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Title: Factors at the initial visit associated with poor visual outcomes in patients with acute retinal necrosis

Running title: Visual prognostic factors in ARN.

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32 Acute retinal necrosis, Ultra-widefield fundus imaging, Circumferential spread,
33 Necrotizing retinitis, Retinal detachment.

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36

Abstract

Background/Objective: Acute retinal necrosis (ARN) is a vision-threatening disease caused by herpesvirus infection. This study aimed to investigate the visual prognostic factors that could be determined at the initial visit.

Subjects and Methods: This retrospective study included 34 patients with ARN. Logistic regression analysis was employed to evaluate the associations between poor final visual outcomes and various factors, including poor initial visual acuity, presence of retinal detachment at the initial visit, posterior extension of necrotizing retinitis, and circumferential extension of necrotizing retinitis. Posterior extension was evaluated with three zonings, from the periphery (zone 3), mid-periphery (zone 2), and macula (zone 1). Circumferential extension was evaluated according to the degree of necrotizing retinitis lesions using ultra-wide fundus imaging.

Results: The mean logarithm of the minimum angle of resolution was 0.63 ± 0.68 at the initial visit and 0.83 ± 0.65 at 12 months after the initial visit. Seven patients had a retinal detachment. The distribution of posterior extension at the initial visit was 5 in zone 1, 20 in zone 2, and 9 in zone 3. The average of necrotizing retinitis lesion angle was 249 ± 115°. The logistic regression analysis revealed that participants with wide angles of necrotizing retinitis were associated with final poor vision, with an odds ratio of 1.28 per 30° increase (95%CI: 1.00–1.65, p = 0.03).

Conclusions: Assessment of the widespread circumferential extension of white necrotizing retinal lesions at the initial visit is a crucial risk factor for the visual prognosis in ARN.

Introduction

Acute retinal necrosis (ARN) is a type of devastating, rare, infectious panuveitis that is characterised by rapidly progressive necrotizing retinitis, occlusive vasculitis, and an inflammatory reaction in the anterior chamber and vitreous in otherwise healthy individuals (1). The first description of ARN was provided by Urayama et al. in the 1970s (2). Subsequently, evidence has emerged indicating that herpesviruses, including varicella zoster virus (VZV) and herpes simplex virus (HSV), are causative agents of ARN (3). While anterior uveitis caused by herpesvirus is a common ocular condition in Japan (4), ARN remains a rare manifestation of these viruses (2, 3). ARN can affect individuals of either sex, regardless of age or immune status. Despite advances in the understanding of the pathogenesis of ARN and development of its treatments, the visual prognosis of affected individuals remains poor. Furthermore, previous studies have reported that 48% of affected eyes have got visual acuity (VA) values worse than 20/200 6 months after the onset of ARN (3, 5).

Patients with ARN typically present with acute onset of vision loss in one eye. Vision deterioration at the initial visit usually occurs due to vitreous haze or other inflammatory changes secondary to pan-uveitis and vitritis, with characteristic necrotic lesions located primarily in the peripheral retina (6). Thus, the evaluation of peripheral lesions is of paramount significance as the disease progresses from the periphery towards the macula. Furthermore, although accurate assessment of peripheral necrotic lesions during the initial presentation is often impeded by opaque media, such as vitreous haze, visual loss at the initial visit is reported as a risk factor for permanent visual impairment (7, 8). Notably, Lei et al. demonstrated that ultra-widefield (UWF) imaging holds promise in detecting peripheral white necrotic lesions in ARN, even under conditions of ocular

opacification (9). UWF imaging is utilized for the assessment of peripheral lesions (10) and vascular anomalies across various ocular pathologies (11), owing to its wide-angle imaging capability. Furthermore, UWF imaging is valuable not only for imaging vitreous opacities but also for examining eyes filled with gas (12). Furthermore, previous studies have reported that necrotizing retinitis lesions that extend from the peripheral retina to the posterior pole (zone 1 lesions) are associated with poor visual outcomes. In addition, retinal detachment (RD), which is the most widely accepted risk factor for poor visual outcomes in ARN, often originates from retinal tears at the peripheral necrotic retinitis (13-17). Moreover, some reports have suggested a relationship between the circumferential extent of peripheral necrotic retinitis and the incidence of RD (14, 17-19). This underscores the importance of meticulous assessment of peripheral necrotic lesions at the time of initial presentation.

In this study, we evaluated the association between poor final visual outcomes and risk factors, including poor initial vision, presence of necrotizing retinitis in zone1 areas, presence of RD, and circumferential extension of necrotizing retinitis at the initial presentation.

Subjects and methods

This study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from the patients using the opt-out method, and the study was approved by the Kyushu University Institutional Review Board for Clinical Research.

We conducted a retrospective cohort analysis of all patients diagnosed with ARN who were treated at the Kyushu University Hospital between 2015 and 2021. At the initial presentation, a clinical diagnosis of ARN was made based on ocular findings, including characteristic peripheral white necrotizing retinitis. Additionally, polymerase chain reaction (PCR) using aqueous samples was employed to confirm positive VZV or HSV infection. Prompt initiation of treatment was a priority for all patients, involving antiviral drugs, corticosteroids and anticoagulants to prevent the posterior or circumferential expansion of necrotic lesions located predominantly in the peripheral retina. Notably, only patients with a confirmed ARN diagnosis, based on positive VZV or HSV PCR results, were included in the study.

In this study, all 34 patients initially received intravenous acyclovir at a dosage of 30–45 mg/kg/day for up to 2 weeks, followed by oral administration of valacyclovir at 3000 mg/day for approximately 1 month. Additionally, all patients received a standardized regimen of systemic steroids over approximately 1 month. This regimen included dexamethasone at 8 mg/day for the initial 3 days, followed by a tapering course of prednisolone. The dosage of prednisolone started at 30 mg for the first week, then decreased weekly to 20 mg, 10 mg, and finally 5 mg. Additionally, oral aspirin was coadministered at a daily dose of 10 mg during the administration of steroids. Moreover, 28 patients underwent vitrectomy and intraoperative prophylactic laser treatment, along with intravitreous perfusion of acyclovir in the presence or absence of encircling band,

126 silicone oil tamponade, or cataract surgery for phakic eyes.

127

128 ***Data extraction***

129 Demographic and clinical variables were collected by reviewing the medical records of
130 patients diagnosed with ARN. The demographic variables included age at diagnosis, sex,
131 immunocompetency status, and history of herpes infection. Immunocompromised
132 patients were defined as those receiving immunosuppressive medications or undergoing
133 treatment for malignancies. Clinical variables included the study eye (when a patient
134 presented with simultaneous bilateral ARN, the eye with the worst presenting best-
135 corrected visual acuity (BCVA) was chosen as the study eye; two cases), PCR results,
136 BCVA, intraocular pressure, extent of peripheral retinitis, lens status, presence or absence
137 of RD, and time from onset to medication or surgery. Postoperative clinical data included
138 BCVA and the presence or absence of RD at 12 months following the initial visit.
139 Furthermore, BCVA at the final visit was compared with that at the initial visit in patients
140 with zone 2 lesions. BCVA was documented using logarithm of the minimum angle of
141 resolution (logMAR) scores, with non-numerical vision assigned scores of 1.85 for
142 counting fingers, 2.3 for hand motion, 2.8 for light perception and 2.9 for no light
143 perception (20). Additionally, dilated funduscopic examination or B-scan ultrasound was
144 used to diagnose rhegmatogenous RD or combined rhegmatogenous and tractional RD.

145

146 ***Imaging***

147 To evaluate the extent of necrotizing retinitis, UWF fundus images were obtained
148 using a UWF scanning laser ophthalmoscope (Optos 200Tx, Optos PLC, Dunfermline,
149 UK) within 24 h of initial presentation and before starting treatment. We used UWF

imaging throughout the course of antiviral treatment and/or prophylactic vitrectomy in patients with ARN. The posterior extension of necrotizing retinitis was evaluated using the zone classification criteria for cytomegalovirus retinitis proposed by Holland et al. (21). Zone 1 included the retinal area within 3000 μm (equivalent to two disc diameters) of the centre of the macula or 1500 μm (equivalent to one disc diameter) of the margin of the optic disc. Zone 2 included the retina anterior to zone 1 and posterior to a circle intersecting the ampullae of the vortex veins (approximately one disc diameter posterior to the equator). Zone 3 included the retinal area anterior to the boundary of zone 2. The circumferential extension of necrotizing retinitis was evaluated by measuring the angles that encompassed the entire lesions from the macula using OptosAdvance® software (Supplemental Figure 1). Two experienced investigators independently evaluated the UWF images and a consensus was reached for each case.

Descriptive and inferential statistical analysis

Statistical analyses were conducted using Jump software version 16 (SAS Institute, Cary, NC). Descriptive data, including demographic data and ocular findings, were summarised as frequencies or means with standard deviations (SDs), as appropriate. Decimal VA values were converted to the logarithm of logMAR for statistical analysis and expressed as mean ± SD. Categorical variables were compared using Fisher's exact test, as appropriate, while normally distributed and non-normally distributed continuous variables were compared using independent or paired t-tests and the Mann–Whitney *U* tests, respectively. To identify the risk factors for poor vision, the associations among factors at the initial presentation were analysed using univariate and multivariate logistic regression models, including: 1) VA at presentation, 2) presence or absence of

RD at presentation, 3) presence or absence of zone 1 involvement and 4) the extent of retinitis in clock hours. Poor vision was defined as logMAR $\geq$ 1.0. P-values $<$ 0.05 were considered statistically significant for all analyses.

Results

Baseline clinical characteristics

The study inclusion criteria were met in 34 eyes of 34 patients. Baseline clinical features and descriptive statistics of patients are presented in Table 1. At presentation, the mean patient age was 56.4 ± 17.2 years, ranging from 10 to 85 years. The study group comprised 15 men and 19 women. The mean logMAR was 0.63 ± 0.68 at the initial visit. At 12 months after the initial visit, the mean logMAR was 0.83 ± 0.65, indicating a significant decrease in VA from the initial examination ($p = 0.001$). Prior herpetic disease within 2 months was reported in 12 (35.3%) patients, including three patients with ARN, two with shingles, two with anterior uveitis, and one with Bell's palsy. Nine patients (26.4%) had immunosuppressive conditions due to chemotherapy for leukaemia (one patient), chemotherapy for other cancer (four patients), prednisolone treatment for uveitis (two patients), Tolosa-Hunt syndrome (one patient), and adult Still's disease (one patient). The median observation period from the initial visit to the final visit was 31 months (interquartile range, 12.5 to 45). In terms of the treatment protocol, the actual duration of antiviral medication was a median of 43 days (interquartile range, 28.3 to 55) for intravenous acyclovir, while for systemic steroids, the administration period was a median of 46.5 days (interquartile range, 32 to 128).

The causative virus was VZV in 28 (82.4%) patients, HSV-1 in 1 (2.9%) patient, and HSV-2 in 5 (14.7%) patients. No patient was found to be infected with the human immunodeficiency virus. Bilateral ARN was observed in five (14.7%) patients, all of whom were women. Among the five bilateral ARN cases, HSV-2 and VZV were identified as the causative viruses in three and two patients, respectively. This indicated that three of five patients with HSV-2 infection had bilateral ARN. For the three patients

with recurrent ARN, the duration between the last episode and recurrence in this study ranged from 5 to 35 years. Necrotizing retinitis lesions at the initial visit were divided into three groups: zone 1 (n = 5), zone 2 (n = 20) and zone 3 (n = 9). The average angles of necrotizing retinitis lesions were 249 ± 115°. Despite presence of vitreous opacity, UWF images of necrotizing retinitis lesions were obtained in all of patients with ARN.

Seven out of the 34 patients (20.6%) presented with RD at their initial visit. Rhegmatogenous RD or a combination of rhegmatogenous and tractional RD developed, while no exudative cases of RD occurred. Eight out of 27 patients (29.6%), who did not initially develop RD, experienced RD after antiviral treatment and prophylactic vitrectomy during the study period. In the seven patients who had RD at the initial visit, the mean logMAR was 1.25 ± 0.96 at the first visit and 1.15 ± 0.80 at 12 months after the initial visit, with the difference not being statistically significant (p = 0.81; Supplemental Table 1). In contrast, in patients who did not initially have RD, the mean logMAR was 0.46 ± 0.42 at the first visit and worsened to 0.74 ± 0.57 at 12 months after the initial visit (p = 0.01; Supplemental Table 1).

Factors associated with poor visual outcomes

In this study, we defined poor visual prognosis as logMAR ≥ 1.0. Then, we devided 34 patients with ARN into two groups based on wheter the parameters were below or above logMAR ≥ 1.0. In patients with poor final visual prognoses, the extent of necrotizing retinitis was predominantly wider (p = 0.005; Table 1). Moreover, the visual prognosis tended to deteriorate as the range of necrotizing lesions moved closer to the fovea, signifying progression from zone 3 to zone 1 in the zone classification (p = 0.03; Table 1). These results imply that the visual prognosis may be influenced not only by the

direction of the necrotizing lesions towards the fovea but also by their lateral expansion. However, other factors, such as age and presence of immunosuppression, were not associated with a poor visual prognosis.

Univariate and multivariate analyses of risk factors for poor vision in ARN

Statistical analysis was conducted to identify factors at the initial presentation which are associated with the poor final VA (Table 2). In comparing patients with poor visual prognosis to others (Table 1), the 'extent of necrotizing retinitis' was significantly associated with poor visual prognosis. Therefore, along with the three previously reported factors for poor visual outcomes—'poor vision at initial presentation', 'RD at initial presentation' and 'zone1 involvement at the initial presentation'—a total of four elements were examined. Among the four potential variables, the circumferential extent of necrotizing retinitis was the only variable significantly associated with poor final VA (≥ logMAR 1.0) in both univariate and multivariable-adjusted logistic analyses ($p = 0.02$, $p = 0.03$, respectively). Notably, the mean circumferential angles of necrotizing retinitis in patients with poor final VA was 312.64º ± 90.89, with 11 out of 14 patients exhibiting a full 360º. Meanwhile, in 10 patients with good final VA (< logMAR 0.4), the average extent of necrotic lesions was 160º ± 88.72. Among them, only one patient exhibited a full 360º of necrotizing retinitis, while eight patients presented with necrotic lesions within 180º. Overall, circumferential extension was found to be associated with poor visual outcomes, with an odds ratio of 1.28 for every 30º of extension (95% CI: 1.00–1.65, $p = 0.03$).

Visual prognosis depending on the circumferential extension of necrotizing retinitis

Based on the above results, we compared the visual outcomes at a range of 180º. At the initial presentation, eyes with necrotizing retinitis encompassing less than 180º and eyes with necrotizing retinitis encompassing 180º and greater did not exhibit a significant difference in VA (Fig. 1). However, at the 6-month mark, the eyes that showed a necrotic retina of 180º or more exhibited a significantly greater loss of VA ($p = 0.012$; Fig.1). Subsequently, their VA was consistently worse than that of patients with a necrotizing retinitis range narrower than 180º (12 months, $p = 0.0011$; Fig. 1). We further investigated the relationship between the circumferential extent of necrotizing retinitis and RD (9, 14, 15). In cases with a circumferential extent of necrotizing retinitis less than 180º, the incidence of RD was 23.0% (n = 3). In contrast, this incidence was 57.1% (n = 12) in cases with an extent equal to or greater than 180º (Supplemental Table 2). This result suggests that an increase in the extent of peripheral necrotic lesions is associated with a higher incidence of subsequent RD with marginal significance ($p = 0.079$).

Visual prognosis depending on the posterior extension of necrotizing retinitis

To further analyse the relationship between the extent of necrotizing retinitis and visual prognosis, we evaluated the progression of necrotizing retinitis towards the fovea using the zone classification (Fig. 2). All five eyes with macular lesions (zone 1) at the initial presentation showed poor visual outcomes, with four eyes (80%) having a final VA of logMAR 1.0 or worse. In contrast, eyes with peripherally restricted lesions (zone 3) largely maintained vision at the same level as the initial presentation, with only one case showing a decline. Notably, eyes with zone 2 lesions showed both favourable and unfavourable visual outcomes, with five eyes (25%) and nine eyes (45%) having a final VA of logMAR0.4 or better and logMAR1.0 or worse, respectively. Due to the observed

274 variability in visual outcomes in patients with zone 2 lesions, we attempted to identify the
275 contributing factors that led to unfavourable results in zone 2 eyes. In our search for
276 relevant factors, we found that the circumferential extent of retinitis was a significant
277 determinant. The results indicated that among the cases in which the posterior extension
278 of necrotizing retinitis was in zone 2, cases with a circumferential extension equal to or
279 greater than 180º had poor visual outcomes ($p = 0.026$; Fig. 3A). In contrast, cases with
280 an extent of less than 180º tended to maintain their VA at the same level as the initial visit
281 (Fig. 3B).
282

Discussion

In contrast to previous studies that based predictions of poor visual outcomes on findings throughout disease progression, we focused on factors associated with the final visual outcomes based on initial clinical presentations. Our data indicate that evaluating the circumferential extension of necrotic lesions at the initial manifestations is essential for determining poor visual outcomes. Specifically, patients with necrotic retinal lesions > 180º had poorer visual outcomes. Furthermore, our study also showed that the assessment of the circumferential extension of necrotic lesions is useful for incorporating the posterior extension of the necrotic retina.

As previously reported, patients with zone 1 lesions typically experienced poor visual outcomes, while those in zone 3 lesions demonstrated relatively better visual outcomes (7, 18); however, patients with zone 2 lesions, which accounted for 60% of all ARN cases, presented with a mix of both. Our analysis revealed that patients with necrotic lesions extending beyond 180º had unfavourable visual prognoses in zone 2 (Fig.3A). These results suggest that fundus examination of peripheral necrotic lesions is pivotal for predicting a more accurate visual prognosis. To evaluate the circumferential and posterior extension of necrotic retina, UWF imaging at the first visit is useful to identify necrotic retinal lesions in patients with ARN, wherein severe vitreous opacity often interferes with observation. In instances where UWF imaging is not available, ophthalmologists should carefully perform fundus examinations using indirect ophthalmoscopy to assess circumferential extent of necrotic lesions at the initial visit in patients with ARN.

The significance of circumferential extension of necrotic lesions at the initial manifestation as a risk factor for poor visual outcomes can be attributed to two key reasons. First, the wider the lesions, the greater the area of retinal, vascular and optic

nerve damage. Notably, previous studies have highlighted the relationship between visual prognosis and optic atrophy (18, 22, 23). Thus, the extent of the lesions at the initial examination could be a risk factor for future optic nerve atrophy. Second, the circumferential extent of peripheral necrotic retinitis is associated with the incidence of RD (9). However, in this study, the combination of antiviral treatment and prophylactic vitrectomy has reduced the incidence of RD to less than 30%, a significant improvement compared with the 47–70% incidence reported in previous studies without surgical intervention (1, 9, 24-26). Furthermore, whether RD is a risk factor for poor visual outcomes remained unconfirmed in ARN (15). For instance, several reports have suggested that while prophylactic vitrectomy is effective in preventing postoperative RD, it may not improve VA (16, 24, 27). This could be attributed to the broader necrotic lesion causing greater retinal damage, including optic nerve involvement, irrespective of the presence or absence of RD (22, 28). Therefore, further studies are necessary to develop new therapeutic strategies for the suppression of optic nerve involvement and occlusive vasculitis to improve visual prognosis.

In the present study, poor visual acuity at the first visit was not a risk factor for poor visual prognosis. Previous studies have demonstrated that decreased VA at the initial presentation is associated with poor final visual outcomes due to involvement of the optic nerve, macular region and occlusive vasculitis when the extent of necrotizing retinitis is greater than 50% of the retina and/or involves the posterior pole (9, 28). However, in our study, only 5 out of 34 patients exhibited such retinal findings. Consequently, the small sample size may have rendered statistically significance challenging to ascertain. Additionally, it is important to note that the initial VA is often affected by the vitreous opacity which can be improved through interventions like corticosteroid administration

and vitrectomy. This aspect could have also contributed to our finding that decreased VA at the initial visit did not emerge as a risk factor for permanent loss of VA.

Limitation

This study has some limitations. First, because this was a single-centre retrospective study, the lack of registration information, patient volume data and assessed variables may have introduced selection bias. Second, the mixed follow-up intervals of the 34 patients with ARN may have influenced the obtained results. Third, owing to the shortage of patients, the sample size of this study was small. Multicentre studies with larger sample sizes are required to clarify whether the circumferential extension of necrotizing retinitis observed at the initial visit using UWF imaging can predict visual outcomes in patients with ARN.

Conclusion

ARN remains a disease with a poor visual prognosis and requires appropriate risk assessment criteria and treatment options for disease control, including addressing RD. Our results indicate that extensive circumferential spread of necrotizing retinitis at the initial presentation is associated with poor visual prognosis, even when antiviral treatment and prophylactic vitrectomy is administered immediately. Moreover, UWF imaging emerged as a helpful tool for identifying the circumferential spread of necrotizing retinitis despite severe vitreous opacity. In addition to existing medical and surgical interventions, the development of effective therapies, such as more potent anti-inflammatory agents for optic neuritis and vasculitis obliterans, is necessary to improve the visual prognosis in patients with ARN.

Supplementary information is available at Eye's website.

Reference

1. Fisher JP, Lewis ML, Blumenkranz M, Culbertson WW, Flynn HW, Jr., Clarkson JG, et al. The acute retinal necrosis syndrome. Part 1: Clinical manifestations. Ophthalmology. 1982;89(12):1309-16.

2. Urayama A, Yamada N, Sasaki T. Unilateral acute uveitis with retinal periarteritis and detachment. Rinsho Ganka. 1971;25:607-19.

3. Cochrane TF, Silvestri G, McDowell C, Foot B, McAvoy CE. Acute retinal necrosis in the United Kingdom: results of a prospective surveillance study. Eye (Lond). 2012;26(3):370-7; quiz 8.

4. Okazawa R, Iwai S, Nagura K, Sora D, Sato T, Takayama K, et al. Epidemiology and characteristics of common forms of anterior uveitis at initial presentation in a tertiary facility in Japan. Jpn J Ophthalmol. 2023;67(1):22-31.

5. Powell B, Wang D, Llop S, Rosen RB. Management strategies of acute retinal necrosis: current perspectives. Clin Ophthalmol. 2020;14:1931-43.

6. Takase H, Okada AA, Goto H, Mizuki N, Namba K, Ohguro N, et al. Development and validation of new diagnostic criteria for acute retinal necrosis. Jpn J Ophthalmol. 2015;59(1):14-20.

7. Kim DY, Jo J, Joe SG, Lee JY, Yoon YH, Kim JG. Clinical feature and visual prognosis of acute retinal necrosis according to the initially involved zone and extent: 10-year experience. Eur J Ophthalmol. 2019;29(2):244-50.

8. Paolo M, Marta Z, Stefania F, Viola T, Giacomo C, Arturo C, et al. Visual outcome and poor prognostic factors in acute retinal necrosis syndrome. Graefes Arch Clin Exp Ophthalmol. 2020;258(9):1851-6.

9. Lei B, Zhou M, Wang Z, Chang Q, Xu G, Jiang R. Ultra-wide-field fundus

381 imaging of acute retinal necrosis: clinical characteristics and visual significance. Eye
382 (Lond). 2020;34(5):864-72.
383 10. Li S, Sun L, Liu C, Wang W, Huang S, Zhang T, et al. Clinical features of ocular
384 toxocariasis: a comparison between ultra-wide-field and conventional camera imaging.
385 Eye (Lond). 2021;35(10):2855-63.
386 11. Patel CK, Fung TH, Muqit MM, Mordant DJ, Brett J, Smith L, et al. Non-contact
387 ultra-widefield imaging of retinopathy of prematurity using the Optos dual wavelength
388 scanning laser ophthalmoscope. Eye (Lond). 2013;27(5):589-96.
389 12. Fukuda Y, Nakao S, Kohno RI, Ishikawa K, Shimokawa S, Shiose S, et al.
390 Postoperative follow-up of submacular hemorrhage displacement treated with vitrectomy
391 and subretinal injection of tissue plasminogen activator: ultrawide-field fundus
392 autofluorescence imaging in gas-filled eyes. Jpn J Ophthalmol. 2022;66(3):264-70.
393 13. Lei B, Wang Z, Shu Q, Gu R, Zhang Y, Jiang R, et al. Observation of varicella
394 zoster virus-induced acute retinal necrosis: viral load detection and visual outcome. Eye
395 (Lond). 2022;36(6):1209-16.
396 14. Bavinger JC, Anthony CL, Lindeke-Myers AT, Lynch S, Xu LT, Barnett J, et al.
397 Risk factors for retinal detachment in acute retinal necrosis. Ophthalmol Retina.
398 2022;6(6):478-83.
399 15. Butler NJ, Moradi A, Salek SS, Burkholder BM, Leung TG, Dunn JP, et al. Acute
400 retinal necrosis: presenting characteristics and clinical outcomes in a cohort of
401 polymerase chain reaction-positive patients. Am J Ophthalmol. 2017;179:179-89.
402 16. Fan S, Lin D, Wang Y. Role of Prophylactic vitrectomy in acute retinal necrosis
403 in preventing rhegmatogenous retinal detachment: systematic review and meta-analysis.
404 Ocul Immunol Inflamm. 2022;30(2):515-9.

17. Ishida T, Sugamoto Y, Sugita S, Mochizuki M. Prophylactic vitrectomy for acute retinal necrosis. Jpn J Ophthalmol. 2009;53(5):486-9.

18. Iwahashi-Shima C, Azumi A, Ohguro N, Okada AA, Kaburaki T, Goto H, et al. Acute retinal necrosis: factors associated with anatomic and visual outcomes. Jpn J Ophthalmol. 2013;57(1):98-103.

19. Luo YH, Duan XC, Chen BH, Tang LS, Guo XJ. Efficacy and necessity of prophylactic vitrectomy for acute retinal necrosis syndrome. Int J Ophthalmol. 2012;5(4):482-7.

20. Schulze-Bonsel K, Feltgen N, Burau H, Hansen L, Bach M. Visual acuities "hand motion" and "counting fingers" can be quantified with the freiburg visual acuity test. Invest Ophthalmol Vis Sci. 2006;47(3):1236-40.

21. Holland GN, Buhles WC, Jr., Mastre B, Kaplan HJ. A controlled retrospective study of ganciclovir treatment for cytomegalovirus retinopathy. Use of a standardized system for the assessment of disease outcome. UCLA CMV Retinopathy. Study Group. Arch Ophthalmol. 1989;107(12):1759-66.

22. Witmer MT, Pavan PR, Fouraker BD, Levy-Clarke GA. Acute retinal necrosis associated optic neuropathy. Acta Ophthalmol. 2011;89(7):599-607.

23. Takase H, Goto H, Namba K, Mizuki N, Okada AA, Ohguro N, et al. Clinical characteristics, management, and factors associated with poor visual prognosis of acute retinal necrosis. Ocul Immunol Inflamm. 2022;30(1):48-53.

24. Hillenkamp J, Nolle B, Bruns C, Rautenberg P, Fickenscher H, Roider J. Acute retinal necrosis: clinical features, early vitrectomy, and outcomes. Ophthalmology. 2009;116(10):1971-5 e2.

25. Zhao XY, Meng LH, Zhang WF, Wang DY, Chen YX. Retinal detachment after

acute retinal necrosis and the efficacies of different interventions: A Systematic Review and Metaanalysis. Retina. 2021;41(5):965-78.

26. Clarkson JG, Blumenkranz MS, Culbertson WW, Flynn HW, Jr., Lewis ML. Retinal detachment following the acute retinal necrosis syndrome. Ophthalmology. 1984;91(12):1665-8.

27. Wu CY, Fan J, Davis JL, Berrocal AM, Haddock LJ, Yannuzzi NA, et al. Surgical 0utcomes of acute retinal necrosis-related retinal detachment in polymerase chain reaction-positive patients: a single-center experience. Ophthalmol Retina. 2022;6(11):992-1000.

28. Meghpara B, Sulkowski G, Kesen MR, Tessler HH, Goldstein DA. Long-term follow-up of acute retinal necrosis. Retina. 2010;30(5):795-800.

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Author contribution Statement

Concept and design of the work: C.F., A.T., N.Y.; Acquisition or interpretation of data: C.F., E.H., K.A., M.S., H.T., K.Y., T.I., K.I., Y.M., T.H.; Analysis of data: C.F., A.T., N.Y.; Drafting of the manuscript: C.F., A.T.; Statistical analysis: C.F., M.A.; Critical revision of the article: E.H., N.Y., KH.S.

Data Availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interests

The authors declare no conflict of interest relevant to the content of this article.

Figure Legend

Figure 1. BCVA in patients with ARN based on necrotizing retinal lesions extents around 180º.

Comparison of best-corrected visual acuity (BCVA) over time for patients with acute retinal necrosis (ARN) with less than 180º (n = 13) and 180º or more (n = 21) necrotizing retinal lesions. The Snellen BCVA values were converted to logarithm of the minimum angle of resolution (logMAR) values. Mo: months, yr: years. Error bars represent the standard error (SE). *p < 0.05, **p < 0.01; Mann–Whitney *U* tests.

Figure 2. Final BCVA in patients with ARN based on zone classification.

Boxplots of the best-corrected visual acuity (BCVA) at the final visit for each zone in patients with acute retinal necrosis (ARN). The Snellen BCVA values were converted to logarithm of the minimum angle of resolution (logMAR) values. NS: not significant. *p < 0.05, **p < 0.01; Dunn's multiple comparisons test after the Kruskal-Wallis test.

Figure 3. BCVA in patients with ARN who had necrotizing retinal lesions in zone 2 based on necrotizing retinal lesions extents around 180º.

Comparison of best-corrected visual acuity (BCVA) in patients with acute retinal necrosis (ARN) with (A) 180º or more (n = 15) and (B) less than 180º (n = 5) between the initial and the final visit. The Snellen BCVA values were converted to logarithm of the minimum angle of resolution (logMAR) values. NS: not significant. *p < 0.05, paired *t*-test.