Research Square

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Clinical Features and Prognostic Factors of Acute Retinal Necrosis Secondary to Varicella Zoster Virus versus Herpes Simplex Virus: A Comparative Retrospective Cohort Study

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Abstract

Background

To compare the demographic characteristics, clinical presentation, management, visual outcomes, and complications of polymerase chain reaction (PCR)-confirmed acute retinal necrosis (ARN) caused by varicella zoster virus (VZV) and herpes simplex virus (HSV), and to identify prognostic factors associated with retinal detachment (RD) and poor visual outcome.

Design:

Retrospective multicenter comparative cohort study.

Methods

Adult patients (≥ 18 years) with PCR-confirmed ARN caused by VZV, HSV-1, or HSV-2 who presented to two tertiary ophthalmic referral centers in Saudi Arabia between January 2015 and June 2025 were included. Demographic characteristics, clinical presentation, treatment, visual outcomes, and ocular complications were compared between the VZV and HSV groups. Multivariable logistic regression was performed to identify independent predictors of RD and poor final visual outcome.

Results

Twenty-seven patients with PCR-confirmed ARN were included, comprising 12 patients with VZV and 15 with HSV infection. Compared with patients who had VZV-associated ARN, those with HSV-associated disease presented with significantly worse visual acuity (1.52 ± 1.00 vs. 0.67 ± 0.68 LogMAR; P = 0.027) and a higher incidence of RD (80.0% vs. 33.3%; P = 0.022). Visual acuity remained significantly poorer in the HSV group during the first three months of follow-up. Mutton-fat keratic precipitates and cystoid macular edema were more common in VZV-associated disease, whereas rapid retinal lesion progression occurred more frequently in HSV-associated ARN. On multivariable analysis, greater retinitis extent was the only independent predictor of RD (OR 4.87; 95% CI 1.49–37.26; P = 0.043), while poorer presenting visual acuity (OR 7.00; 95% CI 1.48–78.16; P = 0.043) and RD (OR 25.14; 95% CI 2.39–721.24; P = 0.019) independently predicted poor final visual outcome.

Conclusions

HSV-associated ARN presented with poorer visual acuity and a substantially higher incidence of RD than VZV-associated disease. However, retinitis extent, rather than viral subtype, was the only independent predictor of RD, while presenting visual acuity and RD independently predicted poor final visual outcome. These findings suggest that disease severity at presentation, rather than viral etiology alone, is the principal determinant of prognosis and underscore the importance of early diagnosis, careful assessment of retinitis extent, and close surveillance of patients at high risk for RD.

BACKGROUND

Acute retinal necrosis (ARN) is a rare but vision-threatening viral uveitic syndrome characterized by peripheral necrotizing retinitis, occlusive retinal vasculitis, and prominent intraocular inflammation. Varicella zoster virus (VZV) is the most common causative pathogen, followed by herpes simplex virus types 1 and 2 (HSV-1/HSV-2), although cytomegalovirus and other herpesviruses have been reported less frequently. (1–4) Despite advances in molecular diagnostics and antiviral

therapy, ARN remains associated with poor visual outcomes, largely because of retinal detachment (RD) and irreversible retinal damage. (5, 6)

ARN is diagnosed clinically using the American Uveitis Society criteria, while PCR analysis of aqueous or vitreous fluid is the gold standard for confirming viral etiology. (3, 7) Early diagnosis and prompt antiviral therapy are critical because delayed treatment increases the risk of progressive retinal necrosis, RD, and bilateral involvement. (6–9)

Although VZV and HSV account for the majority of ARN cases, important differences between these viral etiologies remain incompletely understood. Previous studies have shown that patients with VZV-associated ARN are generally older and more likely to be immunocompromised, whereas HSV-associated disease tends to occur in younger individuals and may be associated with more severe vitreous inflammation and bilateral involvement, particularly in HSV-2 infection (2, 10–13). Morphologic differences in retinal lesions have also been described, including the association of ameboid or scalloped retinitis with VZV infection (2).

The prognostic significance of viral subtype remains controversial. Some studies have associated VZV with poorer visual outcomes (14, 15), whereas others have reported more aggressive disease and higher retinal detachment rates in HSV-associated ARN. (12) Conversely, several multicenter studies found no significant differences after adjustment for disease severity. (1, 16)

Because clinical manifestations overlap considerably among herpesvirus infections, PCR confirmation provides a more reliable basis for evaluating virus-specific clinical characteristics and prognostic outcomes.

Despite advances in diagnosis and management, few studies have directly compared PCR-confirmed VZV- and HSV-associated ARN, and published findings remain inconsistent. Moreover, comparative data from the Middle East are scarce. We therefore conducted a multicenter retrospective cohort study to compare the demographic characteristics, clinical presentation, visual outcomes, complications, and prognostic factors of PCR-confirmed VZV- and HSV-associated ARN.

METHODS

Study design and setting: This retrospective multicenter comparative cohort study was conducted at two tertiary ophthalmic referral centers in Saudi Arabia: King Khaled Eye Specialist Hospital (KKESH), Riyadh, and Dhahran Eye Specialist Hospital (DESH), Dhahran. Medical records from January 2015 to June 2025 were retrospectively reviewed. During the study period, 56 patients were clinically diagnosed with ARN at KKESH, of whom 25 had PCR-confirmed VZV or HSV infection and met the study inclusion criteria. An additional two PCR-confirmed patients managed at DESH during the same period were included, yielding a final study cohort of 27 patients. Data from both institutions were collected using a standardized data collection form and analyzed as a single cohort.

Characteristics of participants

Eligible patients were 18 years of age or older with a clinical diagnosis of ARN according to the American Uveitis Society diagnostic criteria and polymerase chain reaction (PCR) confirmation of varicella zoster virus (VZV), herpes simplex virus type 1 (HSV-1), or herpes simplex virus type 2 (HSV-2) from aqueous or vitreous fluid. Patients were required to have a minimum follow-up of 6 months. Exclusion criteria included incomplete clinical or virologic data, ocular comorbidities likely to influence visual outcomes (e.g., diabetic retinopathy or age-related macular degeneration), intraocular surgery within 3 months before disease onset, and systemic immunosuppressive therapy before ARN onset.

Data collection

Demographic data included age, sex, immune status, smoking history, systemic comorbidities, and previous herpetic disease. Clinical variables comprised presenting symptoms, best-corrected visual acuity (BCVA), intraocular pressure, anterior and posterior segment findings, extent and location of retinitis, retinal vasculitis, macular and optic nerve

involvement, and PCR results. The extent of retinitis was quantified in clock hours using the 360° retinal map recommended by the American Uveitis Society and classified according to the Retinal Society zonal classification (Zones 1–3). Snellen visual acuity was converted to the logarithm of the minimum angle of resolution (LogMAR) for statistical analysis. Treatment variables included systemic and intravitreal antiviral therapy, corticosteroid use, prophylactic laser photocoagulation, pars plana vitrectomy, and intraocular tamponade. Follow-up data included serial BCVA measurements, retinal attachment status, recurrence, fellow-eye involvement, and ocular complications.

Treatment

Treatment decisions were made by the responsible vitreoretinal and uveitis specialists according to institutional practice. Systemic antiviral therapy was initiated as soon as possible after clinical diagnosis. Adjunctive intravitreal antiviral therapy, systemic corticosteroids, prophylactic laser photocoagulation, and vitreoretinal surgery were administered at the discretion of the treating physician when clinically indicated.

Outcome measures

The primary outcome measures were BCVA during follow-up and at the final visit and the incidence of retinal detachment. Secondary outcome measures included clinical presentation, presenting BCVA, treatment patterns, retinal attachment status, disease recurrence, fellow-eye involvement, and ocular complications, including cystoid macular edema, proliferative vitreoretinopathy, epiretinal membrane, cataract, glaucoma, optic nerve complications, retinal vascular occlusion, and rapid progression of retinal lesions.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) and categorical variables as frequencies and percentages. Between-group comparisons were performed using Student's *t* test or the Mann–Whitney *U* test for continuous variables and the χ^2 or Fisher exact test for categorical variables, as appropriate. Kaplan–Meier analysis with the log-rank test evaluated time to retinal detachment. Univariable and multivariable logistic regression analyses were performed to identify predictors of retinal detachment and poor final visual outcome. Variables considered clinically relevant or significant on univariable analysis were entered into multivariable models. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported. A two-sided $P < 0.05$ was considered statistically significant. Statistical analyses were performed using R (version 4.5.2; R Foundation for Statistical Computing, Vienna, Austria) in RStudio (version 2026.01.1 + 403).

Ethical considerations

The study protocol (RP 25154-R) was approved by the Research Department of the King Khaled Eye Specialist Hospital and its Ethics Committee, which waived the requirement for informed consent owing to the retrospective study design involving a review of existing medical records. The study adhered to the tenets of the Declaration of Helsinki.

RESULTS

Patient characteristics: Twenty-seven patients with PCR-confirmed ARN were included: 12 (44.4%) with VZV-associated and 15 (55.6%) with HSV-associated disease. Baseline demographic characteristics were generally comparable between groups (Table 1). Patients with VZV-associated ARN were approximately a decade older on average (48.9 ± 13.0 vs. 38.7 ± 19.6 years; SMD = 0.60), consistent with the recognized predilection of VZV for older adults. Sex distribution, immune status, systemic comorbidities, and prior herpetic disease incidence were similar between groups. Follow-up duration was significantly longer in the HSV group (124.9 ± 102.4 vs. 41.5 ± 29.7 months; P = 0.037), which should be considered when interpreting late complication rates.

Table 1 *Demographic Characteristics of ARN Patients (N = 27)*

Characteristic	VZV Group (n=12)	HSV Group (n=15)	SMD
Age (mean ± SD, years)	48.92 ± 13.00	38.73 ± 19.58	0.599 (meaningful)
Gender			
Male, n (%)	6 (50%)	8 (53.3%)	0.067 (balanced)
Female, n (%)	6 (50%)	7 (46.7%)	0.067 (balanced)
Smoking History, n (%)	1 (8.3%)	0 (0%)	0.426 (meaningful)
Immune Status			
Immunocompetent, n (%)	12 (100%)	14 (93.3%)	0.378 (meaningful)
Immunocompromised, n (%)	0 (0%)	1 (6.7%)	0.378 (meaningful)
Systemic Diseases			
Diabetes Mellitus, n (%)	5 (41.7%)	5 (33.3%)	0.173 (minor)
Hypertension, n (%)	3 (25%)	3 (20%)	0.120 (minor)
Other, n (%)	2 (16.7%)	5 (33.3%)	0.392 (meaningful)
None, n (%)	4 (33.3%)	4 (26.7%)	0.146 (minor)
History of Prior Herpetic Disease			
Ocular herpetic disease, n (%)	3 (25%)	4 (26.7%)	0.038 (balanced)
Oral/genital herpes, n (%)	0 (0%)	0 (0%)	0.000 (balanced)
Shingles (HZV), n (%)	1 (8.3%)	0 (0%)	0.426 (meaningful)
None, n (%)	8 (66.7%)	9 (60%)	0.139 (minor)

Clinical presentation: Presenting clinical characteristics are summarized in Table 2. All patients had unilateral disease at presentation, and the interval from symptom onset to first assessment was similar between groups (14.6 ± 10.0 vs. 14.5 ± 14.9 days; P = 0.730). Presenting BCVA was significantly better in the VZV group (0.67 ± 0.68 LogMAR) compared with the HSV group (1.52 ± 1.00 LogMAR; P = 0.027), a clinically meaningful difference corresponding to approximately four lines on the visual acuity chart. Mutton-fat keratic precipitates were present in all VZV-affected eyes versus just over half of HSV-affected eyes (100% vs. 53.3%; P = 0.008), consistent with the more pronounced granulomatous inflammatory response characteristic of VZV infection. The extent of retinitis at presentation was comparable between groups (4.00 ± 1.21 vs. 4.27 ± 1.22 clock hours; P = 0.584), as were zone distribution, vitreous haze, macular involvement, and other posterior segment findings (all P > 0.05).

Table 2 *Clinical Characteristics at Presentation*

Characteristic	VZV Group (n=12)	HSV Group (n=15)	p-value
Laterality			
Unilateral, n (%)	12 (100%)	15 (100%)	1.000
Right eye	6 (50%)	7 (46.7%)	1.000
Left eye	6 (50%)	8 (53.3%)	1.000
Bilateral, n (%)	0 (0%)	0 (0%)	1.000
Days from Symptom Onset (mean ± SD)	14.58 ± 10.01	14.47 ± 14.92	0.730
Presenting Symptoms, n (%)			
Vision loss	11 (91.7%)	13 (86.7%)	1.000
Pain	2 (16.7%)	4 (26.7%)	0.662
Redness	6 (50%)	6 (40%)	0.707
Floaters	5 (41.7%)	4 (26.7%)	0.448
Photophobia	2 (16.7%)	2 (13.3%)	1.000
Flashes	0 (0%)	0 (0%)	1.000
Initial BCVA (LogMAR, mean ± SD)	0.67 ± 0.68	1.52 ± 1.00	0.027*
Intraocular Pressure at Presentation, n (%)			
<5 mmHg (hypotony)	0 (0%)	1 (6.7%)	1.000
6–10 mmHg (low-normal)	0 (0%)	2 (13.3%)	0.487
11–21 mmHg (normal)	11 (91.7%)	11 (73.3%)	0.342
22–29 mmHg (ocular hypertension)	0 (0%)	1 (6.7%)	1.000
≥30 mmHg (markedly elevated)	1 (8.3%)	0 (0%)	0.444
Anterior Segment Findings			
AC Cells Grade ≥2, n (%)	11 (91.7%)	12 (80%)	0.605
Flare Grade ≥2, n (%)	0 (0%)	3 (20%)	0.231
Mutton-fat KPs, n (%)	12 (100%)	8 (53.3%)	0.008*
Posterior Synechiae, n (%)	0 (0%)	2 (13.3%)	0.487
Corneal Edema, n (%)	1 (8.3%)	4 (26.7%)	0.342
Posterior Segment Findings			
Vitreous Haze Grade ≥2, n (%)	10 (83.3%)	14 (93.3%)	0.569
Extent of Retinitis (clock hours, mean ± SD)	4.00 ± 1.21	4.27 ± 1.22	0.584
Zone of Retinitis, n (%)			
Zone 1 (posterior pole)	3 (25%)	4 (26.7%)	1.000
Zone 2 (mid-periphery)	6 (50%)	5 (33.3%)	0.452
Zone 3 (peripheral)	12 (100%)	14 (93.3%)	1.000

Retinal Hemorrhages, n (%)	5 (41.7%)	6 (40%)	1.000
Optic Nerve Involvement, n (%)	8 (66.7%)	8 (53.3%)	0.696
Retinal Vasculitis, n (%)			
Periphlebitis	0 (0%)	0 (0%)	1.000
Arteritis	1 (8.3%)	0 (0%)	0.444
Mixed	7 (58.3%)	7 (46.7%)	0.704
Macular Involvement, n (%)	6 (50%)	8 (53.3%)	1.000
Choroidal Involvement, n (%)	3 (25%)	6 (40%)	0.683

Virologic confirmation and treatment: PCR confirmed the viral etiology in all 27 patients (Table 3). Among HSV cases, HSV-1 accounted for 80.0% and HSV-2 for 20.0%. Treatment approaches were broadly similar between groups (Table 4). Intravenous acyclovir was used as induction therapy in all patients except one in the VZV group, who was treated with oral valacyclovir. One patient from the same group declined systemic antiviral therapy altogether and elected to receive only two intravitreal 2mg/0.1mL ganciclovir injections. All candidates received oral valacyclovir for maintenance. Adjunctive systemic corticosteroids were administered to all patients in both groups. Eyes with HSV-associated ARN required a greater mean number of intravitreal antiviral injections (3.08 ± 1.36 vs. 1.50 ± 0.00), though this difference did not reach statistical significance (P = 0.067), likely reflecting a trend toward more refractory disease in the HSV group.

Table 3 *Serological and Intraocular PCR Results*

Parameter	VZV Group (n=12)	HSV Group (n=15)	p-value
Intraocular PCR Results, n (%)			
VZV detected	12 (100%)	0 (0%)	—
HSV-1 detected	0 (0%)	12 (80%)	—
HSV-2 detected	0 (0%)	3 (20%)	—
CMV detected	0 (0%)	0 (0%)	—
Co-infection	0 (0%)	0 (0%)	—
Negative PCR	0 (0%)	0 (0%)	—
Blood Serology, n (%)			
VZV IgG positive	0 (0%)	0 (0%)	1.000
HSV-1 IgG positive	1 (8.3%)	0 (0%)	0.444
HSV-2 IgG positive	1 (8.3%)	0 (0%)	0.444
CMV IgG positive	1 (8.3%)	0 (0%)	0.444
HIV positive	0 (0%)	0 (0%)	1.000
Serology not done, n (%)	3 (25%)	2 (13.3%)	0.628

Table 4 *Treatment Details*

Treatment Parameter	VZV Group (n=12)	HSV Group (n=15)	p-value
Time from Presentation to Treatment (hours, mean ± SD)	43.42 ± 77.50	19.27 ± 17.22	0.328
Antiviral Induction Therapy, n (%)			
Acyclovir IV	10 (83.3%)	15 (100%)	0.188
Acyclovir oral	0 (0%)	0 (0%)	1.000
Valacyclovir oral	1 (8.3%)	0 (0%)	0.444
Famciclovir oral	0 (0%)	0 (0%)	1.000
Antiviral Maintenance Therapy, n (%)			
Acyclovir oral	0 (0%)	0 (0%)	1.000
Valacyclovir oral	12 (100%)	15 (100%)	1.000
Famciclovir oral	0 (0%)	0 (0%)	1.000
Valganciclovir oral	0 (0%)	0 (0%)	1.000
Intravitreal Antiviral Therapy, n (%)			
Foscarnet IVT	0 (0%)	1 (6.7%)	1.000
Ganciclovir IVT	4 (33.3%)	7 (46.7%)	0.696
Number of IVT injections (mean ± SD)	1.50 ± 0.00	3.08 ± 1.36	0.067
Adjunct Therapies, n (%)			
Systemic corticosteroids	12 (100%)	15 (100%)	1.000
Prophylactic laser photocoagulation	7 (58.3%)	6 (40%)	0.449
Pars plana vitrectomy (PPV)	3 (25%)	8 (53.3%)	0.239
Silicone oil tamponade	3 (25%)	3 (20%)	1.000
Gas tamponade	0 (0%)	0 (0%)	1.000

Visual outcomes: Visual outcomes are shown in Table 5 and Figure 2. BCVA was significantly better in the VZV group at presentation and remained so through the first three months of follow-up (P = 0.008, 0.010, and 0.022 at months 1, 2, and 3, respectively). Differences at 6 months and at the final visit were no longer statistically significant (P = 0.069 and P = 0.077, respectively), suggesting a degree of late visual recovery in both groups. Overall change in BCVA from baseline was comparable (0.22 ± 0.78 vs. 0.26 ± 1.03 LogMAR; P = 0.555). Retinal attachment rates diverged substantially between groups from the first month onward. At one month, 83.3% of VZV eyes remained attached versus 53.3% of HSV eyes; by three months, all VZV eyes (100%) were attached compared with 61.5% of HSV eyes. This disparity persisted to the final follow-up visit, where 100% of VZV eyes versus 61.5% of HSV eyes remained attached (Figure 3).

Table 5 *Visual Outcomes — Best-Corrected Visual Acuity (LogMAR) Over Time*

Timepoint	VZV Group (mean ± SD)	HSV Group (mean ± SD)	p-value	Retinal Status (% Attached)
Initial visit	0.67 ± 0.68	1.52 ± 1.00	0.027*	—
1 month	0.52 ± 0.60	1.50 ± 0.86	0.008*	VZV: 83.3% / HSV: 53.3%
2 months	0.55 ± 0.54	1.59 ± 1.00	0.010*	VZV: 91.7% / HSV: 50.0%
3 months	0.53 ± 0.53	1.54 ± 1.06	0.022*	VZV: 100% / HSV: 61.5%
6 months	0.53 ± 0.58	1.31 ± 1.05	0.069	VZV: 100% / HSV: 58.3%
Last follow-up	0.89 ± 0.85	1.78 ± 1.24	0.077	VZV: 100% / HSV: 61.5%
Change from baseline	0.22 ± 0.78	0.26 ± 1.03	0.555	—

Complications and prognostic factors: Complications are summarized in Table 6. HSV-associated ARN was associated with a significantly higher incidence of retinal detachment (80.0% vs. 33.3%; P = 0.022) and rapid retinal lesion expansion (46.7% vs. 8.3%; P = 0.043). Cystoid macular edema was significantly more common in VZV-associated disease (75.0% vs. 26.7%; P = 0.021). Among eyes with retinal detachment, rhegmatogenous retinal detachment was the predominant subtype in both groups.

Table 6 *Complications and Adverse Events*

Complication	VZV Group (n=12)	HSV Group (n=15)	p-value
Structural Complications, n (%)			
Retinal Detachment (any)	4 (33.3%)	12 (80%)	0.022*
Rhegmatogenous	3 (25%)	9 (60%)	0.121
Exudative	1 (8.3%)	4 (26.7%)	0.342
Recurrent RD	1 (8.3%)	4 (26.7%)	1.000
Time to Retinal Detachment (days, mean ± SD)	31.50 ± 11.00	100.00 ± 256.81	0.503
Proliferative Vitreoretinopathy (PVR)	0 (0%)	2 (13.3%)	0.487
Retinal Breaks/Holes/Tears	4 (33.3%)	3 (20%)	0.662
Optic Nerve Complications, n (%)			
Optic Nerve Involvement	8 (66.7%)	8 (53.3%)	0.696
Optic Nerve Atrophy	1 (8.3%)	2 (13.3%)	1.000
Optic Nerve Neovascularization	0 (0%)	0 (0%)	1.000
Macular Complications, n (%)			
Cystoid Macular Edema (CME)	9 (75%)	4 (26.7%)	0.021*
Epiretinal Membrane (ERM)	3 (25%)	4 (26.7%)	1.000
Retinal Neovascularization	0 (0%)	0 (0%)	1.000
Disease Recurrence & Fellow Eye, n (%)			
Recurrence of ARN	1 (8.3%)	4 (26.7%)	0.342
Time to Recurrence (days, mean ± SD)	3.00 ± —	1111.50 ± 2181.03	—
Fellow Eye Involvement	1 (8.3%)	3 (20%)	0.605
Other Complications, n (%)			
Cataract	4 (33.3%)	6 (40%)	1.000
Glaucoma	1 (8.3%)	1 (6.7%)	1.000
Rapid Expansion of Retinal Lesions	1 (8.3%)	7 (46.7%)	0.043*
Retinal Vascular Occlusion	3 (25%)	3 (20%)	1.000
Follow-Up			
Total Duration of Follow-Up (months, mean ± SD)	41.50 ± 29.66	124.86 ± 102.43	0.037*

Proliferative vitreoretinopathy developed exclusively in the HSV group (0% vs. 13.3%), though this difference did not reach significance (P = 0.487). Kaplan–Meier analysis demonstrated a trend toward earlier retinal detachment in the HSV group, though this did not reach statistical significance (log-rank P = 0.06; Figure 1). The significantly longer follow-up in the HSV group (124.9 ± 102.4 vs. 41.5 ± 29.7 months; P = 0.037) should be noted, as it may have allowed late complications to occur disproportionately in that group. On univariable logistic regression, HSV infection (OR 8.00; 95% CI 1.53–53.59; P = 0.019), worse presenting BCVA, greater retinitis extent, and macular involvement each predicted retinal detachment (Table 7).

Table 7 *Univariable and Multivariable Logistic Regression for Retinal Detachment (N = 27)*

Predictor	OR	95% CI	p
Univariable analysis			
HSV group (vs VZV)	8.00	1.53–53.59	.019*
Age (years)	0.99	0.95–1.04	.712
Male sex	0.44	0.09–2.09	.313
Initial BCVA (LogMAR)	3.09	1.16–11.43	.046*
Days from symptom onset	1.01	0.95–1.09	.716
Time to treatment (hours)	0.98	0.93–1.00	.308
Clock hours of retinitis	3.57	1.49–12.33	.015*
Macular involvement	5.87	1.16–37.03	.041*
Optic nerve involvement	5.25	1.05–31.26	.052
Vitreous haze grade ≥2	3.33	0.28–78.00	.353
Zone 1 involvement	6.00	0.82–124.48	.125
Prophylactic LPC	2.25	0.48–11.75	.313
Multivariable analysis			
HSV group (vs VZV)	13.07	1.12–454.89	.071
Initial BCVA (LogMAR)	1.50	0.34–7.88	.595
Clock hours of retinitis	4.87	1.49–37.26	.043*

On multivariable analysis, greater retinitis extent remained the sole independent predictor (OR 4.87; 95% CI 1.49–37.26; P = 0.043). For poor final visual acuity (LogMAR ≥1.0), worse presenting BCVA (OR 7.00; 95% CI 1.48–78.16; P = 0.043) and retinal detachment (OR 25.14; 95% CI 2.39–721.24; P = 0.019) were the only independent predictors (Table 8).

Table 8 *Univariable and Multivariable Logistic Regression for Poor Final Visual Acuity (LogMAR ≥ 1.0; N = 27)*

Predictor	OR	95% CI	p
Univariable analysis			
HSV group (vs VZV)	2.80	0.60–14.47	.199
Age (years)	1.02	0.97–1.07	.444
Male sex	0.33	0.06–1.56	.174
Initial BCVA (LogMAR)	5.78	1.79–31.20	.013*
Days from symptom onset	1.09	1.00–1.24	.094
Time to treatment (hours)	1.01	0.99–1.03	.597
Clock hours of retinitis	2.02	1.00–4.94	.077
Macular involvement	4.00	0.84–22.08	.092
Optic nerve involvement	3.85	0.80–21.41	.103
Zone 1 involvement	7.33	1.00–152.37	.089
Retinal detachment	19.50	3.19–186.73	.003*
Multivariable analysis			
HSV group (vs VZV)	0.27	0.01–3.02	.335
Initial BCVA (LogMAR)	7.00	1.48–78.16	.043*
Retinal detachment	25.14	2.39–721.24	.019*

DISCUSSION

This multicenter comparative cohort study demonstrated important differences in the clinical presentation and outcomes of PCR-confirmed HSV- and VZV-associated ARN. HSV-associated disease presented with poorer visual acuity and a substantially higher incidence of retinal detachment. However, after adjustment for baseline disease severity, retinitis extent —not viral etiology—emerged as the only independent predictor of retinal detachment, while presenting visual acuity and retinal detachment independently predicted poor final visual outcome. These findings suggest that disease severity at presentation is a stronger determinant of prognosis than viral subtype alone.

The observation that VZV-associated ARN predominantly affects older patients while HSV tends to affect younger individuals aligns with previously published data and supports the well-recognized age-related distribution of these viral infections. (8, 10, 17)

The significantly worse presenting visual acuity in the HSV group suggests that HSV-associated ARN may present with more advanced functional impairment at diagnosis. Although visual acuity remained poorer during the first three months of follow-up, this difference diminished over time, indicating that early visual status is largely determined by disease severity at presentation rather than by viral subtype alone. The absence of significant differences in other baseline ocular characteristics further supports the notion that factors beyond viral etiology contribute to the heterogeneity of disease presentation.

The higher prevalence of mutton-fat keratic precipitates and cystoid macular edema in VZV-associated ARN suggests a more pronounced granulomatous inflammatory response, consistent with previous reports of VZV-associated herpetic uveitis (2, 4). Despite these inflammatory features, VZV-associated disease demonstrated more favorable anatomical

outcomes, indicating that the severity of anterior segment inflammation does not necessarily reflect the extent of retinal damage or predict visual prognosis.

RD remains the leading cause of severe vision loss in ARN and develops in a substantial proportion of affected eyes despite antiviral treatment (2, 17). Several studies have evaluated prophylactic laser photocoagulation, intravitreal antiviral therapy, and pars plana vitrectomy to reduce the risk of retinal detachment; however, evidence supporting these interventions remains inconsistent (1, 14, 16, 18–32).

The higher incidence of retinal detachment in HSV-associated ARN is consistent with previous reports suggesting a more aggressive disease course (12). However, similar to the findings of Bavinger et al. (10), this association was no longer significant after adjustment for baseline disease severity. Instead, greater retinitis extent emerged as the only independent predictor of retinal detachment, indicating that the increased risk observed in HSV-associated disease is primarily attributable to more extensive retinal involvement rather than viral subtype itself. These findings emphasize the importance of carefully assessing retinitis extent at presentation to guide risk stratification and clinical management.

Final visual prognosis was likewise determined primarily by disease severity at presentation. Poorer presenting visual acuity and the development of RD independently predicted poor final visual outcome, whereas viral etiology was not an independent prognostic factor. These findings are consistent with previous studies identifying presenting visual acuity, RD, and retinitis extent as the principal determinants of visual outcome in ARN (10,17,33), reinforcing the importance of early diagnosis before irreversible retinal damage occurs.

Treatment strategies were broadly similar between groups, suggesting that the observed differences in outcomes were unlikely to be explained by major variations in management. Although eyes with HSV-associated ARN tended to require more intravitreal antiviral injections, this likely reflects greater disease severity at presentation rather than differences in treatment efficacy. Whether patients with extensive retinitis would benefit from earlier or more intensive adjunctive intravitreal antiviral therapy warrants further investigation in prospective studies.

One patient with PCR-confirmed VZV-associated ARN reported symptom onset approximately two weeks after receiving the first dose of the BNT162b2 (Pfizer–BioNTech) COVID-19 vaccine. Although similar cases have been reported following COVID-19 vaccination, the available evidence is limited to isolated case reports and does not establish a causal relationship (35–38). Therefore, this temporal association should be interpreted with caution and may represent coincidental viral reactivation rather than a vaccine-related adverse event.

Strengths and Limitations

This study has several strengths. First, the inclusion of only PCR-confirmed cases represents an important methodological strength by minimizing diagnostic misclassification and allowing more reliable comparisons between viral etiologies. Second, all patients were managed at tertiary ophthalmic referral centers with detailed longitudinal follow-up, permitting comprehensive assessment of both anatomical and functional outcomes.

Third, the inclusion of Kaplan–Meier survival analysis and multivariable logistic regression allowed identification of independent predictors of RD and poor visual outcome rather than relying solely on unadjusted comparisons. Finally, this study provides contemporary data from Saudi Arabia, where comparative studies of PCR-confirmed VZV- and HSV-associated ARN remain limited.

Several limitations should also be acknowledged. Although reflective of the rarity of ARN, the relatively small sample size limited statistical power and resulted in wide confidence intervals for several regression estimates. Accordingly, the multivariable models should be interpreted cautiously and considered hypothesis-generating rather than definitive. Furthermore, follow-up duration differed significantly between the HSV and VZV groups, which may have influenced the observed frequency of late complications despite adjustment in the analyses.

Future multicenter prospective studies with larger cohorts are needed to validate the prognostic models identified in this study and to determine whether virus-specific treatment strategies can improve outcomes. Additional investigations evaluating quantitative measures of retinitis extent, serial inflammatory biomarkers, and modern retinal imaging may further refine risk stratification and guide individualized management.

CONCLUSION

In conclusion, HSV-associated ARN presented with poorer visual acuity and a higher incidence of retinal detachment than VZV-associated disease. Nevertheless, retinitis extent at presentation, rather than viral subtype, was the only independent predictor of retinal detachment, while presenting visual acuity and retinal detachment independently predicted poor final visual outcome. These findings highlight the importance of early diagnosis and careful assessment of disease severity to optimize risk stratification and management. Larger prospective multicenter studies are warranted to validate these observations.

Abbreviations

ARN, acute retinal necrosis; **CME**, cystoid macular edema; **CMV**, cytomegalovirus; **HSV**, herpes simplex virus; **VZV**, varicella zoster virus; **RD**, retinal detachment; **RRD**, rhegmatogenous retinal detachment.

Declarations

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Conflict of Interest:

No conflicting relationships exist for any author.

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Author Contribution

SA conceived the study, collected and analyzed the data, performed the statistical analysis, interpreted the results, prepared the figures and tables, and wrote the first draft of the manuscript. HAA supervised the study, contributed to the study design, interpreted the data, critically revised the manuscript for important intellectual content, and approved the final version. HS, AA, DA, and NA contributed to data collection, manuscript revision, and interpretation of the findings. All authors read and approved the final manuscript.

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Data Availability

The datasets generated and/or analyzed during the current study are not publicly available because of institutional and ethical restrictions related to patient confidentiality.

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Figures

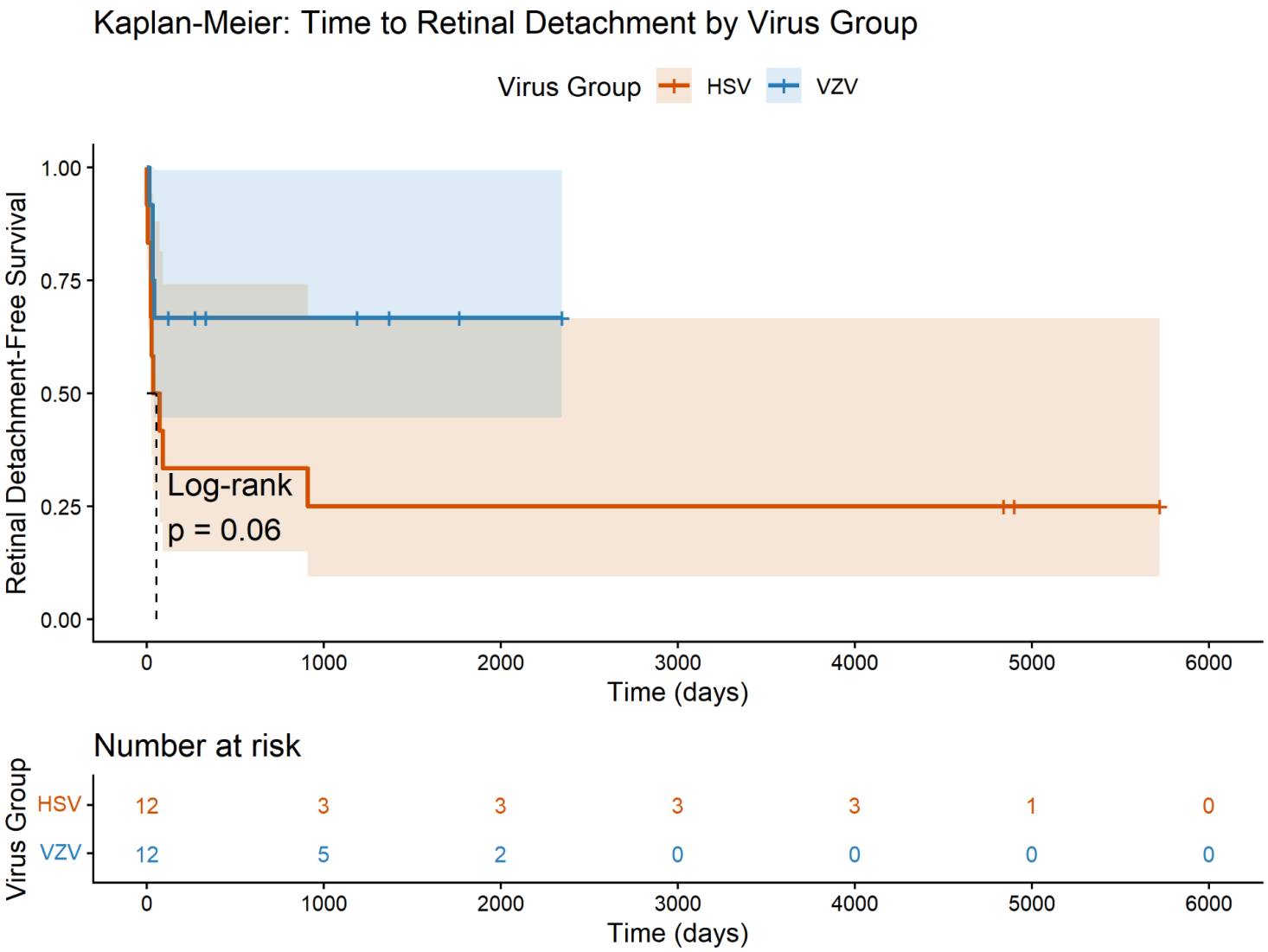


Figure 1

Kaplan-Meier: Time to Retinal Detachment by Virus Group

Kaplan–Meier survival curves comparing time to retinal detachment in eyes with VZV- and HSV-associated acute retinal necrosis. Tick marks indicate censored observations. P value derived from the log-rank test.

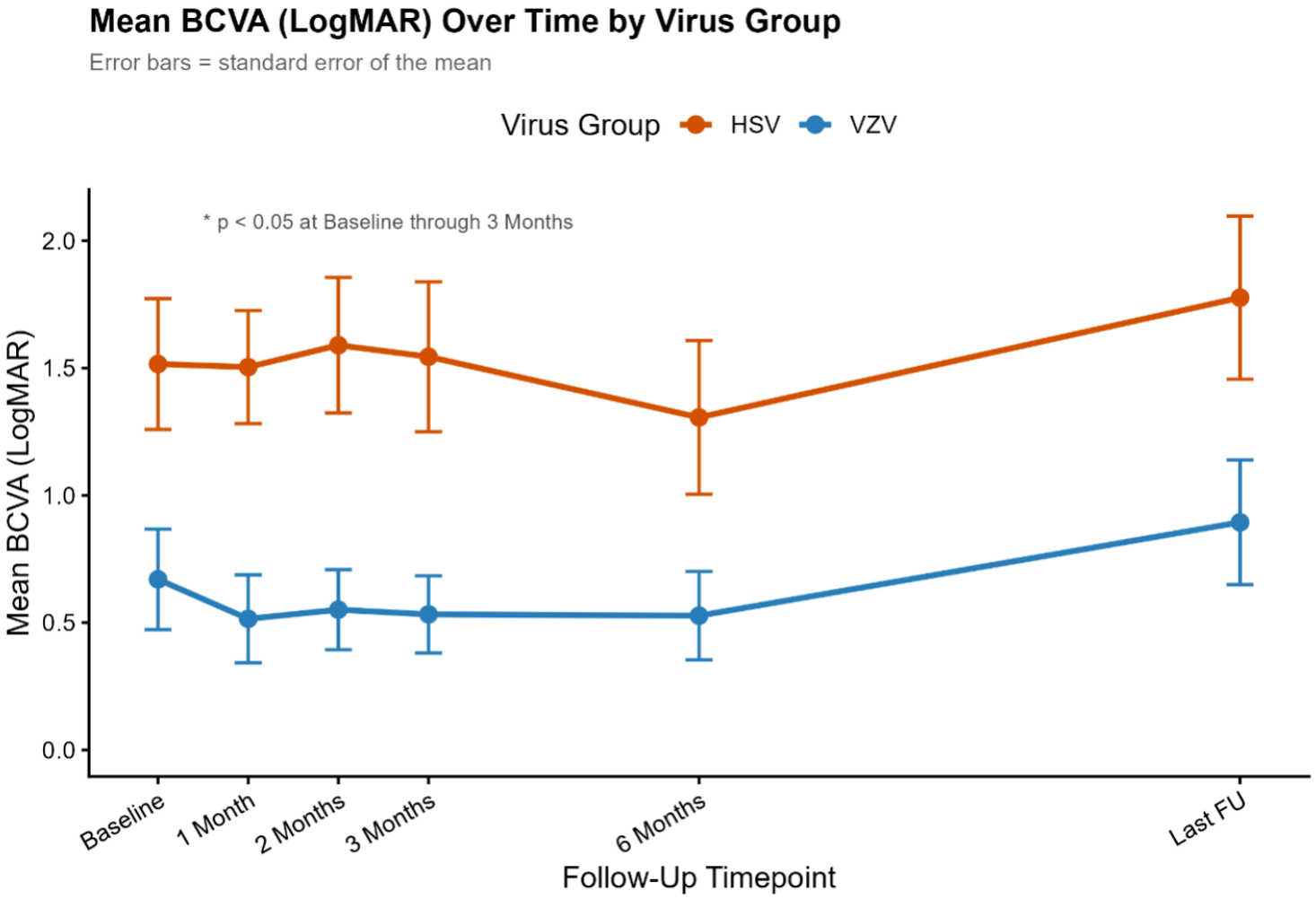


Figure 2

BCVA Over Time

Mean best-corrected visual acuity (BCVA; LogMAR) over time in eyes with VZV- and HSV-associated acute retinal necrosis from presentation to final follow-up. Lower LogMAR values indicate better visual acuity.

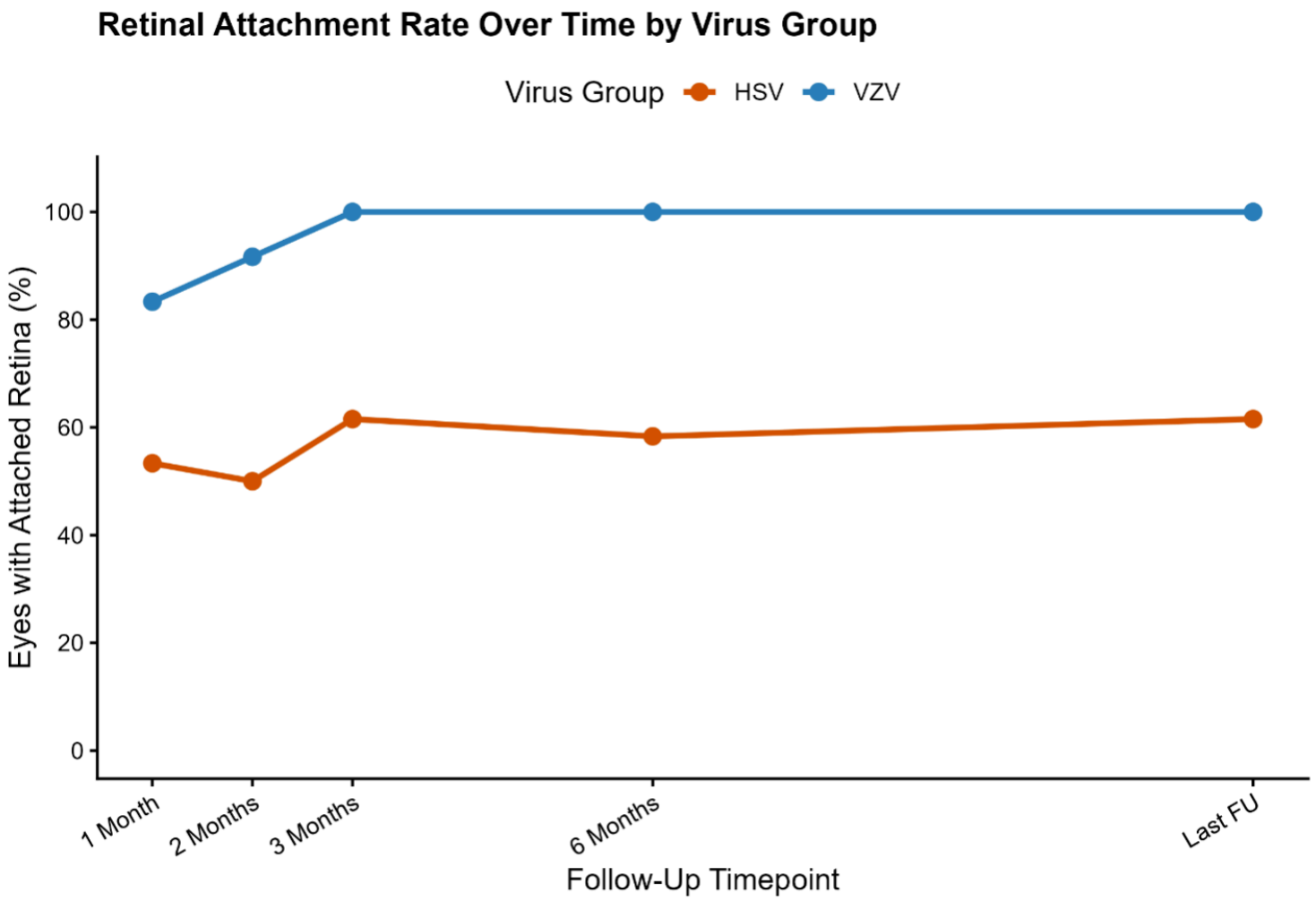


Figure 3

Retinal Attachment Rate Over Time by Virus Group

Retinal attachment rates over time in patients with VZV- and HSV-associated acute retinal necrosis.

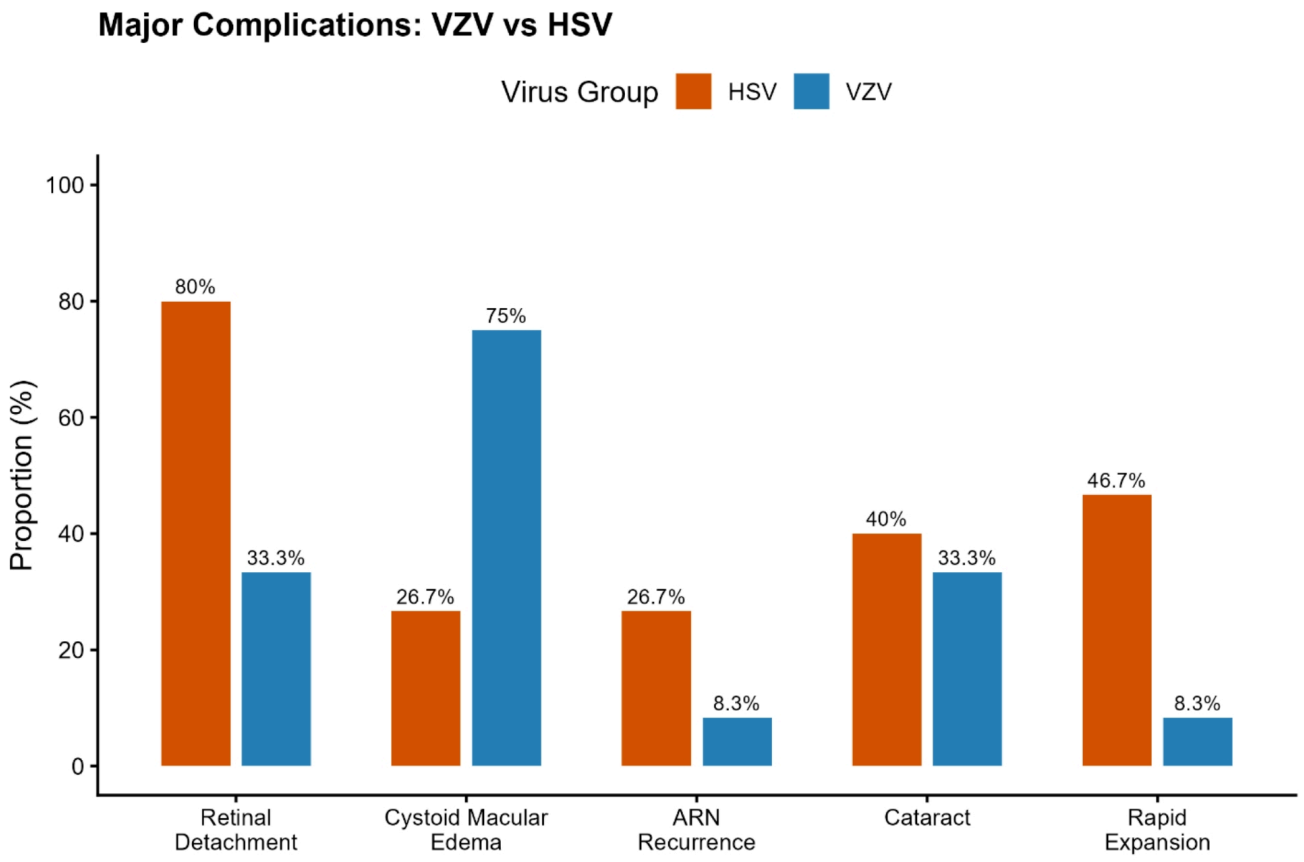


Figure 4

Major Complications: VZV vs HSV

Comparison of the major ocular complications observed during follow-up in VZV- and HSV-associated acute retinal necrosis, including retinal detachment, cystoid macular edema, rapid retinal lesion progression, recurrence, and fellow-eye involvement.