Risk of Rhegmatogenous Retinal Detachment in Acute Retinal Necrosis With and Without Prophylactic Intervention

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• PURPOSE: **To study whether preventive laser or preventive vitrectomy is able to lower the risk of rhegmatogenous retinal detachment (RRD) in patients with acute retinal necrosis (ARN).**

• DESIGN: **A retrospective, interventional case series.**

• METHODS: **We performed a retrospective study of 59 patients (63 eyes) with ARN treated in a single tertiary referral center. We analyzed different groups with either no prophylaxis, prophylactic laser, or prophylactic vitrectomy. Main outcome measure was incidence of RRD.**

• RESULTS: **Overall incidence of RRD was 44.4%, including 13% at presentation. In a crude analysis, the risk of RRD was highest in 33 patients with prophylactic laser (45.5%), lower in 15 patients with no prophylaxis (26.7%), and lowest in 7 patients with prophylactic vitrectomy (14.3%). Baseline best-corrected visual acuity differed between these groups, but zone and percentage of involved retina did not. In a multivariable model including prophylactic laser and ARN severity, only zone was predictive of RRD.**

• CONCLUSION: **When correcting for severity of disease, we did not observe a reduction in the risk of RRD by prophylactic laser in eyes with ARN. Therefore, prophylactic laser may be abandoned. The role of prophylactic vitrectomy is still unclear, but deserves further investigation. (Am J Ophthalmol 2019;206: 140–148. © 2019 Elsevier Inc. All rights reserved.)**

ACUTE RETINAL NECROSIS (ARN) IS A RARE, FULMINANT, and potentially blinding type of herpetic uveitis with an incidence of 0.5–0.63 per million per year.[1–3] ARN accounts for 1.3% of all uveitis patients.[4] Varicella zoster virus (VZV) is the most common causative pathogen, whereas herpes simplex virus (HSV) type 1 and 2 are found less frequently.[4,5] Patients typically present with vision loss owing to vitritis, occlusive vasculitis, and peripheral retinal necrosis with an average duration of symptoms of 15 days.[6] Prognosis regarding visual outcome is poor, with optic nerve involvement and rhegmatogenous retinal detachment (RRD) attributing to severe visual loss.[3,7–9] The literature on diagnosis and treatment has been evaluated recently by the American Academy of Ophthalmology.[10]

The reported frequency of RRD in eyes with ARN varies widely, from 20% to 73%.[10] This wide range may be explained by differences in criteria and definitions, severity of ARN, and time of follow-up. Extensive retinal involvement has been found to increase the risk of RRD.[8,9,11,12] RRD typically presents in the late cicatricial phase, 1–2 months after the onset of symptoms.[13,14] In this phase, which follows the acute herpetic phase, the retina turns necrotic, thereby facilitating the formation of retinal tears at the border of vital and ischemic retina.[15,16] Also, contraction of the vitreous body and formation of membranes contribute to the risk of RRD.[2,15] Therefore, prophylactic vitrectomy in ARN has been suggested to relieve vitreoretinal traction and prevent RRD. An alternative prophylactic strategy is laser demarcation. Its aim is to reduce the risk of RRD by inducing retinal scarring at the central border of the necrotic retina.

However, many observational studies reporting on RRD in ARN patients did not find laser or vitrectomy to be effective for preventing RRD.[13–19] Most of these studies did not control for severity or extent of disease, while this parameter is of great importance in the feasibility to perform prophylactic therapy, since severe vitritis impedes visualization of the retina during laser treatment.[20] Therefore, disease severity may bias the findings on the effect of laser and vitrectomy on RRD risk.

We hypothesized that laser demarcation and preventive vitrectomy may reduce the risk of RRD in eyes with ARN while correcting for severity of disease. We performed a single-center, retrospective study of 59 patients with ARN to investigate the incidence of RRD with and without prophylactic therapy. Also, patient characteristics, risk factors for RRD, and visual outcome of this large single-center cohort are described.

METHODS

• **PATIENTS AND STUDY DESIGN:** This retrospective study was conducted at the University Medical Center Utrecht,

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Utrecht, the Netherlands, a tertiary referral center for patients with uveitis and ARN. We performed the study in accordance with the 1964 Declaration of Helsinki and its further amendments. Before the start of the study, the Institutional Review Board of University Medical Center Utrecht waived approval of the study protocol, since no experimental procedures were performed.

We included all patients with ARN that were seen at the ophthalmology department between January 2001 and January 2017. The diagnosis was verified according to the diagnostic criteria of the American Uveitis Society.[21] Moreover, the diagnosis had to be confirmed by aqueous humor analysis with polymerase chain reaction (PCR) and in some cases (n = 3) a Goldmann-Witmer analysis positive for VZV or HSV. Four patients younger than 18 years at diagnosis were excluded, as well as 1 patient with a PCR positive for cytomegalovirus in aqueous humor. No patients tested positive for Epstein-Barr virus. In case of bilateral ARN (n = 4), both eyes were included in the study. In total, 63 eyes were included.

Within our clinic we have used a standard diagnostic and treatment protocol for more than 10 years, specifying the diagnostic evaluation (aqueous humor analysis), the medical treatment (antivirals, antithrombotics, and steroids), and clinical check-ups. Adjustments to the protocol were made owing to the personalized circumstances of the patients. Most patients (89%) were treated with intravenous antivirals (acyclovir 10 mg/kg every 8 hours) for at least 14 days, followed by oral valacyclovir for at least 3 months but frequently for 1 year. The remaining 11% was treated with oral valacyclovir (1000 mg 3 times a day) only. The use of intravitreal ganciclovir started in the last quarter of 2008. Since then, most patients (n = 28) with VZV received 1 or more injections with intravitreal ganciclovir therapy (4 mg/0.1 mL).

Data were collected regarding age, sex, general health, ocular and medication history, symptoms and clinical characteristics of ARN at presentation, extent of necrosis, best-corrected visual acuity (BCVA) at presentation and follow-up (3 months, 6 months, 1 year, final follow-up, with date), PCR analysis of anterior chamber tap, antiviral and anti-inflammatory treatment, details on prophylactic laser photocoagulation such as date and number of laser coagulates, prophylactic vitrectomy, and occurrence of RRD. BCVA was measured by Snellen charts and converted to logarithm of minimal angle of resolution (logMAR) units for statistical analysis.[22] Apart from the medical records, color fundus photography and fluorescence angiography were assessed, if available. In case patients were sent back to their referring ophthalmologist, the follow-up data were requested by mail.

• **DEFINITIONS:** Retinal zones and the percentage of involved retina were assessed using all available diagnostic imaging and reviewed by 2 individuals (S.R. and R.v.L.). Zones were classified according to the criteria proposed by Holland for cytomegalovirus retinitis[23]: zone 1 was defined as sight-threatening foci of necrosis within 3000 μm of the fovea or within 1500 μm of the optic disc; zone 2 extends onto the clinical equator; zone 3 extends anteriorly from the borders of zone 2. The area of involved retina was categorized into the quadrants.

Prophylactic laser was defined as a session of argon laser within 30 days after diagnosis, in which a barrier of coagulates was applied posteriorly from, or surrounding, necrotic lesions. The option of prophylactic laser demarcation depended on the severity of vitreous opacities. Prophylactic vitrectomy was defined as a standard 20 or 25 gauge 3-port pars plana vitrectomy before the development of RRD, thus excluding vitrectomy in the presence of an RRD. In all vitrectomies the complete vitreous body was removed, laser coagulation was applied, and silicone oil was used as intraocular tamponade.

The primary outcome was the occurrence of a partial or total RRD after diagnosis of ARN. For the determination of RRD incidence, a minimum follow-up time of 6 months was set. For the comparison between prophylactic interventions, we excluded RRD cases within the first 10 days after diagnosis in order to account for the time needed to perform a prophylactic intervention. This interval was based on the median time between diagnosis and first laser session in our cohort. Eyes presenting with an RRD or developing an RRD within this period of 10 days were defined as a subgroup of Early RRD.

• **STATISTICAL ANALYSIS:** Eyes receiving prophylactic laser, receiving a prophylactic vitrectomy, or presenting with an early RRD were compared with the observation group, which consisted of eyes not receiving any form of prophylactic intervention. Analysis of data was performed using SPSS software version 21.0 (SPSS Inc, Chicago, Illinois, USA). Values are presented as numbers with percentage (%), mean with standard deviation (±SD), or median with interquartile range (IQR). Differences between groups were identified via χ^2 test, 1-way ANOVA, or Kruskal-Wallis test. To test for the predictive value of baseline characteristics and prophylactic therapy on the occurrence of RRD, univariable logistic regression was used. Multivariable logistic regression was performed to assess the independent correlation of possible predictors with the occurrence of RRD. A P value of $<.05$ was considered statistically significant.

RESULTS

• **PATIENT CHARACTERISTICS:** In total, 63 eyes of 59 patients were included, as 4 patients had bilateral involvement. Clinical characteristics at presentation are shown in Table 1. Mean age was 58.4 years and 50.8% of eyes were of male patients. Median BCVA was 20/100 (0.7 logMAR), with 15 eyes (23.8%) having a BCVA better

TABLE 1. Clinical Characteristics of 63 Eyes of 59 Patients With Acute Retinal Necrosis for Both the Total Cohort and Subgroups of Early Rhegmatogenous Retinal Detachment and Prophylactic Treatment

	Total	No Prophylaxis	Prophylactic Laser	Prophylactic Vitrectomy	Early RRD	
	N = 63	N = 15	N =33	N = 7	N = 8	P Value
Presentation						
Male	32 (50.8)	8 (53.3)	16 (48.5)	3 (42.9)	5 (62.5)	.87
Age, years[a]	58.4 ± 17.4	65.9 ± 20.5	57.3 ± 15.9	56.1 ± 15.4	50.9 ± 16.3	.21
BCVA, logMAR[b]	0.7 (1.02)	0.80 (1.88)	0.66 (0.61)	0.74 (0.78)	1.39 (2.00)	.05
BCVA, categories (%)						
>20/50	15 (23.8)	4 (26.7)	10 (30.3)	1 (14.3)	0	.03
20/50 to >20/200	27 (42.9)	5 (33.3)	16 (48.5)	3 (42.9)	3 (37.5)	
20/200 to LP	18 (28.6)	5 (33.3)	7 (21.2)	3 (42.9)	3 (37.5)	
LP or no LP	3 (4.8)	1 (6.7)	0	0	2 (25.0)	
Duration of symptoms, days[b]	14.0 (14.0)	21.0 (14.0)	13.5 (11.0)	14.0 (59.0)	17.5 (19.0)	.23
Zone						
1: central	19 (30.2)	2 (13.3)	11 (33.3)	3 (42.9)	3 (37.5)	.56
2: midperipheral	29 (46.0)	9 (60.0)	14 (42.4)	3 (42.9)	3 (37.5)	
3: peripheral	12 (19.0)	34 (26.7)	7 (21.2)	0	1 (12.5)	
Unknown	3 (4.8)	0	1 (3.0)	1 (14.3)	1 (12.5)	
Involved retina						
<25%	3 (4.8)	2 (13.3)	1 (3.0)	0	0	.16
25%–50%	16 (25.4)	3 (20.0)	11 (33.3)	0	2 (25.0)	
50%–75%	11 (17.5)	4 (26.7)	7 (21.2)	0	0	
>75%	30 (47.6)	5 (33.3)	13 (39.4)	7 (100)	5 (62.5)	
Unknown	3 (4.8)	1 (6.7)	1 (3.0)	0	1 (12.5)	
Virus						
VZV	53 (84.1)	12 (80.0)	32 (97.0)	2 (28.6)	7 (87.5)	<.01
HSV	10 (15.9)	3 (20.0)	1 (3.0)	5 (71.4)	1 (12.5)	
Optic nerve involvement						
No	15 (23.8)	4 (26.7)	10 (30.3)	0	1 (12.5)	.26
Yes	31 (49.2)	6 (40.0)	15 (45.5)	5 (71.4)	5 (62.5)	
Unknown	17 (27.0)	5 (33.3)	8 (24.2)	2 (28.6)	2 (25.0)	
Immunosuppression						
No	50 (79.4)	11 (73.3)	25 (75.8)	7 (100)	7 (87.5)	.43
Yes	13 (20.6)	4 (26.7)	8 (24.2)	0	1 (12.5)	
Steroids	8 (12.7)	4 (26.7)	3 (9.1)	0	1 (14.3)	
Other causes[c]	5 (7.9)	0	5 (15.2)	0	0	
Treatment						
Oral antivirals	63 (100)	15 (100)	33 (100)	7 (100)	8 (100)	1
Intravenous antivirals	56 (88.9)	12 (80.0)	31 (93.9)	6 (85.7)	7 (87.5)	.54
Intravitreal antivirals	30 (47.6)	8 (53.3)	15 (45.5)	2 (28.6)	5 (62.5)	.58
Prednisone[d]	48 (85.7)	10 (76.9)	26 (89.7)	6 (85.7)	6 (85.7)	.76
Aspirin	32 (50.8)	6 (40.0)	20 (60.6)	2 (28.6)	4 (50.0)	.34

BCVA = best-corrected visual acuity; HSV = herpes simplex virus; logMAR = logarithm of minimal angle of resolution; LP = light perception; NLP = no light perception; RRD = rhegmatogenous retinal detachment; VZV = varicella zoster virus.

Data are given as number (%) unless otherwise stated.

[a]Data given as mean ± SD.

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

[c]Patients were immunocompromised owing to chemotherapy (n = 1), leukemia (n = 1), treatment with monoclonal antibodies (n = 1), combined immunodeficiency (n = 1), Good syndrome (n = 1).

[d]Eight patients already used systemic steroids before the diagnosis of acute retinal necrosis.

than 20/50 and 3 eyes (4.8%) with or without light perception (LP). Median duration of symptoms before diagnosis was 14 days. Involved retina was limited to the periphery (zone 3) in 19.0% of eyes and included the macula (zone 1) in 30.2%. In 47.6% of eyes, all 4 quadrants of the retina were affected and in 49.2% of eyes the optic nerve was

TABLE 2. Clinical Outcome in Terms of Incident Retinal Detachment and Visual Acuity of 63 Eyes With Acute Retinal Necrosis, for Both the Total Cohort and Subgroups of Early Rhegmatogenous Retinal Detachment and Prophylactic Treatment

	Total	No Prophylaxis	Prophylactic Laser	Prophylactic Vitrectomy	Early RRD	
	N = 63	N = 15	N = 33	N = 7	N = 8	*P* Value
Follow-up, months[a]	24 (0–145)	20 (0–83)	20 (1–145)	28 (6–100)	30.5 (8–80)	.72
Incident RRD	28 (44.4)	4 (26.7)	15 (45.5)	1 (14.3)	8 (100)	<.01
Time to RRD, weeks[a]	7 (0–47)	2.5 (2–8)	9 (3–47)	14	1 (0–1)	.03
BCVA at 6 months, categories						
>20/50	17 (27.0)	5 (33.3)	13 (39.4)	0	0	<.01
20/50 to >20/200	16 (25.4)	2 (13.3)	12 (36.4)	1 (14.3)	0	
20/200 to LP	23 (36.5)	5 (33.3)	6 (18.2)	6 (85.7)	6 (75.0)	
LP or no LP	7 (11.1)	3 (20.0)	2 (6.1)	0	2 (25.0)	

BCVA = best-corrected visual acuity; logMAR = logarithm of minimal angle of resolution; LP = light perception; RRD = rhegmatogenous retinal detachment.

[a]Data given as median (range).

involved. VZV was the causal agent in 84.1% of cases. Thirteen eyes (20.6%) were immunosuppressed at the time of diagnosis, including 8 who were using systemic corticosteroids before the diagnosis of ARN was made. None of the patients suffered from human immunodeficiency virus infection. Regarding antiviral therapy, in 88.9% of eyes the patient was treated with intravenous antivirals in addition to oral treatment (100%). Additional intravitreal therapy was given to 47.6% of eyes, including foscarnet in 2 eyes and ganciclovir in 28 eyes. Systemic corticosteroids were prescribed to 85.7% of ARN eyes and acetylsalicylic acid to 50.8%.

Of 63 eyes, 8 eyes (13%) presented with an RRD or developed an RRD within 10 days after diagnosis. These were not eligible for prophylactic treatment. Thirty-three eyes (52%) received prophylactic laser, 7 eyes (11%) underwent a prophylactic vitrectomy, and 15 eyes (24%) did not receive any RRD prophylaxis. Two patients underwent a vitrectomy because of floaters, 1 and 3 years after diagnosis, respectively; and 1 patient because of a macular hole 3 years after diagnosis. These cases were not classified as prophylactic vitrectomy. Of the 15 eyes not receiving prophylaxis, 13 eyes (87%) had severe vitreous opacities making laser impossible and in 2 eyes the consulting ophthalmologist thought laser would not be effective. Baseline characteristics of the subgroups are also presented in Table 1. Age and sex did not differ between groups. Patients in the early RRD group presented with a worse BCVA ($P = .05$). In the group undergoing prophylactic vitrectomy, HSV was a more frequent causal pathogen compared to the other groups ($P < .01$). Antiviral treatment, including intravitreal medication, was similar among the 4 groups. There was no association between duration of symptoms and zone or percentage involved retina (data not shown). Exclusion of a randomly selected eye of the 4 bilateral affected patients did not change these results.

• **RHEGMATOGENOUS RETINAL DETACHMENT INCIDENCE:** The median duration of follow-up was 24 months, ranging from 0 to 145 months (IQR = 11–47) (Table 2). Of 59 patients, 56 (95.0%) had a follow-up of at least 6 months and 38 (70.4%) of 1 year or longer. Reasons for loss to follow-up were death or referral to another hospital with no response to written inquiries.

In the total group of 63 eyes with ARN, 28 (44.4%) developed an RRD (Table 2). This includes 8 eyes with an RRD at presentation or within 10 days of presentation. In the total group, median time between diagnosis and RRD was 7 weeks, with a range of 0–47 weeks. One patient who had prophylactic laser treatment developed an RRD after more than 6 months. In the group with no prophylaxis, 4 eyes (26.7%) developed an RRD after a median interval of 2.5 weeks. In the group with laser prophylaxis, 15 eyes (45.5%) developed an RRD after a median interval of 9 weeks. Of the 7 eyes with a prophylactic vitrectomy, 1 eye (14.3%) developed an RRD after a median interval of 14.0 weeks, which was statistically significant longer compared to the other groups ($P = .03$). RRD incidence was highest in the prophylactic laser group ($P < .01$). In the Figure, a Kaplan-Meier survival curve for the prophylaxis subgroups is presented.

• **RISK FACTORS FOR RHEGMATOGENOUS RETINAL DETACHMENT:** In univariable analysis, limited to eyes with a follow-up of 6 months and excluding early RRD within 10 days, no statistically significant associations were found between risk factors and incidence of RRD (Table 3). Use of intravitreal antiviral therapy was borderline statistically significantly associated with a higher risk of RRD ($P = .054$). Retinitis limited to the peripheral zone 3 was associated with a lower risk of RRD ($P = .051$). Age, immunocompetence, baseline BCVA, bilateral involvement, percentage of the retina involved, and virus type were not associated with the incidence of RRD.

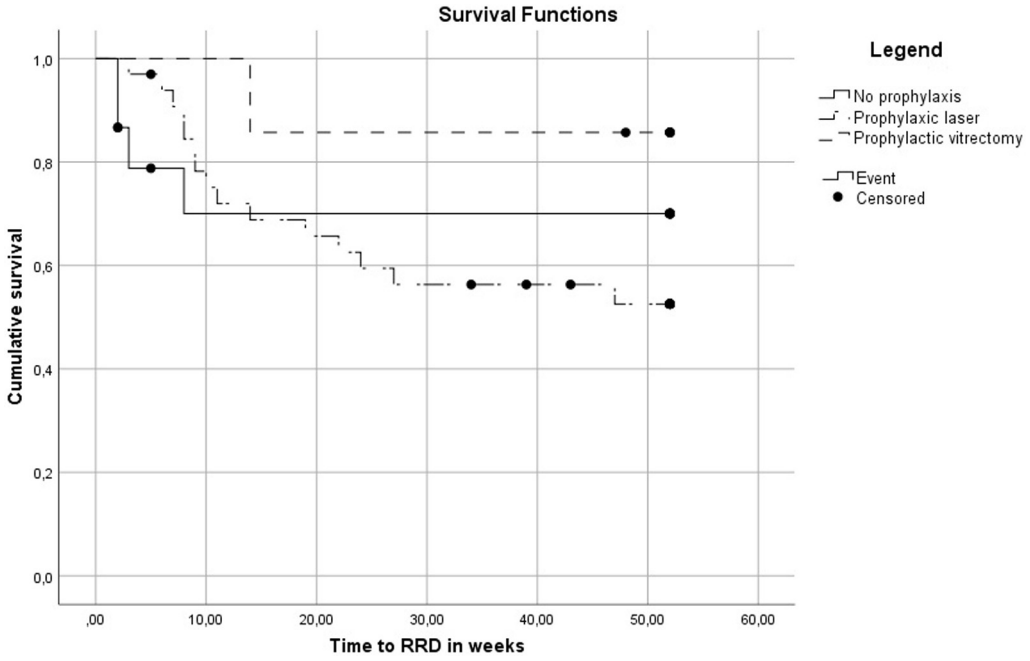

FIGURE. Kaplan-Meier survival curve for rhegmatogenous retinal detachment (RRD) after diagnosis of acute retinal necrosis for 3 subgroups with and without prophylaxis.

Moreover, we did not see an association between prophylactic laser or prophylactic vitrectomy and risk of RRD (Table 3). To further analyze the effect of prophylactic laser, we also performed a multivariable logistic regression analysis to correct for potential confounding by indication, including only the "no prophylaxis" and "prophylactic laser" groups. Based on the univariable analysis and previous studies, we considered zone and extent of involved retina as potential confounders, since they reflect severity of disease. Multivariable analysis confirmed the association between involved zones and risk of RRD, but did not show a protective effect of prophylactic laser (odds ratio = 1.4, 95% confidence interval 0.3–6.7, Table 4). The effect of prophylactic vitrectomy could not be tested in this multivariable analysis because the number of RRD cases was too low.

• **VISUAL OUTCOME:** Of the total cohort, most eyes (44.4%) had a BCVA between 20/200 and LP at the last available examination (Table 2). A final BCVA above 20/50 was seen in 28.6% of eyes, and 11.1% had LP or no LP. These figures differed between the 4 prophylaxis groups, with the worse visual outcome in the prophylactic vitrectomy group (20/200 to LP in 71.4%) and the early RRD group (20/200 to LP in 75%). Best final BCVA was seen in the prophylactic laser group (better than 20/200 in 63.7%).

ARN eyes that developed an RRD had a worse final BCVA (Table 3). Baseline BCVA was statistically significantly associated with final BCVA ($P < .01$). Also, zone and percentage of involved retina were associated with final BCVA. Of 18 patients with zone 1 involvement, 13 (72.2%) had a final BCVA of 20/200 or less, as compared to 55.5% of patients with zone 2 and 25% of patients with zone 3 involvement ($P = .02$). A similar association was found for percentage of involved retina. Of 3 patients with <25% involved retina, 2 had a final BCVA of better than 20/50, while 10.3% of patients with more than 75% involved retina reached this final BCVA ($P < .001$).

All 28 eyes with RRD underwent a vitrectomy with oil tamponade and only 16 (57.1%) had oil removal surgery. Of these 16 eyes with oil removal, 2 (12.5%) had a BCVA at last follow-up of better than 20/50; 5 (31.3%) had a BCVA of 20/50 to 20/200; and 9 (56.3%) had LP or no LP. Of the 12 patients who had no oil removal, 1 (8.3%) had a BCVA at last follow-up of better than 20/50; 8 (66.7%) had a BCVA of 20/50 to 20/200; and 3 (25.0%) had LP or no LP. Of the 7 patients with prophylactic vitrectomy, 6 still had silicone oil in situ at the last follow-up.

DISCUSSION

IN OUR DUTCH TERTIARY REFERRAL CENTER, PROPHYLACTIC laser was included in the treatment protocol for ARN patients some 20 years ago. The basis for this intervention was a plausible hypothesis and the publications of Sternberg and associates[19] and Crapotta and associates[24] in which a protective effect was suggested. Since then no convincing evidence has been put forward and a report

TABLE 3. Comparison Between Eyes With Acute Retinal Necrosis (N = 59) That Did or Did Not Develop a Rhegmatogenous Retinal Detachment and Had at Least 6 Months of Follow-up

		No RRD	RRD		
		N = 35	N = 28	*P* Value	
Age, years[a]		59.5 ± 18.3	54.4 ± 15.3	.23	
Immunosuppressed	N =13	9 (25.7)	4 (14.3)	.60	
Baseline BCVA, categories					
>20/50	N = 15	9 (25.7)	6 (21.4)	.29	
20/50 to >20/200	N = 27	16 (45.7)	11 (39.3)		
20/200 or worse	N = 18	10 (28.6)	8 (28.6)		
LP or no LP	N = 3	0	3 (10.7)		
BARN	N = 8	6 (17.1)	2 (7.1)	.24	
Virus					
VZV	N = 53	30 (85.7)	23 (82.1)	.86	
HSV	N = 10	5 (14.3)	5 (17.9)		
Use of intravitreal antivirals	N = 30	13 (37.1)	17 (60.7)	.054	
Zone					
1: central	N = 19	9 (26.5)	10 (38.5)		
2: midperipheral	N = 29	15 (44.1)	14 (53.8)	Zone 2 vs 1	.8
3: peripheral	N = 12	10 (32.3)	2 (7.7)	Zone 3 vs 1	.051
Unknown	N = 2	0	2 (7.7)		
Involved retina					
<25%	N = 3	3 (8.6)	0	.43	
25%–50%	N = 16	10 (28.6)	6 (21.4)		
50%–75%	N = 11	6 (17.1)	5 (17.9)		
>75%	N = 30	14 (40.0)	16 (57.1)		
Unknown	N = 3	2 (5.7)	1 (3.6%)		
Prophylactic laser[b]					
No prophylaxis	N = 15	11 (37.9)	4 (21.1)	.22	
Laser	N = 33	18 (62.1)	15 (78.9)		
Prophylactic vitrectomy[b]					
No prophylaxis	N = 15	11 (64.7)	4 (80.0)	.48	
Vitrectomy	N = 7	6 (35.3)	1 (20.0)		
BCVA at 6 months, categories					
>20/50	N = 18	14 (40.0)	4 (14.3)	.10	
20/50 to >20/200	N = 10	8 (22.9)	7 (25.0)		
20/200 to LP	N = 28	11 (31.4)	12 (42.9)		
LP or no LP	N = 7	2 (5.7)	5 (17.9)		

BARN = bilateral acute retinal necrosis; BCVA = best-corrected visual acuity; CI = confidence interval; HSV = herpes simplex virus; LP = light perception; OR = odds ratio; RRD = rhegmatogenous retinal detachment; VZV = varicella zoster virus.

Data are given as number (percentage) unless otherwise stated.

[a]Data given as mean ± SD.

[b]Eyes with early RRD (n = 8) were excluded.

by the American Academy of Ophthalmology in 2017 concluded that the available evidence at that time did not support a beneficial effect of laser to prevent RRD in the setting of recent ARN. We decided to study our cohort of 59 ARN patients in order to analyze the effect of prophylactic laser. Because confounding by indication is of major concern in these observational retrospective studies, we decided to adjust for disease severity in the analyses. However, also with this statistical adjustment, we did not see an advantage of prophylactic laser in the prevention of RRD.

The high incidence of RRD and its detrimental effect on the visual outcome in patients with ARN is well known.[3] In our cohort, the overall risk of RRD was 44.4%, which is within the range of 20%–73% reported by previous studies.[1–3,7–9,11,14,17,18,25,26] Less is known about predisposing factors. Butler and associates reported on an association between percentage of initially involved retina and RRD, with a 12 times increased risk of eyes with more than 25% retinal involvement.[25] We could not confirm this relationship in our cohort, although

TABLE 4. Multivariate Model of Risk of Incident Rhegmatogenous Retinal Detachment for Prophylactic Laser, Zone of Acute Retinal Necrosis, and Percentage of Involved Retina

	OR	95% CI	*P* Value
Prophylactic laser (yes is reference)	1.4	0.3–6.7	.7
Zone (1/central is reference)	0.3	0.1–0.9	.03
Percentage of retina involved (25% is reference)	1.3	0.8–2.2	.28

CI = confidence interval; OR = odds ratio.

none of our 3 patients with less than 25% involved retina developed an RRD. The explanation for this discrepancy may be found in a different distribution of the involved retinal area: in our cohort only 6% of eyes had <25% of the retina affected and 47% of eyes >75%, as compared to 34% and 26%, respectively, in the study of Butler and associates.[25] We did, however, find an association between zone and percentage of involved retina and final visual acuity.

Our results are also in line with previous findings on the incidence of RRD after prophylactic laser in eyes with ARN. One study with 27 eyes found a significant reduction of RRD risk in the laser group (35% vs 80% in non-laser eyes, $P = .04$).[7] In contrast, another study observed RRD in all 13 eyes (100%) after laser vs 2 out of 7 in the control group (29%).[17] However, since laser results were not the main outcome and not all findings regarding prophylactic laser were reported, it is difficult to interpret these studies and compare them with others. Other studies were not able to find statistically significant differences in RRD rates between the laser and control group.[8,11,14,18,27] Only 2 studies reported on sample sizes similar to our cohort. One study investigated 58 eyes and found 58% RRD in the prophylactic laser group (11 out of 19) vs 39% in the control group (18 out of 39, $P = .40$).[14] These authors concluded that laser cannot prevent RRD in ARN patients. Another study with 62 eyes with ARN found a 66.1% overall RRD incidence. Twelve out of 19 patients with laser prophylaxis developed an RRD (63%) compared to 29 out of 43 eyes without prophylaxis (67%).[11] It should be noted that these authors did not exclude 18 eyes with an RRD at presentation, causing them to not be eligible for laser. In conclusion, most studies do not support a protective effect of laser on RRD risk in ARN.

Our study is the first to correct for severity of disease. Applying retinal laser requires clear ocular media, and vitreous opacities owing to vitritis will render this option impossible. Since vitritis is likely to express severity of disease, only mild or early cases with a better prognosis will receive laser. Quantifying severity of disease is hard and follows judgment of a treating physician. It seems plausible that severity and extension of disease would influence the risk of RRD and this is supported by the literature for the area of initially involved retina.[25] As severity of ARN affects both risk of RRD and the possibility to apply laser prophylaxis, it can be considered a confounder. Therefore, we corrected for zones and involved retina in a multivariable regression analysis to provide new insights in the efficacy of prophylactic laser in ARN. However, we could not rule out selection bias in our study population. There was no statistically significant difference in affected zone or percentage of involved retina between the 3 intervention groups. Also, correcting for these parameters in a multivariable model did not change our results.

Prophylactic vitrectomy was associated with a lower odds ratio of RRD compared with no prophylaxis, but this was not statistically significant. The numbers in this subgroup were low, with 1 RRD out of 7 prophylactic vitrectomies. Still, this result seems to correspond with the literature. Four studies reported on RRD after prophylactic vitrectomy in ARN, of which 2 studies found a statistically significant reduction of RRD.[9,12,13,17] Considering these limited data, vitrectomy seems to be more promising as potential prophylactic intervention compared to laser. However, we should take into account that all patients in the prophylactic vitrectomy group had a very low BCVA at 6 months. This will be the result of both macular dysfunction owing to the ARN and the deteriorating effect of permanent oil tamponade.

In our multivariable analysis, zone 1 and 2 disease and extent of necrosis proved to be risk factors for developing RRD, corresponding with previous studies.[8,12] Furthermore, VZV was not associated with RRD incidence. This is remarkable, since VZV-ARN is described as the more fulminant type and even increasing risk of RRD in 1 study.[9] It is possible that HSV-2 attributes to poorer outcome in our study, since this has been associated with worse anatomic and visual outcome.[5] However, since the type was not reported consistently, it is not possible to discriminate in outcome between HSV-1 and HSV-2 ARN.

The average visual outcome of our cohort is in conformance to the literature, with 55.5% of eyes achieving a visual acuity of 20/200 or worse.[10] Tibbetts and associates reported that half of all patients had 20/200 or worse vision by 3 months.[14] Roy and associates found a poor functional outcome, defined as BCVA worse than 3/60, in 54.9% of eyes.[11] We found that BCVA at last examination was worst in the early RRD and prophylactic vitrectomy subgroups. This can be explained by the impact of the RRD and the severity of disease in the prophylactic vitrectomy group. In the latter group, all eyes had >75% of the retina involved. In addition, all eyes that had a vitrectomy for RRD treatment (n = 28) or for RRD prophylaxis (n = 7) had silicone oil tamponade. In only 16 (64%) of these eyes the oil was removed. The permanent oil tamponade in the other eyes will in part explain their very low

BCVA. But probably no visual improvement was anticipated by the vitreoretinal surgeon in case of oil removal.

The strength of this study is the relatively large number of patients with ARN confirmed by aqueous humor analysis from a single center with 1 team of uveitis specialists. A diagnostic and treatment protocol was used, but in daily care it was customized according to patient-related conditions. Previous studies on prophylactic laser therapy included a smaller number of patients, varying from 5 to 62, sometimes sampled from different institutions.[7,8,11,14,17,18] In contrast to other studies, the diagnosis of all our patients was confirmed by a positive PCR in aqueous humor. Since most of our panuveitis and posterior uveitis patients undergo an anterior chamber tap, a selection bias in severity is unlikely. In addition, the assessment of disease severity allowed for adjustment in the risk analysis. Some limitations need to be addressed as well. In some patients, data regarding final visual acuity and long-term RRD incidence were missing because these patients returned to their referring ophthalmologists, who did not respond to information requests.

The low number of eyes collected over a 15-year period denotes the rarity of ARN. This inevitably limits statistical power. To illustrate, 220 eyes with ARN would be needed to find a statistically significant difference in RRD incidence of 26.7% in non-laser eyes vs 45.5% in eyes with prophylactic laser (alpha = 0.05, beta = 0.1). As stated in previous articles, such a cohort of ARN patients is impossible to collect in a single institution.[14] A meta-analysis would be an option to solve this problem, but this design also does not correct for confounding, in particular confounding-by-indication. The best design to study the prophylactic effect of laser or vitrectomy on RRD risk in ARN would be a randomized controlled trial. However, vitreous haze is still an obstruction to the application of laser, rendering this option impossible. For prophylactic vitrectomy, a multicenter trial may provide an answer.

Also when correcting for severity of disease, prophylactic laser did not reduce the risk of RRD in our cohort of 63 eyes with ARN. Therefore, prophylactic laser may be abandoned. The role of prophylactic vitrectomy is still unclear, but deserves further investigation.

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