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Review article

Antiviral treatment for acute retinal necrosis: A systematic review and meta-analysis

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ABSTRACT

Acute retinal necrosis is a progressive intraocular inflammatory syndrome characterized by diffuse necrotizing retinitis that can lead to a poor visual outcome, mainly from retinal detachment. The antiviral treatment approach for acute retinal necrosis varies as there are no established guidelines. We summarize the outcomes of acute retinal necrosis with available antiviral treatments. Electronic searches were conducted in PubMed/MEDLINE, EMBASE, Scopus, and Google Scholar for interventional and observational studies. Meta-analysis was performed to evaluate the pooled proportion of the predefined selected outcomes. This study was registered in PROSPERO (CRD42022320987). Thirty-four studies with a total of 963 participants and 1,090 eyes were included in the final analysis. The estimated varicella-zoster virus and herpes simplex virus polymerase chain reaction-positive cases were 63% (95% CI: 55–71%) and 35% (95% CI: 28–42%), respectively. The 3 main antiviral treatment approaches identified were oral antivirals alone, intravenous antivirals alone, and a combination of systemic (oral or intravenous) and intravitreal antivirals. The overall pooled estimated proportions of visual acuity improvement, recurrence, and retinal detachment were 37% (95% CI: 27–47%), 14% (95% CI: 8–21%), and 43% (95% CI: 38–50%), respectively. Patients treated with systemic and intravitreal antivirals showed a trend towards better visual outcomes than those treated with systemic antivirals (oral or intravenous) alone, even though this analysis was not statistically significant (test for subgroup differences P = 0.83).

1. Introduction

Acute retinal necrosis (ARN) is a progressive intraocular inflammatory syndrome characterized by diffuse necrotizing retinitis with associated features of retinal periarteritis, various degrees of vitritis, and vasculitis.[41,50] ARN is often complicated by rhegmatogenous retinal detachment (RRD).[41,50] Diagnosis of ARN, according to the American Uveitis Society, is based on the clinical appearance of (1) one or more foci of retinal necrosis located in the peripheral retina with distinct border, (2) rapid progression with no antiviral therapy, (3) circumferential spread, (4) evidence of occlusive vasculopathy with arterial involvement, and (5) significant inflammatory reaction in the vitreous and anterior chamber.[29,41] The estimated incidence of ARN is 0.5–0.63 new cases per million annually in the United Kingdom[16]; however, the exact incidence of ARN is unknown.[3] The pathology observed in ARN results from viral infections, primarily caused by the varicella-zoster virus (VZV) and herpes simplex virus type 1 and 2 (HSV-1 and HSV-2).[36,41] ARN can lead to poor visual outcomes associated with its complications, including RRD and phthisis bulbi.[28,41] Hedayatfar and coworkers reported that 61.1% of eyes with ARN progressed to RRD within a median time of 12 (6–22) weeks following disease onset. They found that the occurrence of RRD was not associated with the etiologic viral pathogen, the extent of retinitis, the administration of intravitreal antiviral, or the application of prophylaxis laser retinopexy[27]; however, conflicting data exist, as another study found a slight increase in RRD risk (odds ratio of 1.23) among those with a larger extent of retinitis.[7] It was also reported that, with an early vitrectomy, the visual outcome was guarded without significant improvement in the final visual acuity (VA).[28]

Establishing the diagnosis and initiating treatment can be challenging, particularly in the early stages. While investigation using polymerase chain reaction (PCR) on a anterior and/or vitreous chamber tap reveals the causative pathogen in approximately 88% of cases,[41] immediate treatment of ARN is recommended without waiting for PCR results to forestall rapid extension of the retinitis and reduce the risk of severe ocular complications.[1] The treatment approach may vary, however, partly due to its low prevalence, making it difficult to obtain sufficient evidence from prospective studies or clinical trials.[42] The most commonly used treatments are intravenous acyclovir, oral valacyclovir, and intravitreal foscarnet.[50] Limited evidence suggests that oral valacyclovir and intravenous acyclovir resulted in comparable plasma drug levels.[1] Additionally, intravitreal foscarnet can be used alongside mainstream systemic antiviral therapy.[50]

Determining the antiviral of choice could be more challenging due to the increasing concern of acyclovir resistance and drug-related systemic adverse effects. The prevalence of acyclovir-resistant HSV has been estimated at around 0.5% in immunocompetent and 3.5–10% in immunocompromised patients.[15,30,52] Several studies have reported moderate to severe systemic adverse effects that may occur following intravenous acyclovir administration, including nausea and vomiting,[38] encephalopathy, renal toxicity,[5] and neuropsychiatric side effects,[58] though the exact incidence is unknown.

Currently, there is no guideline that addresses the optimal antiviral options and duration of treatment for ARN. Given the wide variety of antiviral options available, this systematic

review aims to summarize relevant antiviral treatments and outcomes of ARN from published studies. Moreover, we attempted to stratify our analysis based on the causative viral pathogens and the approach of antiviral therapy.

2. Methods

This systematic review and meta-analysis adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[46] (Supplementary Table 1). In addition, for observational studies, the Meta-analysis of Observational Studies in Epidemiology (MOOSE)[53] checklist was utilized (Supplementary Table 2). This review was prospectively registered in The International Register of Systematic Review Protocols (PROSPERO; CRD42022320987). Institutional review board approval was not required since this study analyzed publicly available data from published studies and did not involve individual-level data (Table 1).

2.1. *Eligibility criteria for considering studies for this review*

We conducted a comprehensive search for interventional, observational (prospective cohort, retrospective cohort, case-control), and case series studies that reported the use of antivirals in ARN patients. The primary goal of this meta-analysis was to analyze the response to antiviral treatment, with a particular focus on quantifying the estimated proportions of resolution of retinitis and its associated inflammation. Additionally, we analyzed other reported treatment outcomes, such as recurrence of the disease, VA improvement, RRD, and other complications, whenever the data was available.

2.2. *Study selection and data extraction*

We performed a two-stage selection process: first, by evaluating titles and abstracts, and then by assessing full-text articles. Two authors (A. S. R. and M. D.) independently screened the title and abstracts and subsequently evaluated the full texts of the included papers. During this process, we documented the reasons for noninclusion and also identified potential additional articles from reference lists. Any disagreements that arose were resolved through consensus by another author (I. P.). We extracted data from the included full texts, which encompassed the study site and year, patient demographics, diagnostic investigations for ARN (including PCR and its result), details of treatment regimen (antivirals and corticosteroids), treatment duration, follow-up duration, and information regarding our target treatment outcomes (resolution of retinitis, VA improvement, recurrence of the disease, and ocular morbidity or complications). VA improvement was specifically defined as any reported improvement in VA using Snellen or LogMAR notations. Three reviewers (I. P., A. S. R., M. D.) independently extracted the data into a predefined template and cross-verified it for accuracy. In case for any discrepancies, consensus was reached through discussion. If further information was required, we tried to contact the corresponding authors of included studies to the best of our ability.

2.3. *Data collection and risk of bias assessment*

The risk of bias in included studies was assessed by 2 reviewers (A. S. R. and M. D.) using the Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I) tool. In case where any discrepancies arose in the bias assessment, they were resolved through consensus by involving another author (I. P.).

2.4. *Data synthesis and analysis*

We conducted a meta-analysis of proportions to evaluate the pooled outcomes, including resolution of retinitis, VA improvement, recurrence, and complications, as well as PCR positivity for HSV and VZV. We then performed stratified analyses based on the causative viral pathogen and treatment approach. This allowed us to estimate the proportion of VA improvement and RRD in ARN patients who tested positive for VZV or HSV separately. Similarly, we conducted separate analyses to assess VA improvement and recurrence among patients treated with oral antivirals alone, intravenous antivirals alone, and a combination of systemic and intravitreal antivirals. To assess heterogeneity between the studies, we quantified I^2, which estimates the percentage of variability between studies. An I^2 of $> 75\%$ indicated considerable heterogeneity. Given the expected heterogeneity across studies, we utilized random-effect modeling using the DerSimonian and Laird method. We considered P-values < 0.05 as statistically significant. Furthermore, we constructed a funnel plot to inspect the potential for publication bias. The statistical analysis was performed using MetaXL 5.3 (www.epigear.com)

Table 1 – Search strategy used in each database.

Database	Search query	Results
PubMed/MEDLINE	((acute retinal necrosis[Title/Abstract]) AND ((((valacyclovir[Title/Abstract]) OR (acyclovir[Title/Abstract])) OR (foscarnet[Title/Abstract])) OR (treatment[Title/Abstract]))) AND (((outcome[Title/Abstract]) OR (response[Title/Abstract])) OR (resolution[Title/Abstract]))	107
EMBASE	'acute retinal necrosis' AND ('treatment' OR 'foscarnet' OR 'valacyclovir' OR 'acyclovir') AND ('outcome' OR 'resolution' OR 'response')	226
Scopus	TITLE-ABS-KEY (('acute AND retinal AND necrosis') AND (treatment OR acyclovir OR valacyclovir OR foscarnet) AND (outcome OR resolution OR response))	379
Google Scholar	allintitle: treatment OR valacyclovir OR acyclovir OR foscarnet "acute retinal necrosis"	105

add-on in Microsoft Excel 365 for windows and the R package dmetar (dmetar.protectlab.org/#dmetar; doi:10.5281/zenodo.2551803). The latter was used to generate forest plots in the result section.

3. Results

We retrieved a total of 817 publications from 4 databases, out of which 34 were included in the final analysis (Fig. 1). No additional publications were retrieved through manual reference mining. The characteristics of the included studies are displayed in Table 2. Most of the included studies are retrospective cohort or case series studies. The diagnosis of ARN was primarily based on clinical criteria, particularly the American Uveitis Society criteria. From the 34 studies, we identified 963 participants with a total of 1,090 eyes for further analysis. The funnel plot displayed symmetry (Supplementary Fig.), indicating that publication bias is unlikely to affect the interpretation of our results.

3.1. *Risk of bias assessments*

The risk of bias assessment was conducted with the ROBINS-I tool.[43] Across all domains, all studies showed a range of bias from low to serious. Only one study was found to have a serious risk of bias. In some case series studies, bias in the classification of interventions could not be assessed. The summary of the risk of bias assessment is presented in Fig. 2.

3.2. *PCR positivity for HSV-1/HSV-2 and VZV in ARN*

Twenty-four studies reported data on ocular fluid investigation in ARN. Among 963 ARN patients identified on these articles, 700 underwent PCR testing, and 364 of them (52.0%) tested positive for at least one causative pathogen. Specifically, out of 700 patients tested, 566 had reported results for the particular pathogen being investigated. The estimated PCR positivity rates for VZV and HSV (HSV-1/HSV-2) were 63% (95% CI: 55–71%) and 35% (95% CI: 28–42%), respectively (Fig. 3). Fig. 3 also showed slight variability in VZV and HSV positivity rates across different regions that was statistically significant different ($P < 0.01$). Additionally, a small number of cases were positive for cytomegalovirus (CMV) and Epstein-Barr virus (EBV); see Supplementary Table 3.

3.3. *Treatment approaches and general outcomes*

Regarding the treatment approach for ARN, substantial heterogeneity in drug combinations and duration was observed (Table 3). Three main treatment approaches were identified in this study: (1) oral antivirals alone, (2) intravenous antivirals alone, and (3) a combination of systemic antivirals,

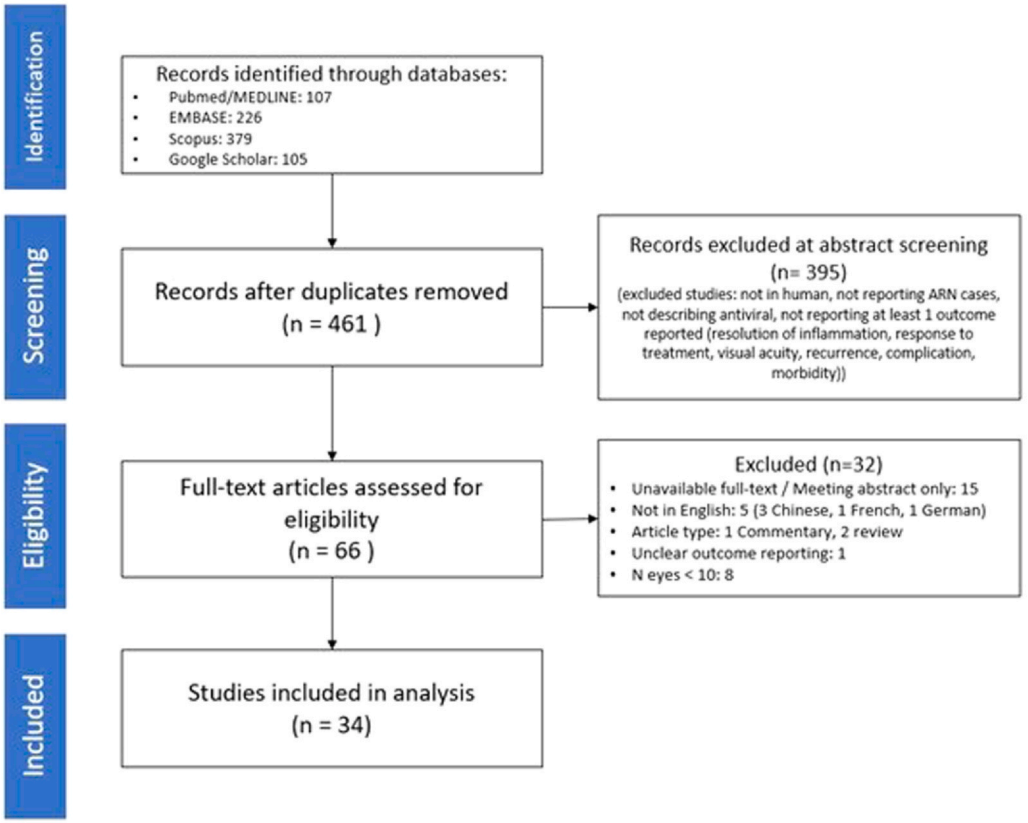

Fig. 1 – PRISMA flowchart.

Table 2 – Characteristics of included studies.

No	Authors (year)	Country	Design	N Patients	N Eyes	N Immunocompromised patients (%)	Diagnosis of ARN
1	Bavinger et al[7] (2022)	USA	Retrospective cohort	47	54	12 (25.5)	Clinical (unspecified)
2	Mayer et al[42] (2022)	Germany	Retrospective cohort	10	16	N/A	American Uveitis Society criteria
3	Choi et al[14] (2022)	Korea	Retrospective cohort	55	61	13 (23.6)	American Uveitis Society criteria
4	Botsford et al[10] (2021)	USA	Retrospective cohort	18	22	N/A	Clinical suspicion with PCR confirmation (HSV or VZV) from aqueous humor
5	Debiec et al[20] (2021)	USA	Retrospective cohort	21	23	2 (9.5)	American Uveitis Society criteria
6	Hedayatfar et al[27] (2021)	Iran	Retrospective cohort	18	18	2 (11.1)	American Uveitis Society criteria
7	Lei et al[37] (2021)	China	Retrospective cohort	20	20	0 (0)	American Uveitis Society criteria
8	Urzua et al[57] (2021)	USA, Chile, Mexico	Retrospective cohort	34	38	N/A	American Uveitis Society criteria
9	Paolo et al[48] (2020)	Italy and Switzerland	Retrospective cohort	39	39	N/A	Clinical (unspecified)
10	Taubenslag et al[54] (2020)	France	Retrospective cohort	24	25	N/A	American Uveitis Society criteria
11	Hafidi et al[26] (2019)	France	Retrospective cohort	24	25	8 (33.3)	American Uveitis Society criteria
12	Kim et al[34] (2019)	Korea	Retrospective cohort	35	43	N/A	(1) Acute onset panuveitis; (2) obstructive retinal vasculitis (arteritis and phlebitis); and (3) peripheral necrotizing retinitis (usually multifocal). Patients who had other ocular diseases that could affect vision were excluded from the study
13	Miserocchi et al[45] (2019)	Italy	Retrospective cohort	15	30	N/A	Clinical, defined by the presence of acute panuveitis, occlusive retinal vasculitis with or without retinal hemorrhages, and peripheral necrotizing retinitis with or without retinal tears and optic disc swelling. PCR supported the clinical diagnosis on intraocular fluids (aqueous or vitreous).
14	Baltinas et al[6] (2018)	UK	Retrospective cohort	62	68	11 (18)	Clinical with confirmation by PCR when possible
15	Dorman et al[21] (2018)	Australia	Retrospective cohort	46	50	3 (6.5)	American Uveitis Society criteria
16	Liu et al[39] (2018)	China	Retrospective cohort	30	34	N/A	American Uveitis Society criteria
17	Butler et al[12] (2017)	USA	Retrospective cohort	36	41	17 (47)	American Uveitis Society criteria
18	Khochtali et al[33] (2015)	Tunisia	Retrospective cohort	12	12	0 (0)	American Uveitis Society criteria
19	Roy et al[49] (2014)	India	Retrospective cohort	53	62	2 (3.8)	Based on the presence of (1) acute panuveitis, (2) occlusive retinal vasculitis (arteritis and phlebitis) with or without retinal hemorrhage, and (3) peripheral patchy necrotizing retinitis (usually multifocal)
20	Brydak-Godowska et al[11] (2014)	Poland	Retrospective cohort	10	11	4 (40)	Clinical presentation and positive serological test results for herpes viruses.
21	Flaxel et al[23] (2013)	USA	Retrospective cohort	24	29	N/A	American Uveitis Society criteria
22	Cochrane et al[16] (2012)	UK	Retrospective cohort	45	52	13 (29)	American Uveitis Society criteria
23	Jeon et al[31] (2012)	Korea	Retrospective cohort	55	62	N/A	Peripheral necrotizing retinitis with or without retinal breaks, acute panuveitis, occlusive retinal vasculitis with retinal hemorrhage, and optic disc swelling.
24	Taylor et al[55] (2012)	UK	Retrospective cohort	9	10	2 (22.2)	American Uveitis Society criteria
25	Meghpara et al[44] (2010)	USA	Retrospective cohort	20	25	0 (0)	Clinical (unspecified)
26	Tibbetts et al[56] (2010)	USA	Retrospective cohort	58	58	11 (19)	American Uveitis Society criteria
27	Sims et al[51] (2009)	Australia	Retrospective cohort	22	23	12 (54.5)	American Uveitis Society criteria
28	Hillenkamp et al[28] (2009)	Germany	Retrospective cohort	27	30	N/A	American Uveitis Society criteria

(continued on next page)

Table 2 – (continued)

No	Authors (year)	Country	Design	N Patients	N Eyes	N Immunocompromised patients (%)	Diagnosis of ARN
29	Aizman et al[2] (2007)	USA	Retrospective cohort	8	10	N/A	Clinical (unspecified)
30	Lau et al[36] (2007)	UK	Retrospective cohort	22	27	N/A	Clinical diagnosis of ARN was based on the presence of (1) acute panuveitis, (2) occlusive retinal vasculitis (arteritis and phlebitis) with or without retinal hemorrhage, and (3) peripheral patchy necrotizing retinitis (usually multifocal) with or without retinal breaks and optic disc swelling. Other symptoms and signs when present are supportive of diagnosis: ocular or periocular pain, conjunctivitis, episcleritis, scleritis, rapid circumferential spreading and coalescence of the necrotizing retinitis, and rhegmatogenous retinal detachment.
31	Muthiah et al[47] (2007)	UK	Prospective cohort	31	34	7 (22.6)	American Uveitis Society criteria
32	Chen et al[13] (2004)	Taiwan	Retrospective cohort	9	11	N/A	American Uveitis Society criteria
33	Crapotta et al[17] (1993)	USA	Retrospective cohort	12	13	N/A	Clinical evaluation and lab results
34	Blumenkranz et al[9] (1986)	USA	Retrospective cohort	12	14	N/A	Clinical (unspecified)

ARN = acute retinal necrosis; HSV = herpes simplex virus; VZV = varicella-zoster virus.

either oral or intravenous, with intravitreal antivirals. No study reported using standalone intravitreal antivirals in ARN treatment. Systemic corticosteroids were frequently administered alongside antivirals; however, we were unable to separate the analysis among ARN patients with and without steroids with the available data. A potential for indication-for-treatment bias could not be ruled out in all analyses.

Overall, the pooled estimate of the resolution of retinitis was 93% (95% CI 80–99%), based on data from 5 studies that clearly stated the number of patients with resolution of retinitis (and associated inflammation) using clinical descriptions of inactive retinal lesions; however, most studies also reported other outcomes, such as VA improvement, recurrence, and complication related to retinal lesions (Fig. 4). Owing to the high variability of the follow-up periods among the included studies, we were unable to specify these proportions over a specific time range or generate the pooled incidence rate of reported outcomes (see Supplementary Table 4). The pooled estimate of VA improvement and recurrences were 37% (95% CI 27–47%) and 14% (95% CI 8–21%), respectively. Additionally, the pooled estimate of RRD as a complication was 43% (95% CI 38–50%). Other reported complications of ARN are presented in Table 4.

3.4. *Outcomes according to the viral etiology*

Figs. 5 and 6 display the pooled estimate of VA improvement and RRD for each viral etiology. Overall, there was a comparable VA improvement rate in VZV and in HSV cases: VZV (58% [95% CI 46–70%]) vs HSV-1/HSV-2 (56% [95% CI 34–76%]), test for subgroup difference, P = 0.84 (Fig. 5). However, there was a trend towards a lower proportion of RRD for VZV than HSV (VZV - 36% [95% CI 20–55%] vs HSV-1/HSV-2 - 56% [95% CI 42–69%], test for subgroup difference, P = 0.09) (Fig. 6).

In general, we observed a difference in the age of ARN patients at the time of presentation between cases proven to be caused by VZV and those caused by HSV. The reported mean age of VZV-positive patients generally ranged between 55 and 85 years old, while HSV-positive patients were between 30 and 50 years old.[7,10,55] From Bavinger and coworkers' study, VZV patients were more likely to be immunocompromised (HSV 3.7% vs VZV 40.7%, P = 0.001).[7]

3.5. *Outcomes according to the antiviral approaches*

Figs. 7 and 8 compare the estimates for VA improvement and recurrence estimates among the three main antiviral approaches. Of note, these approaches are categorized based on the treatment induction phase. In the present analysis, all reported combinations of intravitreal antivirals with either oral or systemic antivirals were analyzed as a unified group. In general, there was a trend towards the best VA improvement with the combination of systemic and intravitreal antivirals (32%, 95% CI: 20–38%) compared to oral antivirals alone (22%, 95% CI: 5–59%) and intravenous antivirals alone (27%, 95% CI: 17–39%), although this difference was not statistically significant (P = 0.83). The decision to give the combination of systemic and intravitreal antivirals was mainly based on clinical judgment, with some explicitly stating a

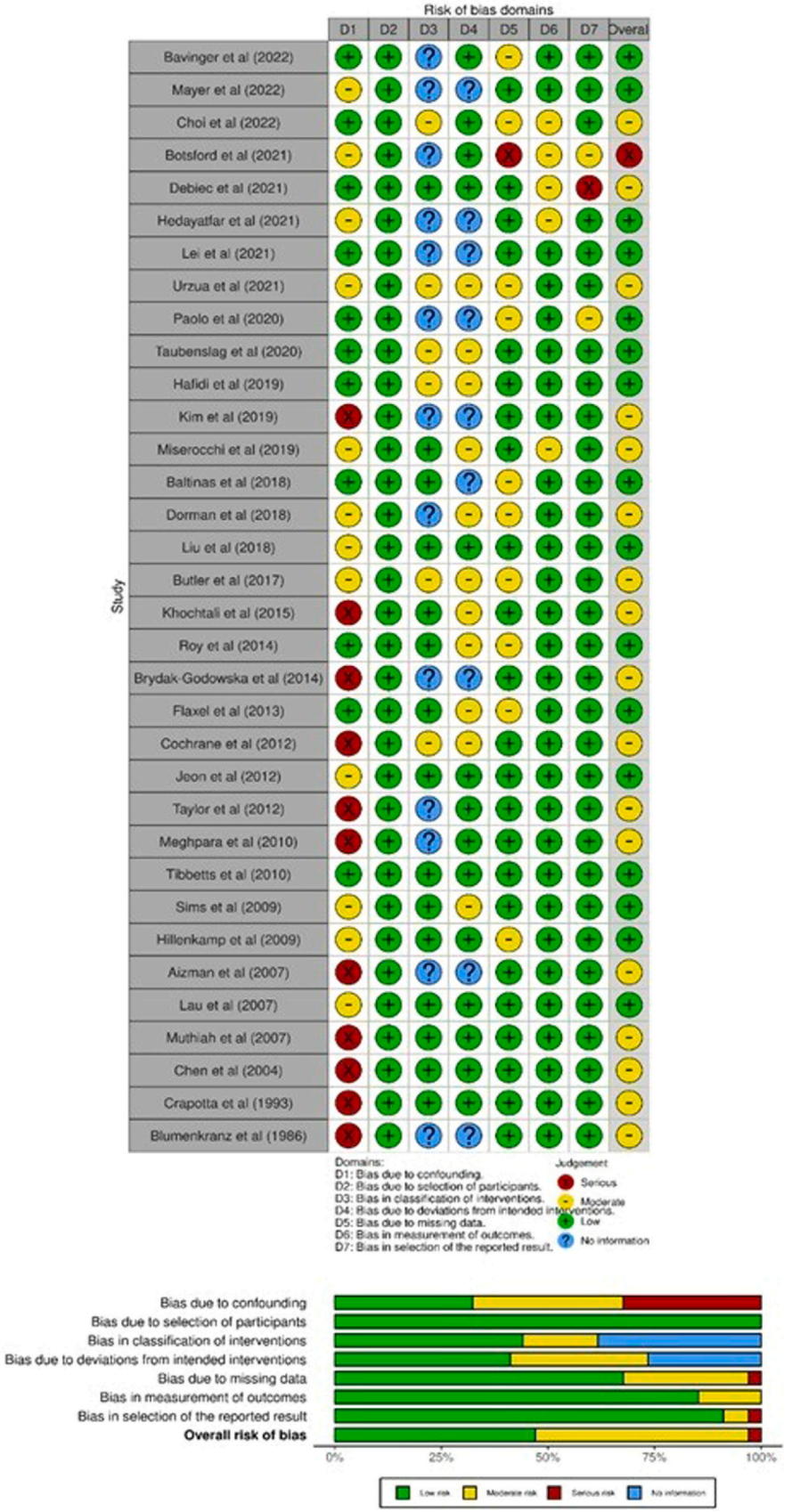

Fig. 2 – Risk of bias assessment using ROBINS-I tool.

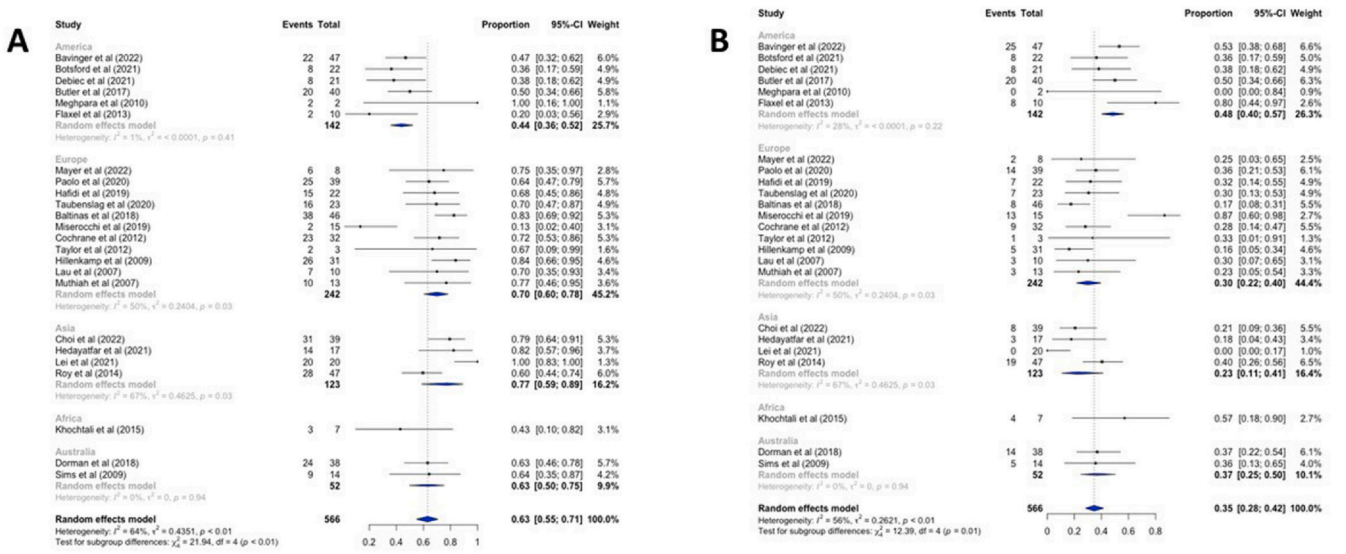

Fig. 3 – PCR positivity rates for VZV (A) and HSV-1/HSV-2 (B) among PCR-confirmed acute retinal necrosis with further region-based analysis. VZV = varicella-zoster virus; HSV = herpes simplex virus.

preference for this option in more severe or progressive cases. In our analysis of the combination of systemic and intravitreal regimens, we could not identify the specific antiviral drugs that performed better than the others for systemic and intravitreal administration. Moreover, we did not find any clear pattern indicating which antivirals would be the superior option for specific pathogen. Additionally, we observed a wide variation in the duration of observation to detect recurrences (Supplementary Table 4).

3.6. *Adverse effects of antivirals in ARN*

Aizman and coworkers reported no clinical or laboratory systemic adverse effects following oral acyclovir treatment.[2] Similarly, Blumenkranz and coworkers did not report any clinical adverse effects either.[9] In a study by Butler and coworkers, however, it was noted that 26% of patients using systemic antiviral treatment experienced systemic adverse effects, including acute renal failure (n = 2), electrolyte and mineral imbalances (n = 4), seizures (n = 1), gastrointestinal disturbance (n = 1), fatigue (n = 1), and hypertension (n = 1). Nevertheless, they did not specify whether these adverse effects specifically associated with intravenous or oral antiviral treatment.[12]

4. Discussion

In this systematic review, we identified 3 main treatment approaches for ARN management: (1) oral antivirals alone, (2) intravenous antivirals alone, and (3) a combination of systemic antivirals, either oral or intravenous, with intravitreal antivirals. When comparing the treatment approaches, the combination of intravitreal and systemic antiviral treatment demonstrated a trend towards better VA improvement and recurrence rates; however, the results did not reach statistical significance. As head-to-head comparisons were lacking in the included studies, we estimated the outcomes for each individual treatment approach and performed indirect comparisons of the outcome estimates among them.

In our analysis, we observed that although the pooled estimate of visual outcome was slightly better in VZV-positive cases than HSV-positive cases, VZV was more prevalent than HSV in causing ARN. Reactivation of HSV typically involves only a limited number of neurons, whereas VZV involves multiple peripheral neurons originating from the host ganglia, with extensive intraganglionic spread of viruses before affecting the peripheral targets. In cases of VZV reactivation in other organs, such as the skin, it is known to cause eruption and may lead to severe chronic pain known as postherpetic neuralgia, which can persist even with treatment.[32,35] Further, we observed that VZV-proven ARN showed a tendency to occur in older age group compared to those with HSV-proven ARN; however, it remains unclear whether the slight difference in visual outcomes between HSV and VZV-proven cases is due to the biological characteristics of each virus mentioned above, differences in the immune response against the viruses (which may also be influenced by age), or differences in vitreous and retinal conditions in different age groups (vitreous syneresis with aging). Unfortunately, we could not perform subsequent analysis considering age as a confounding factor for the outcomes as we did not have access to individual patient data and relied on the reported outcomes in the included studies.

In our study we were unable to determine which specific antiviral (i.e., ganciclovir vs foscarnet) is superior to the other. It is worth mentioning that the availability of certain

Table 3 – Details of antiviral treatment strategies in ARN management extracted from included studies.

Approach of antiviral	Drugs	Summary of antiviral treatment description available from studies	Additional remarks
Systemic (Oral)	Valacyclovir[2,6,12,21,54,55]	Initial phase: Valacyclovir 1–2 g 3 times daily until complete resolution of retinitis (Variable between 7 and 24 weeks) Maintenance phase alternatives: 1. Valacyclovir slowly tapered over 2–6 months (Tapered: up to 24 weeks) 2. Acyclovir 5 × 800 mg or oral valacyclovir 1 g three times daily for VZV; Acyclovir 5 × 400 mg for HSV	Concomitant/adjunct treatment: 1. Oral prednisone (40–60 mg/day) was generally added 1–3 weeks after oral antiviral therapy.[2,11,27] 2. Dosing adjustment in renal failure patient.[6,55] 3. Consideration of combine aspirin with oral acyclovir.[11] 4. Intravenous methylprednisolone.[21]
	Famciclovir[2,12,23]	Initial phase: Famciclovir 500 mg 3 times daily until complete resolution of retinitis (up to 24 weeks) Maintenance phase: Famciclovir slowly tapered over 2–6 months (tapered up to 24 weeks)	
	Acyclovir[11,12,23]	Acyclovir 800 mg 5 times daily	
Systemic (Intravenous)	Acyclovir[6,9,11,13,14,16,17,21,23,26,31,33,34,44,47,51,56,57]	Intravenous acyclovir 10 mg/kg every 8 hours or 1500 mg/m^2/day in three divided doses for 7–21 days (mean/median of 10 days) Maintenance phase alternatives: 1. 400 mg oral acyclovir 5 times/day for 2 weeks–3 months (incl those with HSV) 2. Oral acyclovir 800 mg five times/day for 12 weeks or more*. 3. Oral valacyclovir 1 g three times/day (incl those with VZV) up to but not limited to 12 weeks *Prolonged use up to 24 months is also reported.	Concomitant/adjunct treatment: 1. Consideration of combine with heparin or coumadin, or aspirin.[9] 2. Consideration of prescribe systemic corticosteroid in all or some patients,[6,14,23,26,33] including: a. Oral prednisone in dosages of 30–120 mg daily or 0.5–1 mg/kg/day in response to increasing vitreous inflammation or severe optic nerve dysfunction 2–10 days after acyclovir initiation. b. Routine use of oral prednisolone 1 mg/kg daily for 7–10 days, tapered by 10 mg every 5 days.
	Others: foscarnet or ganciclovir[12,21,54]	Undetailed description (Though foscarnet and ganciclovir were prescribed, the detailed description of intravenous foscarnet and ganciclovir regimen in the cited studies was not provided).	1. A combination of intravenous foscarnet and ganciclovir for very severe cases.[54] 2. Intravenous treatment was continued until complete resolution of retinitis; the median duration was 24 days (range: 15–48 days).[54]

(continued on next page)

Table 3 – (*continued*)

Approach of antiviral	Drugs	Summary of antiviral treatment description available from studies	Additional remarks
Combination of systemic and intravitreal antivirals	Oral famciclovir + Intravitreal foscarnet[2,20,21,23]	Intravitreal foscarnet 2.4 mg/0.1 cc on the day of the initial visit + oral famciclovir 500 mg 3 times daily (Full dose: 8 weeks, tapered up to 18 weeks)	1. Consideration of intravenous acyclovir than oral antiviral for patients with VA poorer than 20/200 or bilateral ARN.[20] 2. Consideration of systemic corticosteroid.[2,10,20,23,26,27,33,39] 3. In severe cases: replacing intravenous acyclovir with a combination of intravenous foscarnet and ganciclovir.[26]
	Intravenous acyclovir + intravitreal foscarnet[10,21,23,26,51]	Initial phase: Intravenous acyclovir 10 mg/kg per dose for 10 days + intravitreal foscarnet injections every 72 hours for a total of three to four. Maintenance phase: either oral acyclovir or valacyclovir for at least 6 months or reduced to 1 g twice daily and tapered to a long-term prophylactic dosage of 1 g daily at the treating physician's discretion.	
	Oral valacyclovir + intravitreal foscarnet[20,21,23,26]	Initial phase: Valacyclovir 1 g orally 2–3 times daily + intravitreal foscarnet 2.4 mg/0.1 mL twice weekly as induction treatment until retinitis stabilized, at which time the frequency was decreased to once weekly until retinitis was considered inactive. Maintenance phase: Oral valacyclovir 1 g twice daily and tapered to a long-term prophylactic dosage of 1 g daily at the treating physician's discretion.	
	Oral valacyclovir + ganciclovir intravitreal injection/ implant[12,20,21,23,26,27]	Initial phase: Valacyclovir 1–2 g orally 2–3 times daily + ganciclovir implant (Vitrasert; Bausch and Lomb, Rochester, NY) or intravitreal ganciclovir 2.0 mg/0.1 mL twice weekly as induction treatment until retinitis stabilized, at which time the frequency was decreased to once weekly until retinitis was considered inactive. Maintenance phase: Oral valacyclovir 1 g twice daily and tapered to a long-term prophylactic dosage of 1 g daily at the treating physician's discretion.	
	Intravenous acyclovir + intravitreal ganciclovir[12,34,39,42]	Initial phase: IV acyclovir 10 mg/kg/day three times daily (7–10 days) + intravitreal ganciclovir 2 mg/0.04 mL or 2 mg/0.1 mL or 3 mg Maintenance phase alternatives: 1. Oral acyclovir 5 × 800 mg (or oral acyclovir 5 × 400 mg for HSV) for 6 weeks–6 months 2. Oral valacyclovir 3 × 1000 mg for 6 weeks–6 months	
	Intravenous acyclovir + intravitreal acyclovir (Surgical option)[28]	Intravenous acyclovir 10 mg/kg three times daily + pars plana vitrectomy with or without scleral buckling and silicone oil or gas tamponade + intravitreal acyclovir lavage 40 ug/mL during vitrectomy	
	Intravenous acyclovir + oral valacyclovir + intravitreal ganciclovir[37,57]	1. Intravenous acyclovir 10 mg/kg for 14 days + ganciclovir 4 mg/0.1 mL twice a week (max 9 injections in 4 weeks) + oral valaciclovir 2000 mg three times daily for 2 weeks followed by 1000 mg for maintenance. 2. Intravenous acyclovir 3 × 10 mg/kg + intravitreal ganciclovir 2000 ug/0.1 mL + oral valacyclovir for 7–10 days followed by oral acyclovir 5 × 800 mg or valacyclovir 3 × 1000 mg for > 12 weeks.	

ARN = acute retinal necrosis; HSV = herpes simplex virus; VZV = varicella-zoster virus; VA = visual acuity.

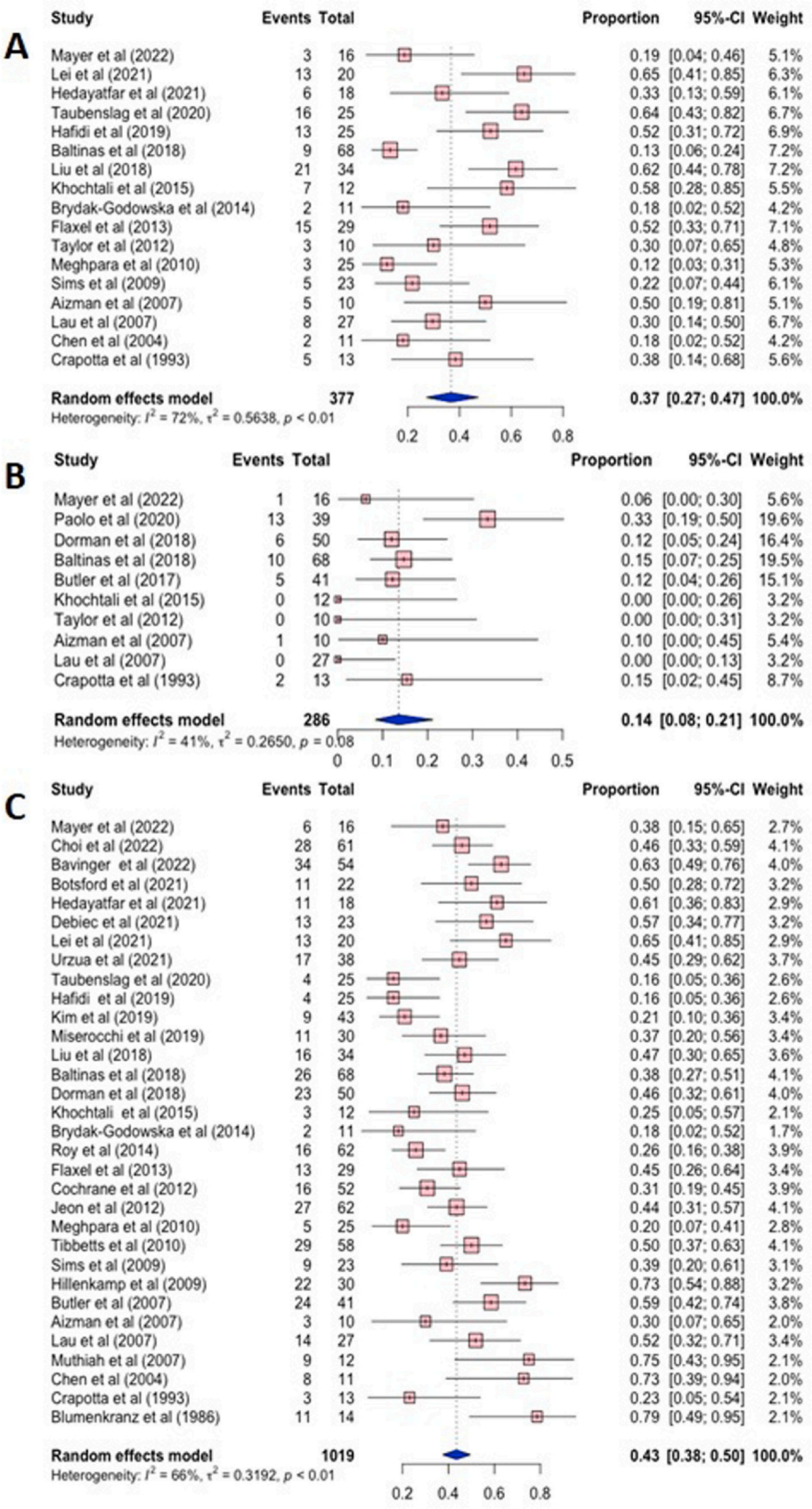

Fig. 4 – Forest plots showing pooled outcomes in acute retinal necrosis patients: visual acuity improvement (A), recurrence (B), and retinal detachment (C).

Table 4 – Reported complications in ARN.

Complications	N studies	N eyes at risk	N eyes affected	Pooled estimate[1] (95% CI)	I^2
Retinal detachment	32	1019	440	43% (95% CI 38–50%)	66%
Cataract	7	178	60	17.03% (1.00–42.71%)	91%
Optic atrophy	10	345	61	17.57% (9.29–27.68%)	79%
Epiretinal membrane	4	144	46	27.16% (13.53–43.23%)	71%
Uveitic macular edema	4	118	28	24.12% (16.83–32.23%)	0%
Phthisical eye/prolonged hypotony	4	165	14	9.02% (5.09–13.90%)	0%
Glaucoma[2]	6	186	11	6.65% (3.48–10.71%)	0%

ARN = acute retinal necrosis.

[*] The pooled estimates were based on the frequency of reported complications in each included study without specifying a particular time period because follow-up duration varied between studies (see Supplementary Table 4). The pooled incidence rates for a specific period of time could not be generated.

[†] Glaucoma complication includes any reported glaucoma (i.e., neovascular glaucoma) as a complication of ARN. There is no restriction in the criteria used for glaucoma diagnosis (i.e., clinical diagnosis or based on visual field testing).

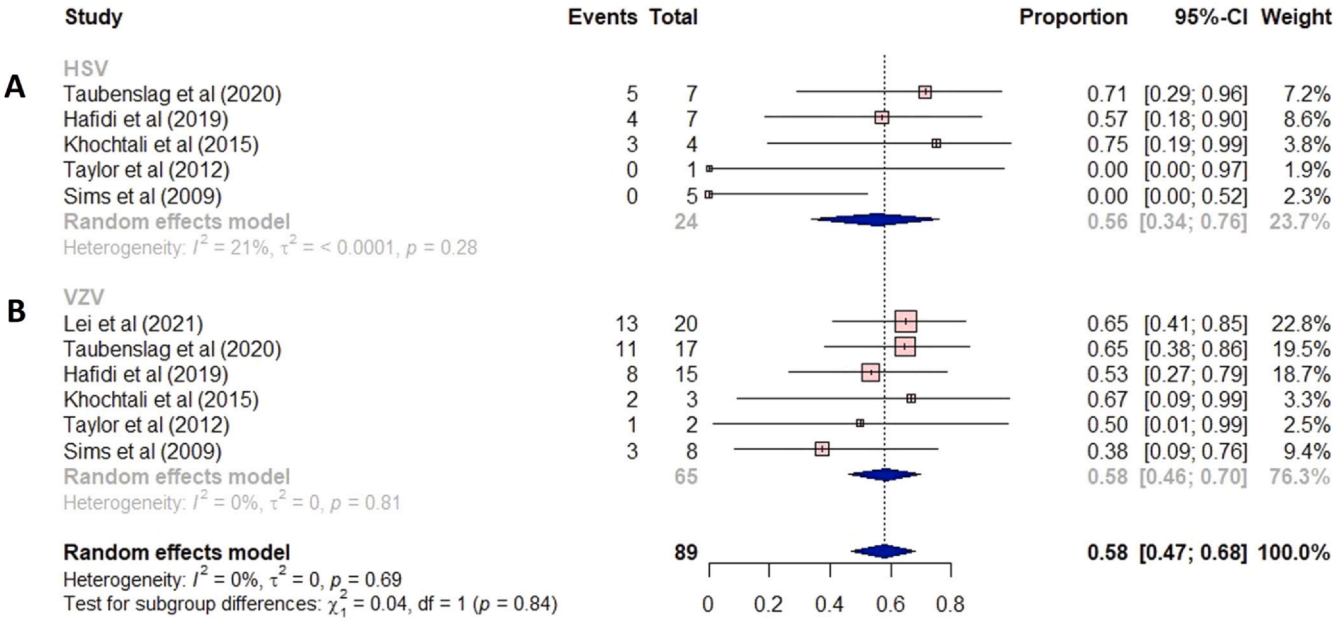

Fig. 5 – Forest plots showing pooled estimates of the proportions of acute retinal necrosis patients who experienced visual acuity improvement. HSV-1/HSV-2 PCR positive (A) and VZV PCR positive (B) VZV = varicella-zoster virus; HSV = herpes simplex virus.

antiviral formulations may vary in different settings, leading to variations in the choice of antiviral and treatment duration based on the preferred practice in each center. Intravitreal injection of antivirals allows for direct delivery to the infection site. Both ganciclovir and foscarnet were used as intravitreal antiviral drugs. Even though we could not directly compare these 2 antivirals, a pharmacokinetic study in rabbit eyes suggested that ganciclovir may be superior to foscarnet.[40] According to this study, intravitreal injection of ganciclovir has better retinal pharmacokinetics than foscarnet.[40] The ganciclovir concentration remains at a higher therapeutic level than foscarnet for 72 hours after intravitreal injection. The ganciclovir concentration in the retina remained higher than that in the vitreous humor 24 hours after injection.[40] By contrast, the foscarnet level in the retina was lower than the vitreous humor level at all time points after injection.[40] The level of ganciclovir in the retina remained above the half-maximal inhibitory concentration (IC_{50}) of herpes viruses even after 36 hours, while this was not the case for foscarnet.[40] Even though it was observed that the clearance rate of foscarnet in the vitreous was slower than ganciclovir, the low level of foscarnet concentration in the retina can be explained by the profile of the drug. Foscarnet is highly ionized and primarily accumulates in the vitreous

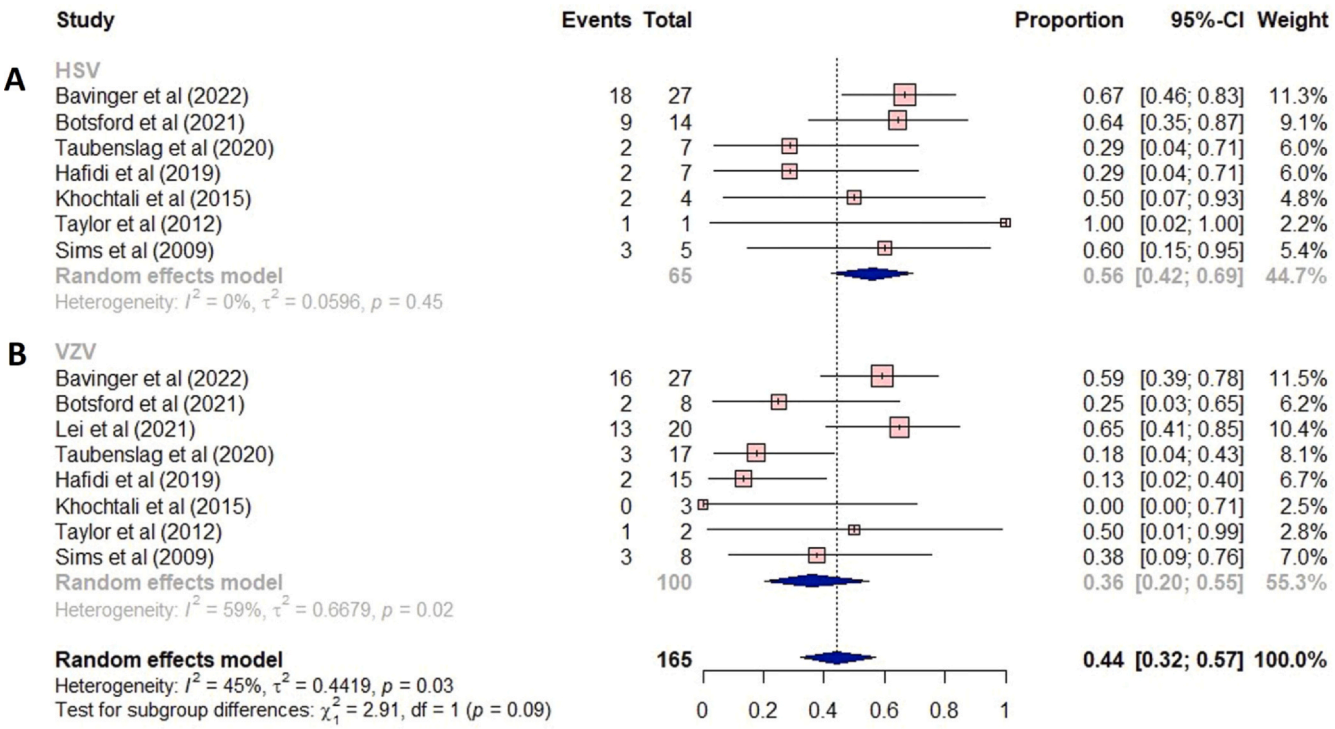

Fig. 6 – Forest plots showing pooled estimates of retinal detachment in acute retinal necrosis. HSV-1/HSV-2 PCR positive (A) and VZV PCR positive (B). VZV = varicella-zoster virus; HSV = herpes simplex virus.

when administered intravitreally. As a result, significant foscarnet retention occurs in the vitreous, but it may not be sufficient to maintain the required IC_{50} level in the retina (vitreous as a drug reservoir).[40] Moreover, two studies on CMV retinitis demonstrated that the vitreous level of ganciclovir, after intravenous administration, reached only half of the serum concentration and was suboptimal for viral control.[19,24] Similarly, even though the concentration of foscarnet in the vitreous was higher than that in the serum of patients receiving intravenous foscarnet, the induction regimen of intravenous foscarnet (120 mg/kg/day) still resulted in a subtherapeutic level for viral control.[4] Daikos and coworkers' study found that individuals receiving the combination of intravenous and intravitreal injections of ganciclovir appeared to have superior preservation of sight in CMV retinitis compared to those receiving only intravenous ganciclovir.[19] Furthermore, they reported no serious adverse events or retinal toxicity after intravitreal ganciclovir injections.[19]

We observed a high pooled estimate of RRD in ARN, with approximately one-third in VZV-positive cases and slightly more than half in HSV. These findings align with our observation of VA improvement in VZV and HSV-positive cases' however, the reason for this phenomenon needs to be confirmed in a well-designed prospective study. One should be aware of the potential of HSV acyclovir-resistant strain that could influence this finding, even though the exact prevalence of this strain across the globe also still require further investigation. Acyclovir-resistant HSV was reported to be caused by a mutation of the thymidine kinase gene at position A156V.[8] It had been previously studied that the acyclovir-resistant HSV would almost triple the time to achieve a viral load of less than 10% upon initial acyclovir treatment (28 days vs 11.6 days).[26] It is noteworthy that the study included both immunosuppressed patients, primarily those receiving immunosuppressives, and immunocompetent patients. Interestingly, there was no tendency for resistance to acyclovir to occur selectively based on the immunocompetency status.[26] Meanwhile, acyclovir-resistant VZV strains were believed to be less common.[25]

Besides antivirals, other therapeutic modalities require further evaluation of their effectiveness in treating ARN. The role of prophylactic laser for ARN has not been thoroughly studied. According to Baltinas and coworkers,[6] prophylactic barrier laser in both the intravenous group (n = 12, 41%) and the oral group (n = 9, 31%) did not reduce the rate of RRD. RRD was observed in 62% of eyes that underwent laser prophylactically with a median time of 56 days. Those who did not undergo prophylactic laser reported an RRD rate of 64%, showing no significant difference compared to those who received prophylactic laser. Cochrane and coworkers,[16] Roy and coworkers,[49] Tibbetts and coworkers,[56] and Urzua and coworkers[57] also reported no significant difference in RRD rates among lasered and nonlasered eyes; however, considering the retrospective design of the aforementioned

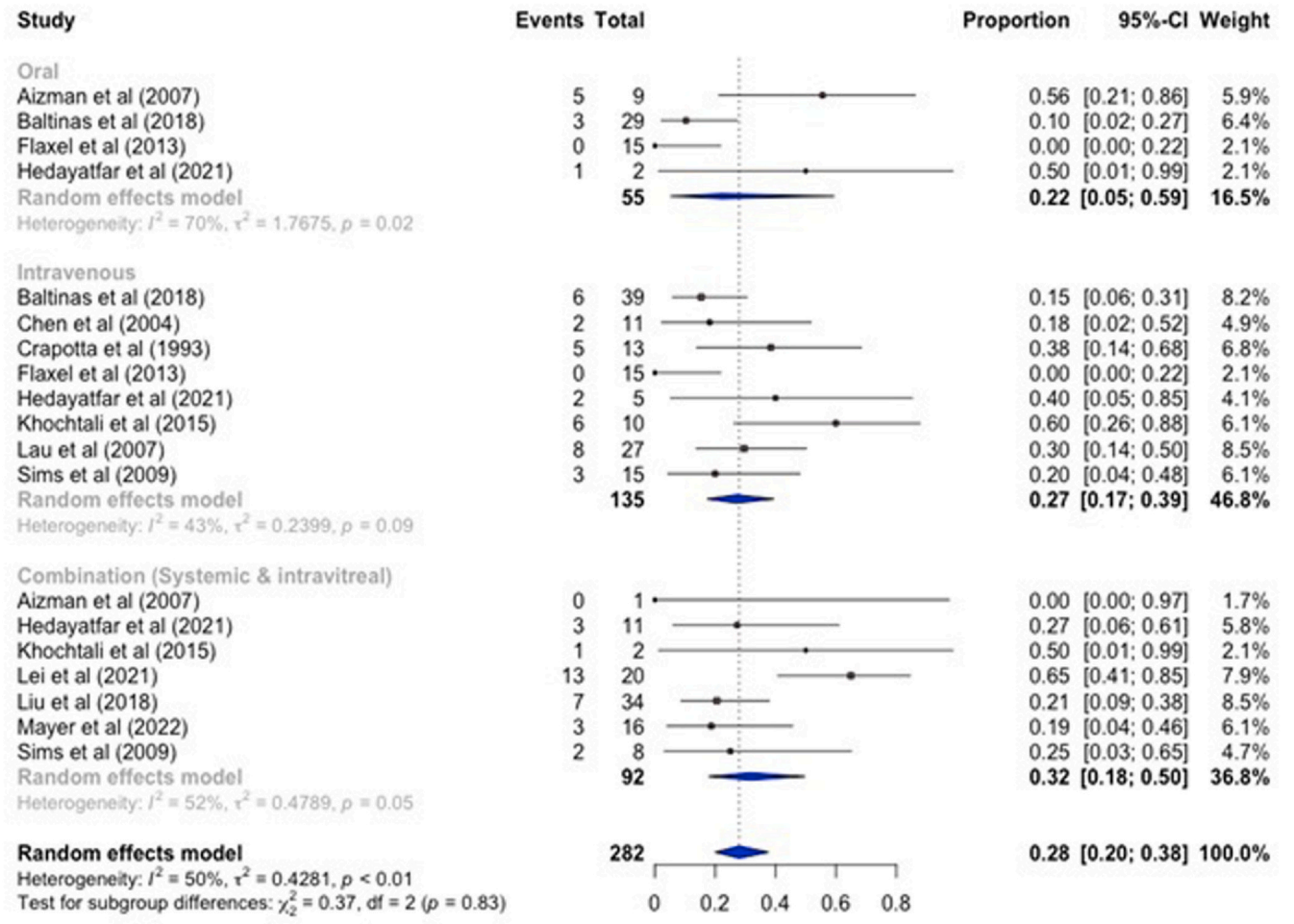

Fig. 7 – Forest plots showing pooled estimates of visual acuity improvement in acute retinal necrosis.

studies, it is possible that the treatment outcomes could have been influenced by differences in the baseline clinical features between eyes that received prophylactic laser treatment and those that did not. Besides prophylactic laser, the role of pars plana vitrectomy in ARN treatment remains uncertain. Liu and coworkers[39] concluded that prophylactic pars plana vitrectomy did not show a difference in RRD incidence and VA improvement rate; however, a recently published meta-analysis found that prophylactic pars plana vitrectomy could significantly reduce the risk of RRD compared to antiviral treatment alone.[22] Interestingly, the final VA of those receiving pars plana vitrectomy was worse than those only receiving antiviral treatment.[22] Therefore, given the limited availability of high-quality data, the potential benefits of prophylactic measures using laser and vitrectomy still require further evaluation.

We acknowledge some limitations of this review. Some outcomes were derived from a limited number of studies. Our result of recurrence estimates should also be interpreted cautiously due to the variable duration of follow-up. Herpes viruses can remain latent for a lifetime and may undergo episodic reactivation triggered by various stimuli, such as immunosuppression, exposure to ultraviolet, and stress.[18] Regarding the final antiviral approach-stratification analysis (as shown in Figs. 7 and 8), the limited number of studies necessitates careful interpretation. Nevertheless, the statistical meta-analysis with 2 different statistical packages yielded relatively similar results (Supplementary Table 6) and supported the direction of the obtained conclusions. The comparison of efficacy between different routes of the same drug (e.g., intravenous ganciclovir and intravitreal ganciclovir) could not be definitively concluded based on the available data. Additionally, determining the optimal duration of the maintenance phase with valacyclovir or acyclovir and the significance of the interval before the initiation of antiviral treatment were not feasible with the currently available data. Further well-designed prospective studies are required to investigate the effectiveness of each particular antiviral treatment. While a randomized control trial would be ideal, the considerable logistical challenges and the low incidence of ARN make it difficult to conduct. A multinational collaborative project would be beneficial to facilitate patient recruitment.

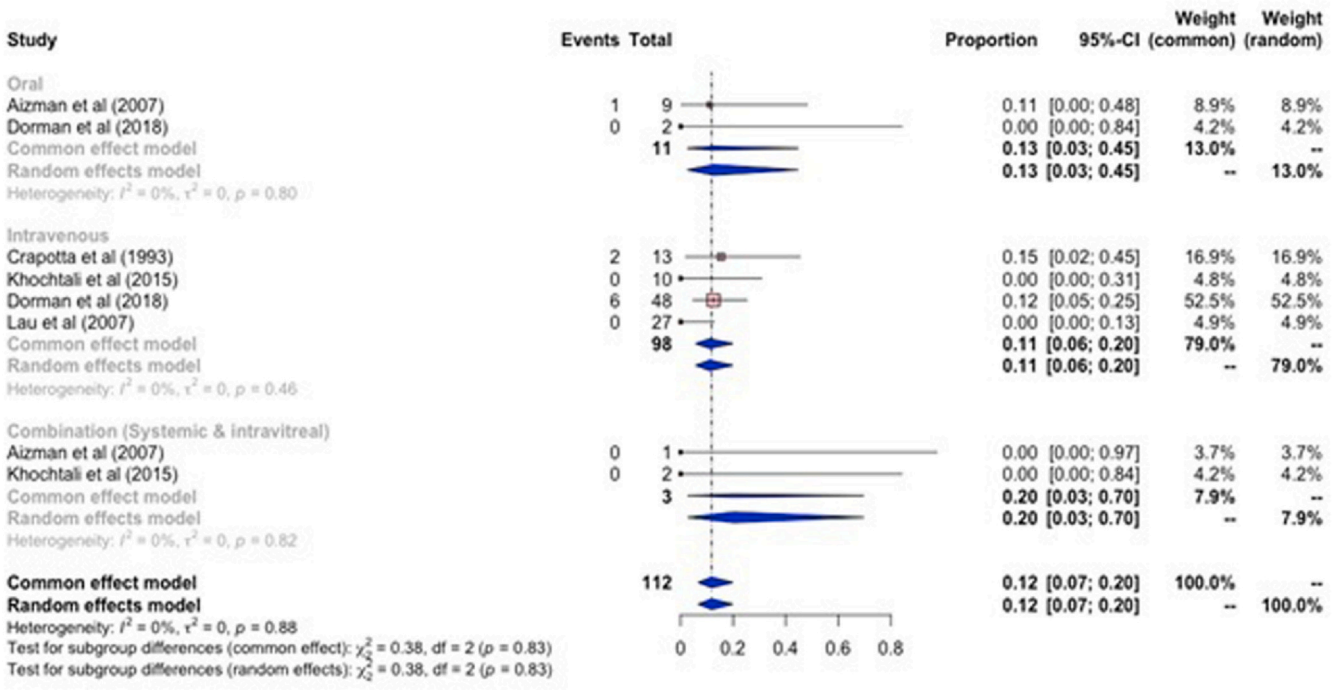

Fig. 8 – Forest plots showing pooled estimates of recurrence in acute retinal necrosis.

Furthermore, the establishment of a standardized registry to uniformly report treatment regimens and outcomes is necessary to enhance future research in this field.

5. Conclusion

In conclusion, we provide quantitative evidence of different antiviral approaches affecting the outcomes of ARN. Regarding PCR positivity, VZV was more prevalent than HSV, but the latter had a worse visual prognosis and a higher proportion of RRD. Compared to oral antivirals alone or intravenous antivirals alone, the combination of systemic and intravitreal antivirals showed a trend towards better visual recovery outcomes, even though this was not statistically significant. Moreover, we could not provide which specific antiviral is better than the others as varied antiviral dosages and duration were used in different settings. This variation may be attributed to the availability of antiviral options in different countries. Although we could not assess the timing of treatment initiation and its association with outcomes, prompt diagnosis and immediate antiviral treatment are crucial due to the high occurrence of RRD in ARN. Our limitations primarily stem from the data availabile in existing publications and a lack of reporting standardization. For future studies, we recommend prospective designs to evaluate treatment outcomes, duration, complications, loss to follow-up, and follow-up duration with well-defined antiviral regimens. Such standardized studies will provide more robust evidence and facilitate the advancement of ARN management.

6. Method of literature search

We searched the electronic databases of PubMed/MEDLINE, EMBASE, Scopus, and Google Scholar for studies published in English until June 1, 2022. The terms “acute retinal necrosis,” “antiviral (i.e., acyclovir, valacyclovir, foscarnet),” and “outcome or resolution or response” were used to search relevant articles (Table 1). We included studies that reported at least 10 eyes of ARN patients, described the antiviral regimen used, and provided at least one outcome of interest. Diagnosis of ARN could be with or without confirmatory PCR for the causative viral pathogen. For the first stage, abstract screening was performed by two authors for each study (I. P., A. S. R., and/or M. D.).

7. Disclosure

The authors declare no competing interests.

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Author contributions

Ikhwanuliman Putera: Conceptualization, Methodology, Investigation, Resources, Data curation, Formal analysis, Writing – original draft, Writing – review and editing. **Asri Salima Ridwan**: Conceptualization, Methodology, Investigation, Resources, Data curation, Formal analysis, Writing – original draft. **Metta Dewi**: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft. **Carlos Cifuentes-González**: Methodology, Data analysis, Supervision, Review and editing. **William Rojas-Carabali**: Methodology, Supervision, Review and editing. **Ratna Sitompul**: Methodology, Supervision, Review and editing. **Lukman Edwar**: Methodology, Supervision, Review and editing. **Made Susiyanti**: Methodology, Supervision, Review and editing. **Yulia Aziza**: Methodology, Supervision, Review and editing. **Carlos Pavesio**: Supervision, Validation, Review and editing. **Soon-Phaik Chee**: Supervision, Validation, Review and editing. **Padmamalini Mahendradas**: Supervision, Review and editing. **Jyotirmay Biswas**: Supervision, Validation, Review and editing. **John H. Kempen**: Supervision, Review and editing. **Vishali Gupta**: Conceptualization, Validation, Review and editing. **Alejandra de-la-Torre**: Conceptualization, Validation, Review and editing. **Rina La Distia Nora**: Conceptualization, Validation, Writing, Review and editing. **Rupesh Agrawal**: Conceptualization, Validation, Coordination, Review, and editing.

Declaration of Competing Interest

All authors: None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.survophthal.2023.09.004.

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