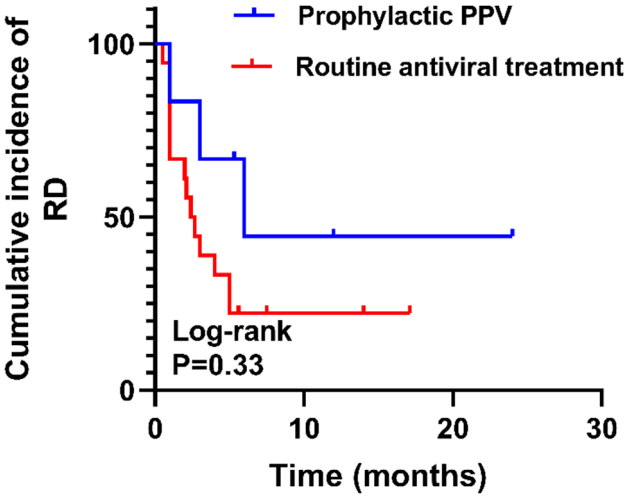

Fig. 5 Kaplan–Meier survival estimate of the incidence of RD in late-stage diagnosed eyes, stratified by whether prophylactic PPV was performed. There is no difference in the risk of RD between the prophylactic PPV group and the routine antiviral treatment group ($P = 0.33$, log-rank test). RD, retinal detachment; PPV, pars plana vitrectomy

univariate analysis was developed (Fig. 6). In this model, the vitritis grade (odds ratio [OR], 3.630; 95% confidence interval [CI], 1.025–12.855; $P = 0.046$) and clock hours of retinitis (OR, 1.235; 95% CI, 1.015–1.533; $P = 0.045$) at presentation showed statistical significance for the risk of RD. Owing to the high correlation between different disease stages and other clinical characteristics, these were included separately in the regression analysis. The results showed that the RD rate in early-stage eyes was nearly 17 times lower than that in late-stage eyes (OR, 0.059; 95% CI, 0.006–0.554; $P = 0.013$).

The relationships between the clinical characteristics and final VA are listed in Table 3. The VA (logMAR) at the last follow-up was evaluated using a stepwise multivariate regression model. The variables that remained independently associated with VA (logMAR) at the last follow-up were the initial VA at presentation (β = 0.291, $P = 0.009$), the occurrence of RD (β = 0.209, $P = 0.033$), and the clock hours of retinitis (β = 0.323, $P = 0.008$).

Table 3 Relationship between the clinical characteristics and final VA

Characteristic	VA (logMAR) at the last follow-up	
	r	*P*-value
Age, years	0.327	0.030
Male/Female	0.039	0.800
Duration from first visit	0.273	0.073
IOP at presentation	-0.181	0.252
Intraocular inflammation		
AC cells	-0.299	0.049
KPs	0.067	0.665
Iris nodules	-0.282	0.055
Vitritis grade	0.527	0.001
Clock hours of retinitis	0.689	< 0.001
Zone involved	-0.691	< 0.001
Initial VA	0.498	0.001
Complicated with RD	0.478	0.001

VA, visual acuity; IOP, intraocular pressure; RD, retinal detachment

Discussion

Our study demonstrated that patients with ARN had significantly improved VA and a low RD rate with early diagnosis. In addition, we found that 50%, 65.9%, 11.6% of eyes had an elevated IOP, KPs, and iris nodules at presentation, respectively. These findings suggest that the signs in the anterior segment, except the fundus findings, were important for early diagnosis. We also found that the vitritis grade and clock hours of necrotic retinitis were associated with RD. Initial VA at presentation, clock hours of retinitis, and RD occurrence during the follow-up period were associated with the final VA.

ARN is a fulminant eye disease that progresses rapidly, and early diagnosis is of great significance. In our study, we found that the duration of symptoms before the first visit differed significantly among subgroups.

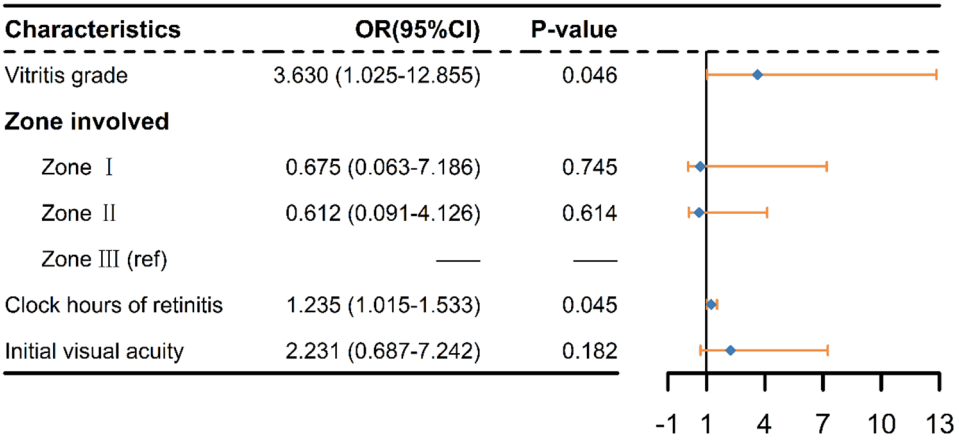

Fig. 6 Logistic regression analysis of prognostic factors related to retinal detachment. OR, odds ratio; CI, confidence interval

Short symptom duration was associated with mild disease severity and positive clinical outcomes. Of note, we initially observed mild-to-moderate elevation of IOP in half of the eyes and prominent anterior chamber inflammation, even before the retinal lesions were noticed. The Japanese ARN Study Group proposed that anterior chamber cells or mutton-fat KPs and elevated IOP are early stage ocular findings in ARN and emphasized their significance in early diagnosis [13, 15]. Our results showed that 65.9% of patients with ARN had KPs at the first visit. Importantly, 59.1% of our patients had already been prescribed topical corticosteroids elsewhere before visiting our hospital due to inflammatory response in the anterior segment of the eye, which may alleviate anterior segment inflammation and result in the disappearance of KPs. Therefore, we may have underestimated the prevalence of KPs in our study. In addition, we found that some patients had fluffy-appearing Koeppe nodules, which were previously reported in infectious uveitis [24, 25]. Together, these findings suggest that an elevated IOP, KPs, and iris nodules could be significant anterior segment signs of ARN, and further detailed fundus examinations, especially peripheral retinal examination, are needed. In addition, ultrawide-field imaging allows clear documentation of peripheral retinal lesions even under obvious media opacity, which also facilitates the early diagnosis of ARN [20].

With the development of biological technology, PCR analysis has become widely accessible to confirm the diagnosis of ARN and identify the causative virus. However, the sensitivity of PCR varies among different studies and many factors can influence PCR results [26]. Recently, a case of ARN with a negative PCR result in the aqueous humor in the very early stage due to the low aqueous virus DNA load was reported [27]. In 1994, the American Uveitis Society emphasized that PCR testing was not required to initiate treatment [5]. This principle was upheld in 2021 by the Standardization of Uveitis Nomenclature working group, which advised that treatment should be initiated based on the clinical characteristics, even with negative PCR results [28]. The Japanese ARN Study Group developed new diagnostic criteria for ARN in 2015 [13]. The new criteria do not require all five late-stage characteristics to be met; rather, more early-stage ocular signs are included, and a diagnosis of "virus-unconfirmed ARN" can be made without positive PCR results, which could assist in early diagnosis. Therefore, antiviral treatment could be initiated before PCR testing of intraocular samples if a diagnosis can be made based on the clinical manifestations.

In our study, 90.5% of the patients who underwent aqueous humor PCR testing had VZV-positive ARN. Only two patients had HSV-positive ARN, and both were children. Multiple studies have indicated that VZV is the organism that most frequently causes ARN, which mostly varies from 50 to 75%, then followed by HSV [9, 15, 29]. Remarkably, the rate of VZV is even higher among the Chinese population, which could up to 97% [20, 30, 31]. Accordingly, the notably high rate of VZV in our study possibly due to geographical differences. Recent findings suggest that HSV-2, HSV-1, and VZV are the most frequent causes in young patients (< 25 years), young adults (> 25 years), and the elderly, respectively [4, 32, 33]. Several studies have reported that CMV and Epstein–Barr virus (EBV) can cause ARN; however, they are usually identified in conjunction with VZV or in immunocompromised patients [3, 4, 34]. The interpretation of positive EBV results detected by PCR testing is controversial because EBV can be detected in 20% of normal ocular tissues [35]. In this study, all patients tested negative for cytomegalovirus or EBV. This may be because all patients were immunocompetent.

ARN is mainly managed with timely antiviral therapy and adjunct therapies, including corticosteroids, anticoagulation, and PPV. A recent meta-analysis suggested that patients treated with systemic and intravitreal antivirals showed a trend towards better visual outcomes than those treated with systemic antivirals (oral or intravenous) alone [8]. Because of the high risk of RD, some ophthalmologists have advocated using prophylactic PPV and laser photocoagulation [25]. However, whether these prophylactic interventions can decrease the incidence of RD and improve the final VA remains controversial [36, 37]. Previous studies have reported that prophylactic vitrectomy can prevent RD but that it did not improve the final VA because of long-term complications [37, 38]. Here, prophylactic PPV showed no advantage in terms of recurrent RD or improved final VA in late-stage diagnosed eyes, in accordance with other studies [39, 40]. This suggests that patients with late stage ARN have a worse anatomical and functional prognosis even if prophylactic PPV is performed. We also found that corticosteroids were associated with a better final VA and a decreased RD rate than non-corticosteroids, although the associations were not statistically significant. We did not perform prophylactic laser photocoagulation mainly because its efficacy in preventing RD remains unclear and it is difficult and sometimes impossible to perform in cases with dense vitritis.

In the present study, we found that the VA returned to normal in most early-stage eyes. However, this was not the case in eyes with advanced disease at the time of antiviral therapy initiation [3, 13]. These results suggest that although the ideal treatment protocol for ARN remains unclear, early diagnosis and initiation of antiviral therapy are related to improved prognosis. Patients in the late stage had a worse final VA and RD occurred frequently, even though aggressive antiviral and prophylactic

vitrectomy had been performed [37, 40]. Further, we found that worse VA at presentation, the occurrence of RD, more clock hours of retinitis, and posterior involvement were possibly associated with poor visual outcomes, which confirmed that late diagnosis leads to a poor prognosis [18, 41].

The high incidence of RD and its damaging effect on visual outcomes in patients with ARN are widely known [9, 39]. RD has been reported to occur in 20–73% of cases, and even in up to 85% of cases [9, 39, 42–44]. Although the overall risk of RD in our study was 52.3%, RD was hardly observed in early diagnosed eyes, and only one pediatric HSV-ARN patient who presented with exudative RD at the first visit developed RRD. The relentless progression of the disease, despite early maximal treatment with intravenous and intravitreal antivirals, may reflect a more severe spectrum of the syndrome [45, 46]. Our regression analysis indicated that RD occurred in late-stage eyes nearly 17 times more often compared to early-stage eyes. Therefore, early diagnosis before the retinal lesions begin to merge can largely reduce the rate of RD and improve the visual prognosis [16]. Two of the most important findings in our study are that a severe vitritis grade and more clock hours of necrotic retinitis are risk factors for RD. Notably, the duration of symptoms before diagnosis was not associated with VA (logMAR) at the last follow-up or RD occurrence. Differences in the rates of disease progression among patients with varying immunological statuses may account for these results.

This study has some limitations. First, because this was a retrospective study, there was a lack of clinical data. Moreover, the sample size was small; therefore, a larger number of patients is required in future studies. Third, the staging of ARN may have been rough and subjective since it was based on the analysis of fundus examinations and medical records. Fourth, prophylactic PPV was only performed in eyes in the late stage. Further research should include middle-stage eyes to evaluate the effect of prophylactic PPV on reducing the occurrence of RD and improving the final VA. Lastly, the follow-up time varied among the patients, which may have led to underestimation of the RD rate.

Conclusion

Our study suggests that patients with ARN have favorable clinical outcomes with early diagnosis and antiviral treatment alone. Conversely, in the advanced stages of the disease, prophylactic PPV may not prevent recurrent RD and subsequent vision loss. Anterior segment signs are important for early diagnosis. For patients showing the triad of anterior segment signs (mildly or moderately elevated IOP, KPs, and iris nodules), a detailed fundus examination, especially a peripheral retinal examination, is necessary. The presence of the identified risk factors (poor VA at initial presentation, severe vitritis, or a greater extent of retinitis) may predict a poor visual prognosis, and patients should be closely monitored and surgical intervention might become necessary in these cases.

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Author contributions
HL, F wrote the main manuscript text and analysed the data. QQ, T and FH, Y participated in the data collecting. XM, Z reviewed the manuscript.

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Data availability
All the data are included in the manuscript.

Declarations

Human ethics approval and consent to participate
This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Tianjin Medical University Eye Hospital. All patients were informed that their participation was voluntary and informed consent was obtained.

Consent for publication
Informed consent for publication was obtained from every individual whose data are included in this manuscript.

Competing interests
The authors declare no competing interests.

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